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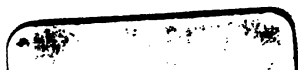
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VOL. 69

MAY 10, 1967

NO. 10

Editor: J. H. S. Y.

Report from
**BELL
LABORATORIES**

Making voices from the depths sound deeper

Bell Telephone Laboratories has had a long-term interest in speech research—tracing back, indeed, to the work of Alexander Graham Bell. It was for this reason that the U. S. Navy asked us to investigate a

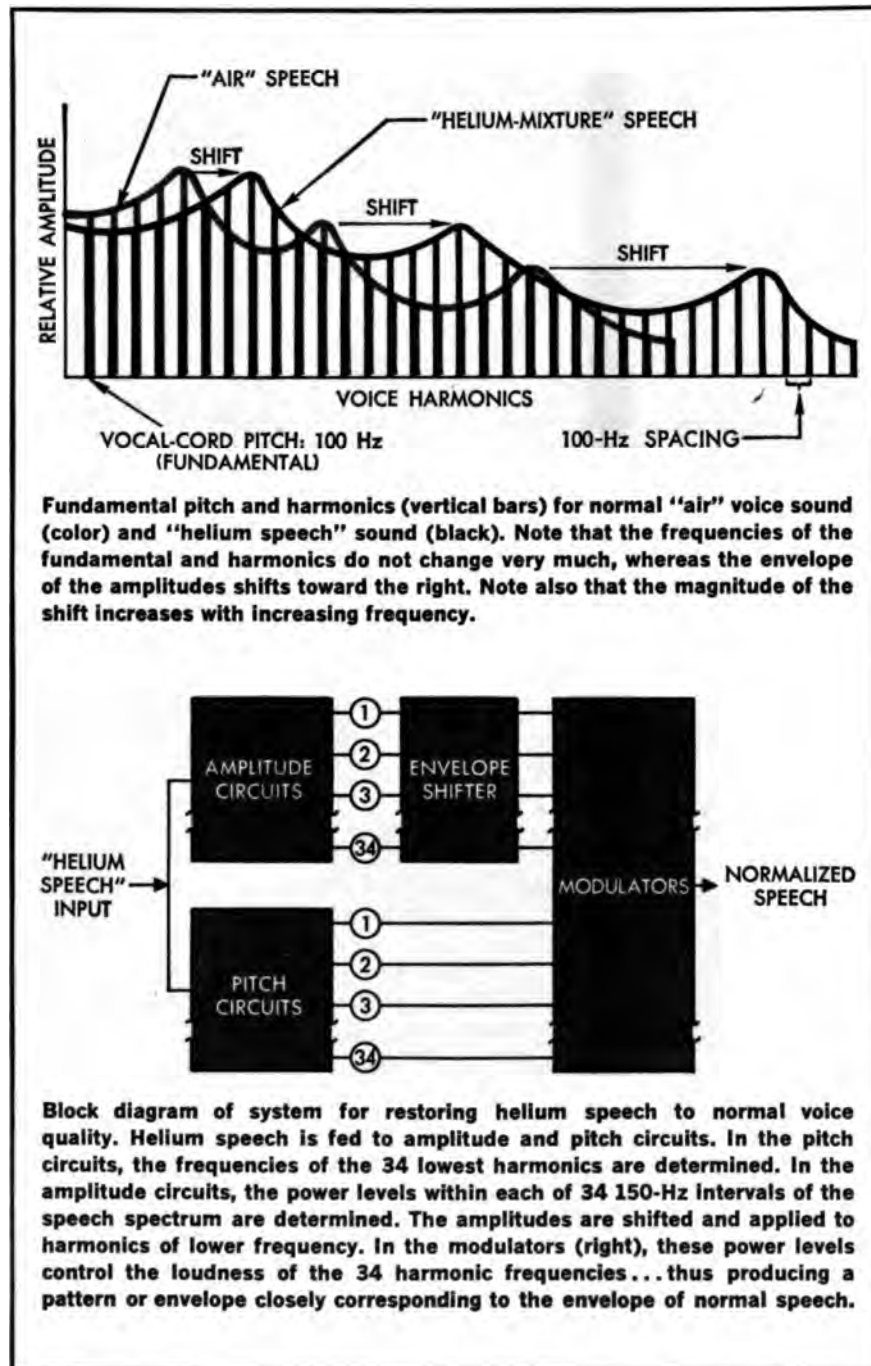
problem encountered in Sealab II. To prevent "bends" and nitrogen narcosis, the divers breathe a pressurized mixture of oxygen, nitrogen and helium, but the helium gives their voices an unnatural,

squeaky, Donald-Duck-like quality. As a result, voice communication between divers and people on surface are seriously impaired.

THE MAJOR PROBLEM is that the velocity of sound in the helium mixture is much higher than in air. This does not appreciably affect a vocal-cord frequency, but it strongly affects the acoustic resonances of the vocal tract—which give the voice its characteristic sound quality. So, though fundamental voice pitch remains approximately the same (about 100 Hz in men), the amplitude-loudness values of the various harmonics change markedly. Specifically, the pattern of these resonances (the envelope shown toward the higher frequencies in graph), and voice timbre is greatly distorted.

THE SOLUTION to this problem was found at Bell Laboratories by research scientists M. R. Schroeder, J. L. Flanagan, and R. M. Golub. The distorted "helium speech" is separated into harmonic frequencies and their amplitudes are measured (see diagram). Then the envelope of the harmonic amplitudes is shifted back toward more normal or low-frequency condition. In other words, amplitudes of the harmonics are adjusted to match a more normal envelope.

As a test, the technique has been used on recordings of helicopter speech made in the U. S. Navy Sealab II. The processed voice is readily understandable and sounds enough like the speaker's original voice to be identifiable.



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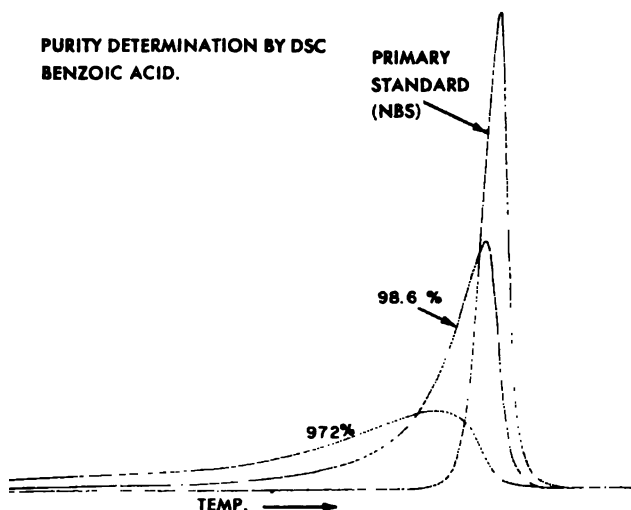
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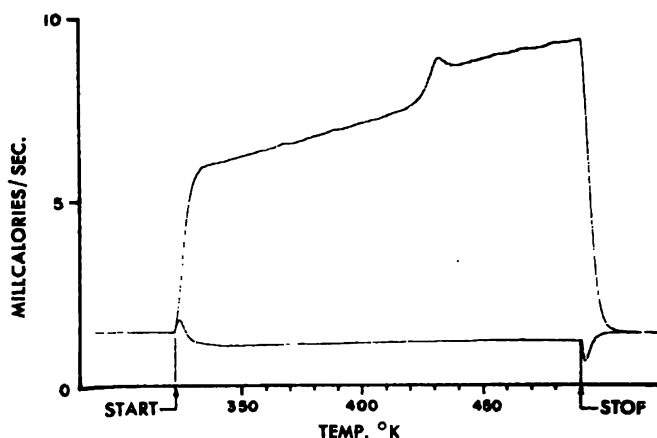
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"Interpretation of Mass Spectra of Organic Compounds" by the same authors was published in 1964 and immediately became one of the most popular and widely quoted texts in the field. The explosive growth of the subject matter in only three years has required three-fold expansion of the subject matter as well as virtually complete rewriting of the earlier material. For this reason the new book bears a different title, since it is not just a revised edition of the 1964 pioneering text. The present volume of over 700 pages covers in 27 chapters the fragmentation behavior of all the important functional groups in organic chemistry. In addition, a summarizing chapter has been included which greatly aids in the interpretation of mass spectra of organic molecules. The literature is complete through early 1967, and the book should prove to be indispensable as a text in organic chemistry courses as well as a guide for the expert and novice alike who wish to become familiar with the numerous organic chemical applications of mass spectrometry.

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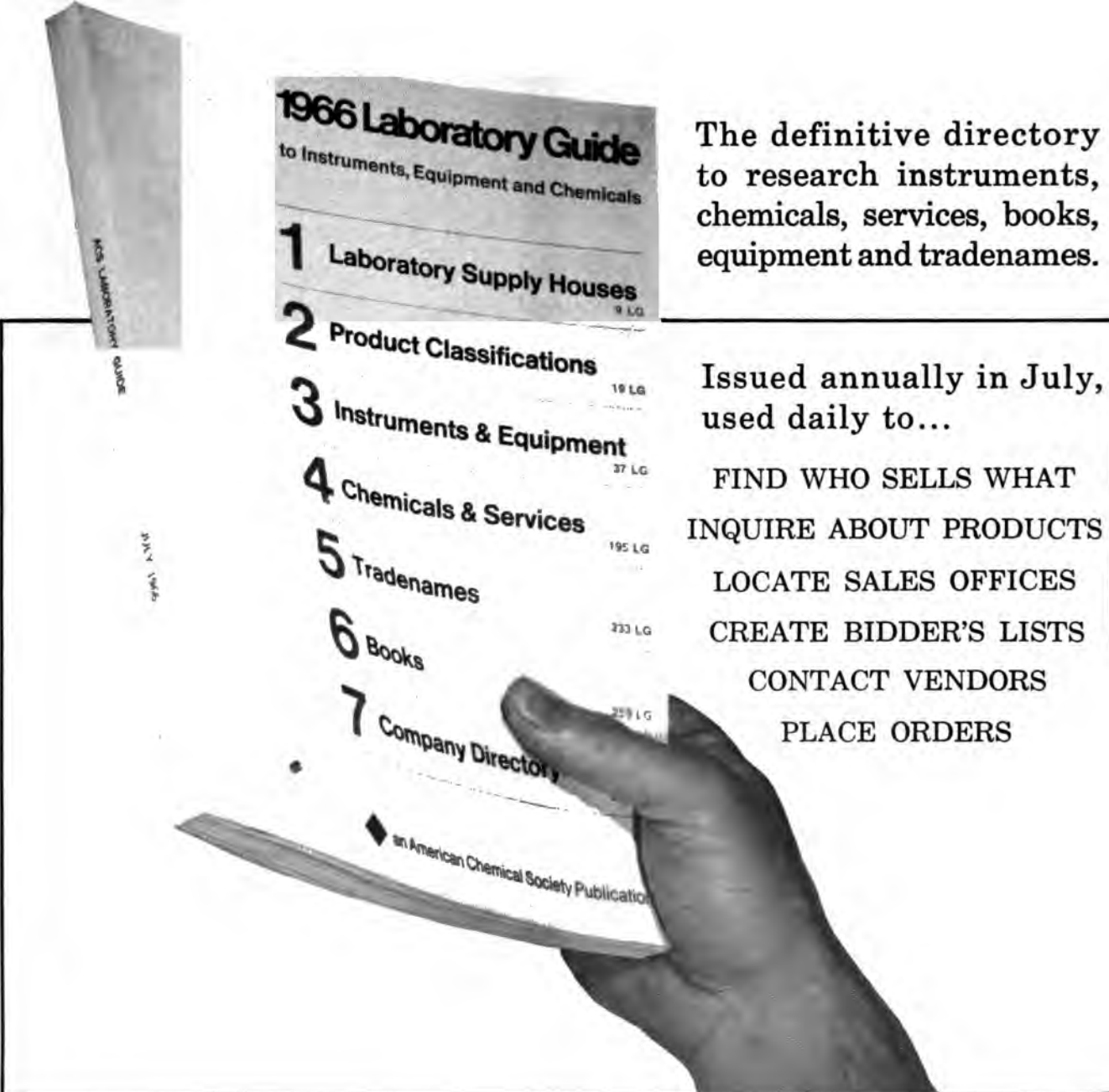
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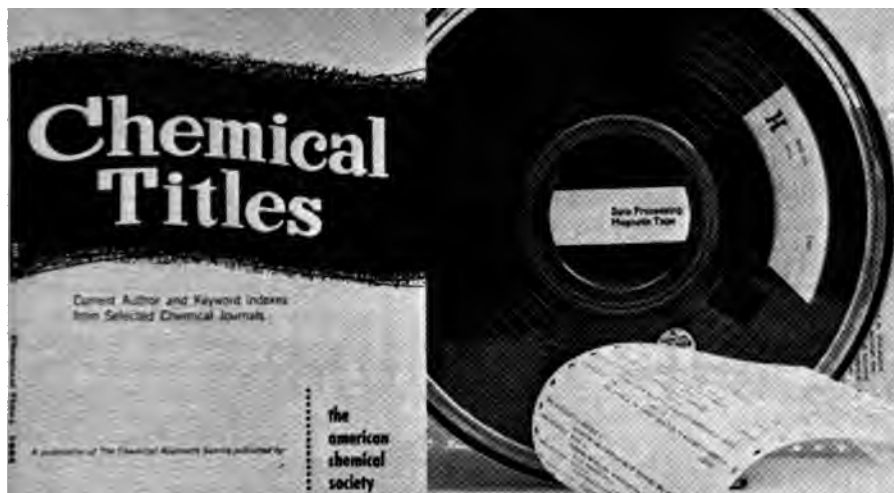
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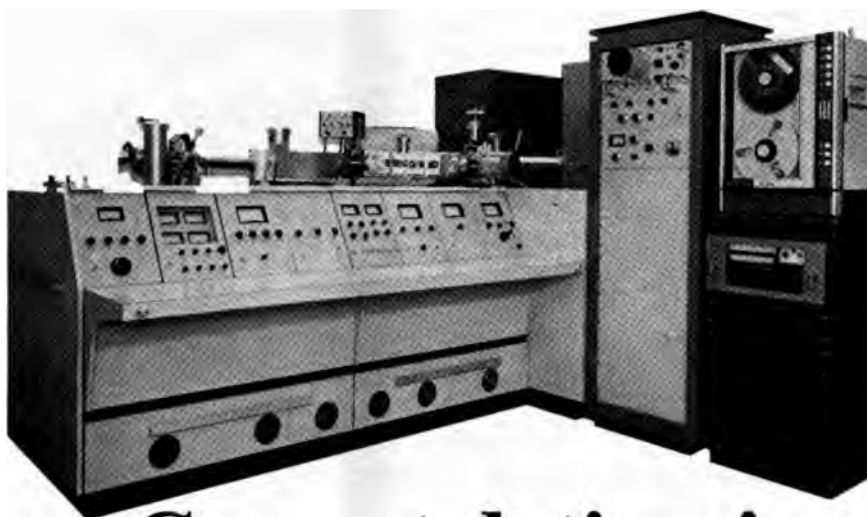
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Physical and Inorganic Chemistry

Microwave Absorption and Molecular Structure in Liquids. LXIX. Atomic Polarization and Relaxation in Several Siloxanes and Hexamethyldisilazane¹

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Contribution from the Frick Chemical Laboratory, Princeton University, Princeton, New Jersey. Received January 3, 1967

Abstract: The dielectric constants and losses of hexamethyldisiloxane, hexaethyldisiloxane, hexamethylcyclotrisiloxane, octamethylcyclotetrasiloxane, and hexamethyldisilazane have been measured over a range of temperature at 2.2 mm wavelength and at centimeter wavelengths. The data have been used to calculate the dielectric relaxation times, the atomic polarizations, and the dipole moments. Use of the very large values found for the atomic polarizations in the calculation of the dipole moments gives much smaller moment values than those previously reported in the literature which did not take account of the atomic polarization. The large atomic polarizations and the short relaxation times found are consistent with the great flexibility which has been ascribed to the Si-O-Si bonds. They are discussed in terms of the structures of the molecules.

An anomalously low value for the dielectric relaxation time of hexamethyldisiloxane obtained from centimeter wavelength measurements² indicated the desirability of higher frequency measurements to establish the low value more exactly. The unexpectedly small dipole moment,^{2,3} the large atomic polarization,^{2,3} the wide Si-O-Si valence angle,⁴ and the frequency of occurrence of the silicon-oxygen bond give additional reasons for the extension of the measurements to 2.2 mm wavelength. Four other silicon compounds have also been measured in the hope of throwing additional light upon the problems involved.

Measurements and Calculations

Hexamethyldisiloxane, hexamethyldisilazane, hexamethylcyclotrisiloxane, and octamethylcyclotetrasiloxane were obtained from the General Electric Co. in

very pure form. Hexaethyldisiloxane of similar purity (99.5%) was obtained from the Dow-Corning Corp. Measurements of dielectric constant ϵ' and loss ϵ'' were made at wavelengths of 0.22, 1.25, 3.22, 10.01, and 25.00 cm at 21, 40, and 60°, using the methods already described.⁵⁻⁹ The ϵ' value at 25 cm, or at an even shorter wavelength, depending on the loss, was indistinguishable from the so-called static dielectric constant ϵ_0 obtained with a heterodyne beat apparatus.¹⁰ For hexamethylcyclotrisiloxane, the loss ϵ'' was so low that the dielectric constant ϵ' at 3.22 cm was used for ϵ_0 . The values for these quantities given in Table I have been used for Cole-Cole¹¹ analysis in the IBM 7094 computer. The values of ϵ_∞ , the infinite-frequency or optical dielectric constant, τ_0 , the most probable re-

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Table I. Dielectric Constants and Losses

Temp, °C	ϵ_0	λ_0 , cm	ϵ'	ϵ_∞	ϵ''
Hexamethyldisiloxane					
2.0	2.223	0.216	2.185	2.102	0.046
20.0	2.179	0.216	2.152	2.098	0.042
40.0	2.130	0.216	2.108	2.056	0.033
Hexaethyldisiloxane					
25.0	2.259	0.22	2.224	2.198	0.013
		1.25	2.246		0.013
		3.22	2.253		0.011
		10.01	2.257		0.005
40.0	2.229	0.22	2.194	2.172	0.012
		1.25	2.221		0.011
		3.22	2.225		0.008
		10.01	2.229		0.004
60.0	2.195	0.22	2.163	2.150	0.011
		1.25	2.189		0.009
		3.22	2.192		0.007
		10.01	2.194		0.003
Hexamethylcyclotrisiloxane					
70.0	2.139	0.22	2.132	2.131	0.006
		1.25	2.138		0.003
		3.22	2.139		0.001
Octamethylcyclotetrasiloxane					
23.0	2.390	0.22	2.350	2.318	0.030
		1.25	2.383		0.017
		3.22	2.388		0.009
		25.00	2.390		0.003
40.0	2.346	0.22	2.316	2.285	0.028
		1.25	2.343		0.016
		3.22	2.345		0.006
		25.00	2.347		0.002
60.0	2.298	0.22	2.267	2.245	0.025
		1.25	2.291		0.012
		3.22	2.295		0.005
		25.00	2.300		0.002
Hexamethylsilazane					
21.0	2.273	0.22	2.205	2.190	0.029
		1.25	2.265		0.027
		3.22	2.273		0.014
		10.01	2.274		0.005
40.0	2.232	0.22	2.165	2.156	0.027
		1.25	2.219		0.021
		3.22	2.230		0.010
		10.01	2.232		0.004
60.0	2.184	0.22	2.128	2.116	0.025
		1.25	2.177		0.017
		3.22	2.184		0.008
		10.01	2.184		0.003

laxation time, α , the distribution parameter, and C_2 , the amplitude or relative weight of the contribution of the second relaxation process, if one exists, thus obtained are tabulated in Table II. ϵ_∞ is used to calculate the induced polarization $P_E + P_A = M(\epsilon_\infty - 1)/d(\epsilon_\infty + 2)$ where M is the molecular weight and d the density. The total polarization P is obtained similarly from ϵ_0 . The electronic polarization P_E is calculated from n_∞ , the refractive index at infinite wavelength. The refractive indices n are measured at at least two wavelengths, the sodium D-line and the H_α or H_β line, to calculate¹² n_∞ from

$$n_\infty = \frac{\lambda_1^2 n_1 - \lambda_2^2 n_2}{\lambda_1^2 - \lambda_2^2}$$

The dipole moment μ has been calculated by means of the Onsager equation¹³ with ϵ_∞ used instead of n^2 .

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Table II. Polarization (cc) and Dipole Moment (D.) Values

Temp, °C	P	P_A	Temp, °C	P	P_A
Hexamethyldisiloxane			Octamethylcyclotetrasiloxane		
2.0	60.42	9.4	23.0	98.11	22.1
20.0	60.25	9.6	40.0	97.80	22.2
40.0	60.04	9.5	60.0	97.34	22.1
Hexaethyldisiloxane			Hexamethylsilazane		
25.0	86.61	11.0	21.0	62.27	9.9
40.0	86.37	11.0	40.0	62.12	9.9
60.0	86.10	10.9	60.0	61.86	9.9
Hexamethylcyclotrisiloxane					
70.0	65.84	9.7			
Compound		P_E	μ_{lit}	μ_n	μ
Hexamethyldisiloxane		47.60	0.46 ^a 0.74 ^b 0.80 ^c	0.73	0.38
Hexaethyldisiloxane		72.85		0.72	0.38
Hexamethylcyclotrisiloxane		55.82	0.0 ^c	...	(0.14)
Octamethylcyclotetrasiloxane		74.55 ^d	0.67 ^c	1.00	0.42
		72.5 (est)	1.09 ^b		
Hexamethylsilazane		49.40		0.74	0.37

^a Reference 2. ^b R. O. Sauer and D. J. Mead, *J. Am. Chem. Soc.*, **68**, 1794 (1946). ^c Reference 3.

Table III. Relaxation Times, Distribution and Weight Parameters, and Energy of Activation

Temp, °C	α	τ_0^a	τ_1^a	τ_2^a	C_2	ΔF , kcal/mole
Hexamethyldisiloxane						
2.0	0.14	0.74	2.1	0.5	0.60	2.5
20.0	0.00	0.27	...	0.3	1	
40.0	0.00	0.21	...	0.2	1	
Hexaethyldisiloxane						
25.0	0.44	2.4	11.4	0.6	0.54	2.4(τ_2)
40.0	0.44	1.6	10.7	0.4	0.62	0.7(τ_1)
60.0	0.38	1.1	10	0.4	0.67	
Hexamethylcyclotrisiloxane						
70.0	0.04	(2.7)				
Octamethylcyclotetrasiloxane						
23.0	0.00 ^c	1.9				1.3
40.0	0.00	1.7				
60.0	0.00	1.6				
Hexamethylsilazane						
21.0	0.05	2.7				1.2
40.0	0.00	2.4				
60.0	0.00	2.0				

^a 10^{-12} sec.

For comparison, values calculated with n_∞^2 are listed as μ_n in Table III. As the measurements were made at three different temperatures, the free energies of activation ΔF^\ddagger could be calculated in the usual manner.¹⁴

Discussion of Results

Dipole Moments. The dipole moments in Table II tend to be much lower than those in the literature, in which the effects of the large atomic polarizations are neglected. When n^2 is used in the moment calculation instead of ϵ_∞ , the moment value μ_n obtained is almost twice as large and in satisfactory agreement with previous literature values calculated in this way. The values of $P_E + P_A$ and P for hexamethylcyclotrisiloxane differ by no more than the total probable error, and

(14) C. P. Smyth, ref 12, p 63.

very small apparent moment value in Table II is distinguishable from zero. This zero moment is in contrast with the planar structure of the molecule deduced by electron diffraction¹⁵ and X-ray analysis¹⁶ and is not correctly represented by Kurita and Kondo³ as indicating a zero dipole moment. With zero dipole moment Kurita and Kondo took the total polarization $P = P_E + P_A$ and thus obtained a value of 10.9 for P_A , which is larger than the value 9.7 in Table II because their value of P was 66.7 as compared to 65.8 in Table II. The estimated atomic polarization for hexamethylcyclotrisiloxane was only 4.9 and that for octamethylcyclotetrasiloxane was 14.5, the estimates being made from comparison with hexamethylcyclotrisiloxane. Consequently, their dipole moment values for these two compounds are more than twice as large as those listed for μ in Table II. The presumably correct moments μ for the four unsymmetrical molecules in Table II are identical.

Atomic Polarizations. The atomic polarizations of hexamethyldisiloxane and hexamethyldisilazane are equal, indicating that the Si-N bonds have the same unusual flexibility that the Si-O bonds have in hexamethylcyclotrisiloxane. The atomic polarization of hexaethylidisiloxane is 1.5 larger than that of the hexamethyl compound, the small increase coming from the six CH_2 groups in the former compound. The main distortion in hexaethylidisiloxane is evidently associated with the Si-O-Si angle of the molecule. The virtual identity of the atomic polarization of hexamethylcyclotrisiloxane with that of hexamethyldisiloxane and hexamethyldisilazane indicates that the binding of the six Si-O bonds in the planar ring considerably reduces their flexibility. The indication of this reduction of flexibility by comparison is given by the fact that the atomic polarization found in this laboratory¹⁷ for the corresponding chain compound is 19.0, about twice as large. The available instruments did not cover the range of frequencies for the extrapolation of the refraction of octamethylcyclotetrasiloxane to infinite wavelength. The refraction for the sodium D-line marked with D before, given in Table II, and used to estimate a value for P_E . A reasonable estimate of the extrapolated P_E is 72.5 ± 0.5 , which gives the value 22 for μ in Table II. This value, which is only a little larger than that found in this laboratory for the corresponding open-chain compound, shows much greater flexibility than that of the symmetrical, planar hexamethylcyclotrisiloxane molecule. Kurita and Kondo³ took the moment found for this substance as suggesting the existence of its molecules in a mixture of (crown, cradle, and tub) or in a single, slightly distorted intermediate between these. There would be a possibility of shift from one form of the six-membered ring to another with greater flexibility as found in the present work for the symmetrical, six-membered ring.

Relaxation Times. The most probable relaxation time found for hexamethyldisiloxane, 0.7 at 2°, and the 0.14 of the distribution parameter α agree well with the experimental uncertainty with the values 0.2, respectively, previously obtained² with no

measurement below 1.2 cm wavelength. However, the values of τ_0 at 20 and 40° show an abrupt drop from the 2° value and the distribution apparent at 2° is absent at the higher temperatures. The data at 2° can be well represented in terms of two relaxation times,¹⁸ the longer of which should be associated with a molecular rotational motion and the shorter with an intramolecular motion. The intramolecular process appears to take over almost entirely at 20 and 40°, where the values of τ_0 , presumably τ_2 , are consistent with that of τ_2 at 2° as evidenced by the linearity of the plot of $\log \tau_2$ against $1/T$. The existence of two relaxation processes at lower temperatures is also suggested by the increase of the distribution parameter to 0.4 at -60° in the earlier measurements.² For hexaethylidisiloxane, the large value of the distribution parameter indicates more than one relaxation time, and the data are well represented in terms of two relaxation times. The larger of these is about what might be expected for the rotational relaxation of a molecule of this size. The values of τ_2 for hexaethylidisiloxane are somewhat larger than those for hexamethyldisiloxane as would be expected from the larger size of the ethyl groups as compared to the methyl. Although the values of C_2 show increase in importance of the shorter relaxation process with rising temperature, the shorter process does not dominate completely in this temperature range as it does in the case of the smaller molecules.

Since the molecular dipole moment of hexamethylcyclotrisiloxane has been concluded to be zero, it is evident that the relaxation time obtained for it in Table III cannot be for molecular dipole rotation. Indeed, the dielectric loss 0.006 at 2.1 mm wavelength and 70° is lower than the value 0.0073 found for nonpolar benzene at 20° at the same wavelength—further evidence of the absence of any permanent moment in the molecule. This relaxation time, although of the same order of magnitude as the others in Table III, is presumably associated with a different mechanism and will be considered with those of other nonpolar liquids to be discussed in another paper.

The molecule of octamethylcyclotetrasiloxane is large and its dipole moment is small but real. The single relaxation time found for it (Table III) is too small to correspond to simple rotational orientation of a rigid molecule of this size. In spite of the fact that the molecule is a closed ring, it seems probable that sufficient bending and twisting of the flexible Si-O bonds can occur to produce the equivalent of an orientation of the net molecular dipole moment, somewhat like that proposed^{19,20} for diphenyl ether and similar molecules, though different in detail. Hexamethyldisilazane, which has a molecule similar in size to that of hexamethyldisiloxane, shows only a single relaxation time in the temperature range investigated here. It is much larger than the τ_0 values found for hexamethyldisiloxane, but not far from the value of τ_1 attributed to the rotational orientation of the molecule of this substance. There is no evidence in these results of the very rapid intramolecular relaxation process indicated for hexamethyl- and hexaethylidisiloxane.

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Dasgupta and C. P. Smyth, to be published.

The values of the free energy of activation may be too approximate to have significance. The free energies for the shorter relaxation processes in hexamethyldisiloxane and hexaethyldisiloxane appear unexpectedly to be higher than that for the longer relaxation process in hexaethyldisiloxane and those for the only relaxation process evidenced in octamethylcyclotetrasiloxane and hexamethyldisilazane.

From viscosity measurements on hexamethyldisiloxane and octamethylcyclotetrasiloxane^{21,22} values of η have been interpolated by means of the Arrhenius equation to the temperatures corresponding to those of the relaxation times. The ratios τ/η are shown in Table IV. The ratio of τ_2/η for hexamethyldisiloxane is much closer to that of τ_0/η for octamethylcyclotetrasiloxane than is τ_2 to τ_0 in Table III. A considerable part of the difference between the two would appear to be due to viscosity. However, the rapid increase of τ/η with temperature for octamethylcyclotetrasiloxane points also to an intramolecular motion less susceptible to the influence of viscosity than molecular rotation is.

Table IV

Temp, °C	τ , 10 ⁻¹² sec	η , cp	τ/η
Hexamethyldisiloxane			
	τ_2		
2	0.45	0.659	0.68
20	0.27	0.512	0.53
40	0.21	0.402	0.52
Octamethylcyclotetrasiloxane			
	τ_0		
23	1.91	2.243	0.85
40	1.72	1.638	1.05
60	1.59	1.180	1.32

The fact that the values of τ/η in Table IV are smaller by a factor not far from 10 than those found for effectively rigid molecules²³ gives further evidence of relaxation by intramolecular motion. In the reference cited the relaxation times are expressed in 10⁻¹¹ sec, instead of 10⁻¹² sec as in the present paper.

Conclusions

The low moments of these compounds are due to the reduction of the Si-O and Si-N bond moments by d_π-p_π bonding below those to be expected from the considerable difference between the electronegativities of the bonded atoms.^{4,24} In the case of hexamethyldisiloxane, the widening of the Si-O-Si angle²⁴ to about 150° also reduces the resultant moment.

Lazarev and Tenisheva²⁵ have concluded from an analysis of infrared data that the oxygen in the Si-O-Si

group possesses considerable freedom of displacement in the Si-O-Si plane and perpendicular to it and that the motions involved in such displacements have such low energies as to be substantially excited even at ordinary thermal energies. Analyses of a quasi-linear triatomic molecule²⁶ and of disiloxane²⁷ have shown that, if the potential function for siloxane has minima at angles not far from 180° (150° may be near enough), the vibrational spectroscopic properties of the molecule may be indistinguishable from those of a linear molecule (180° angle). The motion may be that of a bent molecule with rotational motion superimposed on the bending vibration about the minimum of potential energy.²⁸ It would appear that the very short relaxation time τ_1 for hexamethyl- and hexaethyldisiloxane in Table III may be associated with dipole orientation by bending of the Si-O-Si angle from 150° through a maximum at 180° to another minimum at 150°, while the slower relaxation is molecular rotation, which, in the case of the almost linear, nearly symmetrical hexamethyldisiloxane molecule encounters little hindrance.

In octamethylcyclotetrasiloxane the Si-O-Si angle is found²⁸ by X-ray analysis to be 142.5°, probably wide enough to permit frequent bending through the potential maximum at 180° to reverse the direction of the dipole and thus give intramolecular relaxation, which may be too close to the frequency for molecular rotational relaxation to permit of analytical separation of the two processes in our data. The Si-N-Si angle is reported²⁴ to be 120° with the H and the two Si's coplanar with the N in hexamethyldisilazane. This structure does not give two potential minima separated by a maximum which can be crossed easily to give intramolecular dipole orientation or relaxation. The one relaxation time found for the molecule should, therefore, be that for molecular rotational motion. It should be longer than τ_1 for hexamethyldisiloxane because of the closeness of the latter's shape to that of a cylinder.

The abnormally high atomic polarizations which have received comment evidently arise from infrared absorptions, which have been treated from the spectroscopic point of view in the papers referred to²⁶⁻²⁷ and in others. These atomic polarizations are several times larger than the orientation or dipole polarizations which arise from the orientation of the dipoles fixed in the molecules. With these polarizations we are beginning to enter a doubtful territory in which it may be difficult or arbitrary to distinguish between dipole polarization and atomic polarization.

Acknowledgment. The writers wish to express their gratitude to Dr. O. K. Johansson of the Dow-Corning Corporation for the hexaethyldisiloxane and to Dr. R. V. Viventi of the General Electric Company for the other four compounds.

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A Study of the Primary Processes in CH₂O and CD₂O Photolyses¹

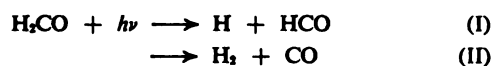
Benjamin A. DeGraff and Jack G. Calvert

Contribution from the Evans Chemical Laboratory, The Ohio State University, Columbus, Ohio 43210. Received November 25, 1966

Abstract: The primary processes occurring on photolysis of CH₂O and CD₂O have been delineated at 3340, 3130, 2654, and 2537 Å, through experiments with added olefin, neopentane, and biacetyl. The data provide estimates of primary quantum efficiencies of the processes: CH₂O + $h\nu$ → H + HCO (I), and CH₂O + $h\nu$ → H₂ + CO (II). Information is also obtained on the nature and the lifetimes of the excited states involved in these processes. The data show process I is favored at the longer wavelengths (3340 Å), while II dominates at the shorter wavelengths (2537 Å). Data from the photolyses of pure formaldehyde and its mixtures with propylene show values of $\Phi_{\text{CO}} - \Phi_{\text{H}}$, which are significantly greater than zero. The data are most consistent with the occurrence of a newly postulated reaction sequence (H + CH₂O → CH₂O; CH₂O + CH₂O → CH₂OH + HCO), which leads to methanol formation and a carbon monoxide excess. The additional possibility exists of a contribution to the carbon monoxide excess from a third primary process, CH₂O* + CH₂O → CH₂OH + HCO (III), particularly in photolyses at the very long wavelengths (3660 Å).

The structural simplicity of formaldehyde and the extensive knowledge of its spectroscopy give added interest to the study of the primary processes in formaldehyde photolysis. In this case it should be possible to describe the intimate details of the photochemistry which follow light absorption and precede photodecomposition. Considerable information has been reported on both the singlet-singlet (¹A₂ ← ¹A₁) and the singlet-triplet (³A₂ ← ¹A₁) transitions.²

The photochemistry of formaldehyde has been studied by numerous workers. Particular attention has been given to the secondary or thermal reactions of the hydrogen atom and formyl radical fragments formed in the photolysis.³ However, there is still no general agreement on the activation energies for the formyl radical decomposition and the hydrogen-atom abstraction reactions.⁴ The photolysis of formaldehyde has been interpreted in terms of two distinct primary photodissociative processes⁵



Attempts have been made to determine the relative importance of the two processes using both iodine inhibition⁶ and isotope exchange methods.^{3d} However, the two studies lead to opposite views as to the relative importance of I and II as a function of photon energy. The results of a more recent study using flash photolysis of CH₂O-CD₂O mixtures have been interpreted to show

that process II is dominant at the lower photon energies.⁷ This is in contrast with the behavior observed for the C₂-C₄ aldehydes, RCHO, where the intramolecular formation of RH and CO is favored over the cleavage to form R and HCO at the higher energies of the absorbed quantum.⁸ However, the treatment of the H-D scrambling produced in the CH₂O-CD₂O mixture flash photolysis experiments, which were used to derive the wavelength dependence of ϕ_{I} and ϕ_{II} , is very complex and required that certain assumptions of questionable validity be made.

In this work we have studied the primary processes occurring on photolysis of formaldehyde at selected wavelengths within the first absorption band through experiments with added olefin, neopentane, and biacetyl. The data provide direct estimates of ϕ_{II} and also information on the nature and the lifetime of the excited states involved in the formaldehyde photolysis.

Experimental Section

Formaldehyde was prepared from polyoxymethylene according to the procedure of Spence and Wild.⁹ Formaldehyde-d₂ was obtained in polymeric form from Merck Sharpe and Dohme, Ltd., with a stated purity of 99% deuterium. All hydrocarbon gases were Phillips research grade and were used without further purification. Biacetyl (Eastman White Label product) was outgassed, dried over calcium sulfate, and bulb-to-bulb distilled at reduced pressure with the middle third retained for use.

The apparatus consisted of a quartz photolysis cell mounted in an air thermostat with the usual associated glass pump, traps, and tubing. These were connected to a conventional high-vacuum system by bakable metal valves. Pressures were read with a triple-spoon gauge-manometer combination. All components which had direct contact with formaldehyde were heated to avoid polymerization. The thermostat was such that the average temperature of the cell remained constant to within ±0.2° of a desired temperature over the 3-5-hr photolysis period.

The light source was a Hanovia S-500 medium pressure arc. The various wavelength regions (3340, 3130, 2654, and 2537 Å) were isolated by chemical filters.¹⁰ The spectral distribution of the lines so isolated was checked using a Hilger medium quartz spectrograph and was in accord with the published information on the filters.¹⁰

The bulk of the analyses were performed on a modified Aerograph A-90-P2 gas chromatograph. The product gases were

(1) Presented in part at the Seventh Informal Conference on Photochemistry, Rensselaer Polytechnical Institute, Troy, N. Y., June 1966. Submitted by B. A. D. in partial fulfillment of the requirements for the Ph.D. degree in chemistry, The Ohio State University, Sept 1965. The authors acknowledge gratefully the support of this work through a research grant from the National Center for Air Pollution Control, U. S. Public Health Service, Bethesda, Md.

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(3) (a) E. I. Akeroyd and R. G. W. Norrish, *J. Chem. Soc.*, 890 (1936); (b) J. G. Calvert and E. W. R. Steacie, *J. Chem. Phys.*, **19**, 176 (1951); (c) F. H. Dorman and A. S. Buchanan, *Australian J. Chem.*, **9**, 41 (1950); (d) R. Klein and L. J. Schoen, *J. Chem. Phys.*, **24**, 1094 (1956).

(4) (a) J. G. Calvert, *J. Phys. Chem.*, **61**, 1206 (1957); (b) R. Klein and L. J. Schoen, *J. Chem. Phys.*, **29**, 953 (1958); (c) W. R. Brennen, I. D. Gay, G. P. Glass, and H. Niki, *ibid.*, **43**, 2569 (1965).

(5) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, p 371.

(6) E. Gorin, *J. Chem. Phys.*, **7**, 256 (1939).

(7) R. D. McQuigg, Ph.D. Dissertation, The Ohio State University, 1964.

(8) See ref 5, p 369.

(9) R. Spence and W. Wild, *J. Chem. Soc.*, 338 (1935).

(10) See ref 5, pp 729-733.

Table I. Data from the 3130-A Photolyses of Pure Formaldehyde and Its Mixtures with Propylene and Neopentane

Run no.	Temp, °C	Pressure, mm			I_a , quanta/cc sec $\times 10^{-11}$	Φ_{CO}	Φ_{H_2}
		CH ₂ O	C ₃ H ₆	C ₅ H ₁₂			
1	156.0	169	23.6	2.70	1.95
2	127.8	161	22.9	1.89	1.43
3	128.5	160.5	47.5	...	22.0	3.17	0.67
4	128.2	159	128.2	...	21.7	3.52	0.56
5	128.7	159	205.5	...	21.7	3.63	0.49
6	128.7	159	308.5	...	21.6	3.68	0.44
7	128.9	160	...	290	21.5	2.50	1.62
8	128.9	159.5	194	116	21.5	3.08	0.46
9	129.2	79	18.4	1.55	1.30
10	129.1	78	10.1	1.58	1.26
11	129.2	78	23.5	...	9.36	2.48	0.59
12	129.3	78	51	...	9.27	3.08	0.49
13	129.2	78	102	...	9.42	3.02	0.48
14	129.0	80.5	103.5	...	18.4	2.52	0.47
15	129.6	78	155.5	...	9.15	2.66	0.44
16	129.6	78	102	53	8.93	2.67	0.45
17	128.7	81	102.5	101	17.9	2.30	0.43
18	129.0	79.5	105	208	18.2	2.31	0.42
19	128.9	80.5	103.5	309	19.0	1.82	0.40
20	129.1	82.5	106	408	18.8	1.76	0.39
21	129.5	78.5	...	205	7.58	2.23	1.92
22	129.5	79	...	102.5	7.65	2.39	1.89
23	104.9	81	52.5	...	18.8	2.04	0.46
24	91.0	80	8.50	...	1.14
25	90.8	78	8.37	1.45	1.16
26	90.9	79	21.2	1.43	1.08
27	91.2	80	21.5	...	8.28	1.99	0.55
28	91.6	80.5	103	...	21.6	1.89	0.45
29	91.0	81.5	105	113.5	7.96	1.84	0.42
30	91.4	81.0	102	206	21.7	1.67	0.39

Table II. Data from the Photolyses of Pure Formaldehyde and Its Mixtures with Propylene at Several Wavelengths

Run no.	Wave-length, Å	Temp, °C	Pressure, mm		I_a , quanta/cc sec $\times 10^{-11}$	Φ_{CO}	Φ_{H_2}
			CH ₂ O	C ₃ H ₆			
31	3340	109.1	201	...	4.31	1.67	0.82
32	3340	109.3	113.5	...	3.06	1.28	0.90
33	3340	109.3	63	...	1.56	1.55	1.44
34	3340	109.2	110	95	2.84	1.15	0.41
35	2654	109.1	103.5	...	5.00	1.72	1.37
36	2654	109.1	101	54	4.63	3.01	0.80
37	2654	109.1	119.5	67.5	6.59	3.57	0.82
38	2654	109.1	109	104.5	4.28	3.22	0.81
39	2654	108.7	108	154.5	5.79	3.44	0.81
40	2537	109.0	116	...	2.90	1.99	1.46
41	2537	109.0	110	...	3.87	2.00	1.36
42	2537	109.3	110.5	62	2.70	3.38	0.89
43	2537	109.0	111	87	2.94	3.00	0.81
44	2537	109.2	109	108.5*	3.84	3.21	0.85
45	2537	109.0	105.5	112	2.95	3.37	0.90

* Isobutene was used in place of propylene in this run.

separated using an 8-ft column of 5A molecular sieve (30–60 mesh) maintained at 105°. Argon was used as the carrier gas. The response of the instrument was calibrated using standard mixtures which closely approximated in both size and composition the samples of product gases.

Mass spectra were obtained using a Consolidated Electrodynamics Corp. Model 21-620 mass spectrometer. Isotope ratios were determined with a similar mass spectrometer modified for that purpose. The infrared analyses were performed using a Perkin-Elmer Model 21, 40-m long-path spectrometer.

Actinometry was performed at frequent intervals. Acetone was used in experiments at 3130, 2654, and 2537 Å with Φ_{CO} taken as

Table III. Data from the Photolyses of Pure CD₂O and Its Mixtures with Propylene

Run no.	Wave-length, Å	Temp, °C	Pressure, mm		I_a , quanta/cc sec $\times 10^{-11}$	Φ_{CO}
			CD ₂ O	C ₃ H ₆		
46	3340	109.2	112	34	2.30	0.25
47	3130	129.1	87.5	...	30.3	0.83
48	3130	129.8	82.5	27	28.7	0.89
49	3130	129.6	84.5	62	28.9	0.86
50	3130	130.2	87.5	108	29.6	0.83
51	2654	109.3	107	...	4.53	1.10
52	2654	109.5	106	...	5.46	1.17
53	2654	109.2	110.5	65	5.44	1.41
54	2654	109.1	112	120	5.19	1.43
55	2654	109.2	104.5	170.5	4.31	1.33
56	2537	109.5	126	...	2.45	1.05
57	2537	109.1	104	53	2.33	1.52
58	2537	109.1	106	87	2.63	1.41
59	2537	109.1	104.5	89.5*	2.81	1.62

* Isobutene was used in place of propylene in this run.

unity for our conditions. At 3340-Å azomethane was used Φ_{N_2} assumed equal to unity. Extinction coefficients were measured at each wavelength and temperature using an RCA 935 phototube whose output was displayed on a strip chart recorder. The intensity was also monitored continuously during each run using a photometer.

The experimental conditions and the quantum yields of carbon monoxide and hydrogen products are summarized for pure CD₂O and CH₂O-olefin and/or -neopentane mixtures at 3130 Å in Table II. Similar experiments for 3340, 2654, and 2537 Å are listed in Table III. Data for CD₂O and CD₂O-olefin mixtures at all four wavelengths are given in Table III.

Discussion

The Primary Processes in Formaldehyde Photolysis. The olefin inhibition studies herein reported allow determination of Φ_{H_2} values and a delineation of wavelength dependence of the two primary photodissociative processes I and II in formaldehyde photolysis. Free-radical production of molecular hydrogen following I was suppressed in this work through the addition of added olefin. The common radical "getters" used in thermal and photochemical studies, NO, O₂, and acetone are rather unsatisfactory for photochemical applications since their interaction with electronically excited molecules is not well understood. There is evidence that each is capable of strongly perturbing the course of the photolysis.¹¹ Monoolefins are efficient hydrogen-atom scavengers at high pressures, but the possible perturbing influence of the olefin under these conditions should be examined in light of Cundall's work on the possibility of triplet energy transfer to the olefin must be considered. Our experimental conditions were such that the mean time between collisions of an excited molecule and propylene was of the order of 10⁻⁸ sec. From the experiments with added biacetyl described below, we estimate that the longest lived excited state of formaldehyde formed at 3130 Å, presumed to be

(11) (a) C. Reed, *Quart. Rev.* (London), 12, 205 (1958); (b) C. Martin and H. C. Sutton, *Trans. Faraday Soc.*, 48, 812 (1952); (c) Pitts, Jr., and F. E. Blacet, *J. Am. Chem. Soc.*, 74, 455 (1952); (d) McMillan and J. G. Calvert, "Oxidation and Combustion Reviews," Vol. 1, C. F. H. Tipper, Ed., Elsevier Publishing Co., Amsterdam, p. 83.

(12) (a) R. B. Cundall, F. J. Fletcher, and D. G. Milne, *Trans. Faraday Soc.*, 60, 1146 (1964); (b) R. B. Cundall and A. S. Davies, *ibid.*, 62, 2793 (1966); (c) R. B. Cundall and A. S. Davies, *Proc. Roy. Soc. (London)*, A290, 563 (1966).

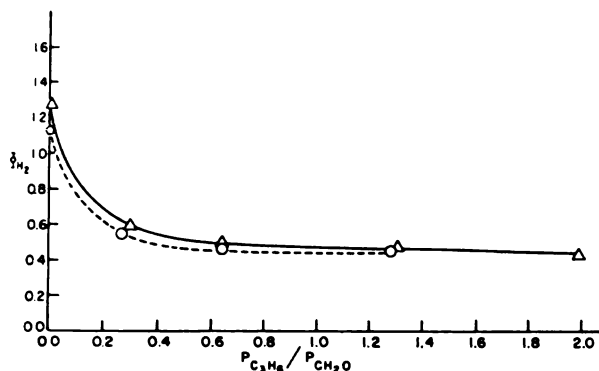


Figure 1. The quantum yield of hydrogen vs. the propylene to formaldehyde ratio for photolyses at 3130 Å and temperatures of 91°, O; and 129°, Δ.

triplet state, has a lifetime of about 10^{-8} – 10^{-9} sec. Thus the excited aldehyde will suffer relatively few collisions with propylene before dissociation. The work of Rebbert and Ausloos¹³ has suggested that monoolefins are only a factor of about 10^{-5} times as efficient as conjugated olefins in quenching acetone's phosphorescence. Although the work of Cundall's group suggests a much higher efficiency of triplet acetone quenching as measured by isomerization of *cis*-ethylene-*d*₂ and *cis*-2-butene, it is difficult for us to exclude the effects of radical addition to the olefin in their experiments. Direct measurement of acetone phosphorescence as used by Rebbert and Ausloos should be a more reliable measure of acetone triplet. If one accepts the results of Rebbert and Ausloos and arbitrarily assigns unit energy-transfer probability to the conjugated olefins, a molecule such as propylene is expected to be a very poor triplet energy acceptor for formaldehyde and other similar molecules of very short triplet lifetime.

To test the effectiveness of propylene as a radical scavenger in the photolysis of formaldehyde, several series of experiments were performed. Figure 1 shows graphically the results of propylene inhibition on the quantum yield of hydrogen in experiments at 3130 Å and at two temperatures. The limiting quantum yield of hydrogen is the same within the experimental error for experiments at 91 and 129°. The rather small change in temperature is not expected to alter significantly the value of ϕ_{II} , but the result suggests that the efficient scavenging of radicals occurs for the high olefin pressures which give the limiting value of Φ_{H_2} . The initial pressure of formaldehyde and the incident intensity were both varied by a factor of 2 without changing the limiting value. Mass spectral (isotope ratio) analysis of the product deuterium from the photolysis of CD_2O – C_3H_6 mixtures showed that abstraction from propylene was unimportant under our conditions. Also mixtures of CH_2O , CD_2O , and C_3H_6 at the partial pressures which gave limiting hydrogen quantum yields were photolyzed. On the basis of the very small amounts of HD found for CH_2O and CD_2O photolyses, ϕ_{II} , estimated from limiting Φ_{H_2} data, may be in error due to incomplete scavenging by at most 3–5 and 5–8%, respectively.

(13) R. E. Rebbert and P. Ausloos, *J. Am. Chem. Soc.*, **87**, 5569 (1965).

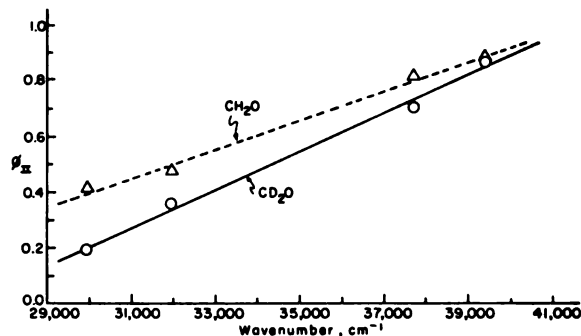


Figure 2. The quantum yields of primary process II, CH_2O (or CD_2O) + $h\nu \rightarrow CO + H_2$ (or D_2), as a function of wavenumber for photolyses of CH_2O and CD_2O in the vapor phase.

The estimates of the primary quantum yields for the molecular process II were obtained from the limiting Φ_{H_2} or Φ_{D_2} values at high olefin concentrations for both CH_2O and CD_2O at four wavelength regions, 3340, 3130, 2654, and 2537 Å. Figure 2 shows the resulting quantum yields as a function of wavenumber. Within the scatter of the data, the primary yield is a linear function of photon energy. The observed monotonic increase in the importance of the molecular mode of dissociation with energy is consistent with the trends found for the other simple aldehydes.¹⁴

McQuigg found that the volume of products from formaldehyde flash photolysis was proportional to the number of quanta absorbed by the formaldehyde, independent of the wavelength of the light absorbed from 2500 to 3300 Å.⁷ If $\phi_I + \phi_{II}$ equal unity at the shorter wavelengths, as seem very likely, then $\phi_I + \phi_{II}$ is near unity over this whole range of wavelengths. Thus a reasonable estimate of ϕ_I may be derived from the relation $\phi_I = 1 - \phi_{II}$. Following this procedure it can be estimated that ϕ_{II}/ϕ_I increases from ~ 0.7 at 3340 to 7.3 at 2537 Å for CH_2O . The question arises as to what factors determine the relative importance of each of these processes. Of course, the two processes may arise simply as competitive reactions which involve the same electronic state or states. Another possible answer to this question is that two different excited states are involved and that the competition between the two decomposition modes is determined by the rates of population of these states and their reactivities. The most obvious choice of states would be the 1A_2 and 3A_2 electronic states. If spin is conserved in processes I and II then triplet decomposition to molecular hydrogen and carbon monoxide is not possible at the photon energies used in this study, and only the free-radical process could originate from the triplet species.

To evaluate the possible role of the triplet formaldehyde in the photolysis of formaldehyde several experiments were performed.

Few aldehydes and ketones show measurable phosphorescence. Formaldehyde phosphorescence has never been reported although it has been searched for in many laboratories. The participation of a triplet state in the photodecomposition of the aldehydes and ketones has been inferred largely from indirect evidence, but this evidence has been rather convincing. Spe-

(14) (a) F. E. Blacet and J. N. Pitts, Jr., *ibid.*, **74**, 3382 (1952); (b) C. S. Parmenter and W. A. Noyes, Jr., *ibid.*, **85**, 416 (1963).

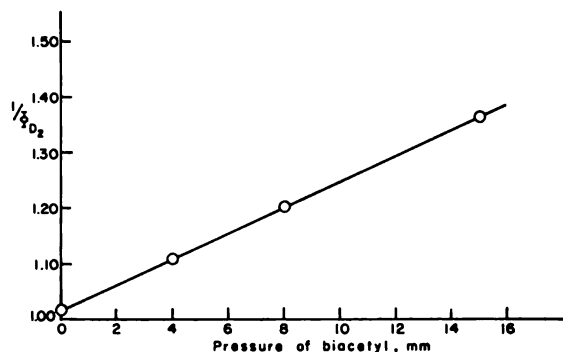
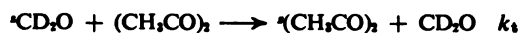
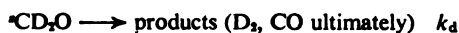
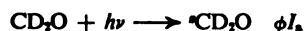


Figure 3. Plot for the biacetyl quenching of the quantum yield of deuterium in the photolysis of CD_2O -biacetyl mixtures at 109° and about 75 mm pressure of CD_2O .

cifically, photosensitized emission from biacetyl and the decomposition of biacetyl have been used as triplet diagnostic tests in the gas phase.¹⁵ The strong emission and low energy (about 2.5 eV) of its first excited triplet state make biacetyl particularly attractive.

In conjunction with a study of the formaldehyde-sensitized emission of biacetyl, to be reported in a subsequent paper, we also studied the effect of biacetyl on the photodecomposition of formaldehyde- d_2 . The deuterio isomer was used in this study with a knowledge of the longer excited lifetime for the deuterio compound and with the hope of reducing troublesome abstraction reactions. The data summarized in Figure 3 show that the diketone is effective in deactivating some state of the excited aldehyde formed at 3130 Å; Φ_D decreases with increasing biacetyl pressure. At this wavelength biacetyl is almost transparent. However, experiments with biacetyl alone were performed as an added check, and negligible product formation occurred under these conditions. That energy was being transferred from formaldehyde to the biacetyl in the CD_2O - $(\text{CH}_3\text{CO})_2$ mixture photolyses was shown by the presence of C_2H_6 , CH_3D , and excess CO in the products. HD was not found and thus a D-atom sensitized decomposition is unlikely. However the presence of a small quantity of CH_3D indicates that the methyl-sensitized decomposition of formaldehyde may be occurring.

If we write a general mechanism for energy transfer to biacetyl as



one can show that $1/\Phi_D = k_t[(\text{CH}_3\text{CO})_2]/k_d\phi + \text{constant}$. Here z represents the excited state multiplicity. It is assumed that biacetyl does not interfere with the formation of products by the usual paths which are operative in its absence. With this choice of mechanism, coupled with an assumed energy-transfer rate constant of 10^{14} cc/mole sec, and $\phi = 1$, the data of Figure 3 lead to an estimate of the lifetime of the excited state of about 5×10^{-9} sec. If one assumes that processes I and II originate exclusively from the triplet and singlet excited states, respectively, and that the biacetyl addition does not alter significantly the mechanism of hydrogen formation from the free-radical

(15) (a) H. Okabe and W. A. Noyes, Jr., *J. Am. Chem. Soc.*, **79**, 801 (1957); (b) J. Heicklen and W. A. Noyes, Jr., *ibid.*, **81**, 3858 (1959); (c) R. P. Borkowski and P. Ausloos, *ibid.*, **84**, 4044 (1962).

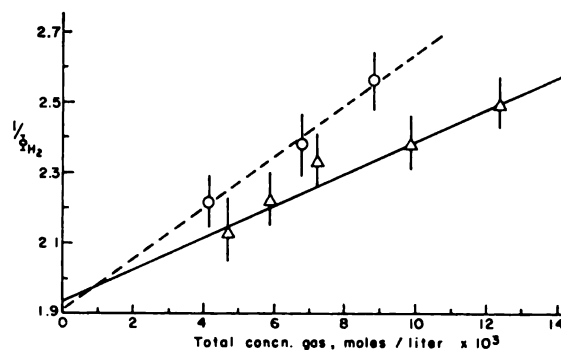


Figure 4. Plots for the quenching of the primary process formaldehyde photolysis at 3130 Å for experiments at 91° , 129° , Δ ; in each experiment approximately 100 mm of propylene and 80 mm of formaldehyde were present, and varied amounts of neopentane were added to obtain the gas concentration changes.

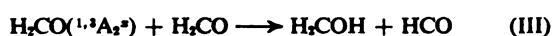
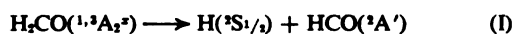
mechanism, then a plot of the function $(1 - \phi_{II})/(\phi_I)$ vs. $[(\text{CH}_3\text{CO})_2]$ yields an estimate of $k_t/k_d(1 - \phi_{II})$ from its slope. Assuming $k_t = 10^{14}$ cc/mole sec, $k_d(\text{triplet}) \cong 1 \times 10^8$ sec $^{-1}$ and $\tau(\text{triplet}) \cong 10^{-9}$ sec, computations based on the sensitized emission yield a similar value.¹⁶ The quenching efficiency is greater than can be accounted for through collisional deactivation (see the results of added neopentane described below), and it is most likely a result of electronic energy transfer. Some care must be used in assigning the donor state since both singlet and triplet energy transfer are possible and would lead to a partial decrease in the decomposition quantum yield of the donor. However, the companion study of formaldehyde-sensitized emission of biacetyl conducted under the same experimental conditions as the reported here shows that formaldehyde preferentially excites biacetyl phosphorescence.¹⁶ This is compelling evidence that triplet energy transfer is occurring. Thus it appears probable that triplet formaldehyde is produced and decomposition does originate from this state. As stated previously, spin conservation suggests that this decomposition reaction involves free-radical split (process I); obviously this cannot be tested unambiguously from the data at hand.

Further experiments were designed to elucidate the nature of the state leading to process II, molecular hydrogen formation. The pressure dependence of the quantum yield of hydrogen was studied at 3130 Å, at temperatures of 91 and 129° to evaluate the efficiency of collisional deactivation of this excited state. Hydrogen formation from the free-radical process I was suppressed in all of these runs through the addition of approximately 100 mm of propylene. Neopentane was used as an "inert" gas since it has many degrees of freedom, and under our conditions abstraction reactions involving its primary hydrogens would be unimportant. These results are summarized in Figure 4. It is apparent that some deactivation occurs at 129° , although rather inefficiently. Of course, partial vibrational relaxation of excited formaldehyde would not eliminate process II completely, but lower its efficiency. The ϕ_{II} data for 2537 and 3130 Å suggest that relaxation of vibrational energy by 1 kcal/mole lowers ϕ_{II} by 50%. If one assumes th

(16) From a study which is to be published by A. Zahra of the University of Toronto.

collision cross section for the deactivation process is $3.6 \times 10^{-15} \text{ cm}^2$, and that each collision is effective in deactivating completely the excited molecule, then the data of Figure 4 lead to an excited state lifetime of about $2 \times 10^{-11} \text{ sec}$. This must represent a minimum lifetime in view of the nature of the assumptions made. However, it seems clear that the lifetime of the excited state responsible for the concerted process II is very short at 3130 Å, and it is probably near 10^{-10} sec .

The present data and the other information on formaldehyde photolysis may be considered in terms of the following general mechanism for the primary processes.



In the mechanism shown, the right-hand superscript denotes the degree of vibrational excitation above the lowest level of that state where $q > p > \dots n > m > \dots$. The observed wavelength dependence of ϕ_{II} (Figure 2) proves that vibrational relaxation of the excited formaldehyde is incomplete before reaction for the conditions employed here. Regardless of the multiplicity of the state or states involved in primary processes I and II, it is evident that the higher the degree of vibrational excitation, the higher is the efficiency of the process II. Of course we expect the rate constant for both processes I and II to be a function of the vibrational level and multiplicity of the particular state involved. Although it is probably an oversimplification, it seems attractive to the authors to suggest that process II originates largely from the excited singlet state, and that I and III are derived largely from the triplet. With this assumption one may rationalize the increase in the extent of II at the shorter wavelengths in terms of the shortened lifetime of the singlet and the increased magnitude of k_{II} compared to k_3 . The primary quantum efficiencies of processes I and II are about equal at 3130 Å. If they originate largely from the different states as suggested, then the rate of intersystem crossing must be about the same as the rate of process II; that is, $k_3 \cong 10^{10} \text{ sec}^{-1}$ a surprisingly high value. In any case the evidence presented here for the short-lived excited states implies that the rate of intersystem crossing of formaldehyde is very fast. For the formaldehyde molecule the similarity in the geometry of the singlet and triplet excited states must favor large Franck-Condon overlap factors.

The molecular orbital picture of the states to which the initially excited n, π^* carbonyl states pass enroute to photodissociation by processes I and II was first put forward by Peters¹⁷ and later expanded by Abrahamson, Littler, and Vo.¹⁸ It depicts the state giving rise to the concerted process as one in which considerable H-H bonding exists, i.e., an $n, \sigma^*_{\text{CH}_2}$ state.¹⁸ The free-radical process may arise from a state in which H-H

antibonding is dominant such as an $n, \sigma^*_{\text{CH}_2}$ state. Unfortunately, the relative energies of these states are not known even approximately, and their energies relative to the n, π^* carbonyl states also are a matter of speculation. Abrahamson has pointed out that, due to the nonplanarity of the excited state, some overlap occurs between the $\sigma^*_{\text{CH}_2}$ orbital and the $2p_z$ orbital of oxygen. This effect may lower the energy of the $\sigma^*_{\text{CH}_2}$ state sufficiently so that the energy necessary for the free-radical process is equal to or less than that required for the molecular decomposition. A quantitative interpretation of the primary processes in terms of the transfer of excitation from the excited carbonyl $^1(n, \pi^*)$ or $^3(n, \pi^*)$ states to intermediate states will certainly add greatly to our understanding of the internal energy-transfer processes involved in molecular photochemistry. However, the meaningful interpretation of these details must await the more accurate determination of the appropriate molecular orbital energies.

Primary process III is included to account for the apparent presence of H atoms in the photolysis of formaldehyde at the long wavelengths.^{3d} At 3600 Å absorption is in the well-known α band which originates from the ground state with 1 quantum of ν_4 excitation. Hence a molecule absorbing in this band is about 81.6 kcal/mole above the ground state. It now appears likely that $87 \pm 1 \text{ kcal/mole}$ is necessary to dissociate formaldehyde,¹⁹ and a process such as III seems necessary to explain the photochemistry of formaldehyde at 3660 Å.^{19,20} In view of the low activation energy associated with H-atom abstraction from formaldehyde, it is quite possible that triplet formaldehyde may abstract an H atom from formaldehyde analogous to the triplet state reactions of carbonyl compounds in liquid systems.²¹ Primary process III is also in accord with the mechanism proposed by Kistiakowsky and co-workers for the high-temperature pyrolysis of formaldehyde.²²

Formaldehyde Photolysis Mechanism and the Excess of Carbon Monoxide over Hydrogen in the Products. During the course of this study, sufficient data accumulated to allow some interesting and new observations on the mechanism of the secondary reactions in the photolysis of formaldehyde. For the usual conditions employed in this study, notably high formaldehyde pressures and low light intensities, the quantum yield of carbon monoxide exceeded that of hydrogen by an amount far outside the experimental error (see the data of Tables I and II). The product imbalance was much smaller for the CD_2O data (see Table III). Kutschke and Venugopalan also found a carbon monoxide excess at 3130 Å for both CH_2O and CD_2O photolysis at high temperatures which was inversely dependent on the absorbed light intensity.²³ However, McQuigg found the ratio of products $\text{H}_2/\text{CO} \cong 1.0$ for CD_2O and CH_2O photolyses at the high intensities of flash photolysis.⁷ In view of these apparently conflicting results, we

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(21) (a) G. S. Hammond, W. P. Baker, and W. M. Moore, *J. Am. Chem. Soc.*, **83**, 2795 (1961); (b) C. Walling and M. J. Gibian, *ibid.*, **87**, 3361 (1965).

(22) I. D. Gay, G. P. Glass, G. B. Kistiakowsky, and H. Niki, *J. Chem. Phys.*, **43**, 4017 (1965).

(23) M. Venugopalan and K. O. Kutschke, *Can. J. Chem.*, **42**, 2451 (1964).

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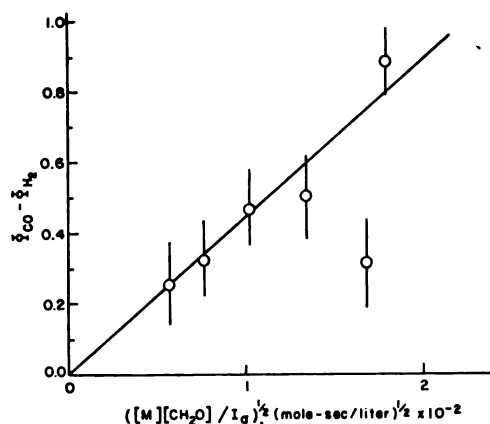
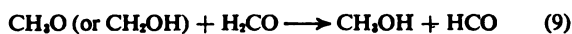
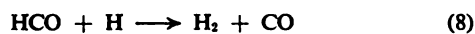
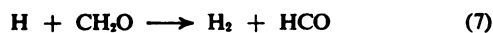
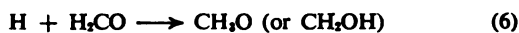
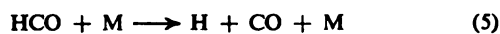


Figure 5. A plot of the carbon monoxide excess function, $\Phi_{\text{CO}} - \Phi_{\text{H}_2}$, vs. the variables of function 13 of the text; data are from 3130-A photolysis of formaldehyde and formaldehyde-neopentane mixtures at 129°.

examined the photolysis of formaldehyde using the full arc in one series of runs. The incident intensity was approximately 10^4 times greater than that used for the routine experimental work. Formaldehyde pressures were varied over the range 24–120 mm, with up to 266 mm of added neopentane; the ratio of H_2 to CO was 1.03 ± 0.03 for all runs, confirming McQuigg's observations from the photolyses at the very high intensities. Thus it appears that the mechanism which leads to carbon monoxide and hydrogen changes as a function of the light intensity.

The carbon monoxide excess is not the result of direct mechanical loss of hydrogen, nor is it formed in these experiments from a dark reaction such as has been observed previously for other conditions.^{3d,24} Some process which produces carbon monoxide and not hydrogen or that consumes H_2 or H atoms must be involved. An H-atom addition to the formaldehyde molecule with the ultimate formation of methanol seems an attractive possibility.²⁵ Consider the following simplified mechanism to occur following primary process I.²⁶



(24) J. E. Longfield and W. D. Walters, *J. Am. Chem. Soc.*, **77**, 6098 (1955).

(25) An extensive effort was made to detect unambiguously the photochemical generation of methanol in the products. Methanol is present after a condensation and work-up of the products for analysis, but it is difficult to evaluate the extent to which it is formed in the photochemical runs. This results from the fact that polymerization of pure formaldehyde induces the thermal formation of small amounts of methanol as identified by infrared and mass spectrometric analyses. Thus the prior removal of formaldehyde to facilitate identification of methanol in the photochemical products is impossible. Furthermore, when small amounts of methanol are added to pure formaldehyde and a polymerization is effected, both formaldehyde and much of the methanol are removed. No quantitative method could be found to determine the methanol unambiguously, but its presence seems highly probable from the qualitative results which were obtained.

(26) At the lowest intensities employed in this work, a first-order chain termination step should be included in the mechanism, since Φ_{H_2} is nearly independent of I_a for these conditions. However, the accuracy of the $\Phi_{\text{CO}} - \Phi_{\text{H}_2}$ data does not warrant the sophistication and complication of this added reaction.

One can show from the assumption of this mechanism that relation 10 will define the carbon monoxide excess

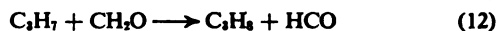
$$\Phi_{\text{CO}} - \Phi_{\text{H}_2} = \left[\frac{[\text{CH}_2\text{O}][\text{M}]\phi_1 k_5}{I_a(k_6 + k_7)k_8} \right]^{1/2} k_8 \quad (10)$$

The data from the 3130-A experiments are in accord with this mechanism and relation 10 as seen in Figure 5. From a thermochemical standpoint, reaction 6 is favored over 7 since the heats of reaction are -25 and -16 kcal/mole, respectively. Radical addition to the carbonyl bond in acetone has not been observed in acetone photolysis, but in this case the addition of the methyl radical would occur with the liberation of only 5 kcal/mole. Radical attack on the carbonyl bond has been observed previously for hexafluoroacetone.²⁷

A number of experimental observations are explicable on the basis of the above mechanism. At lower temperatures, reaction 5 will be slow, and chains, if any, will be quite short. Thus $\Phi_{\text{CO}} - \Phi_{\text{H}_2}$ will be small. However, at higher temperatures and pressures, the chain sequence 5, 6, 9, 5, . . . , may repeat many cycles before chain termination occurs. As the data of Kutschke and Venugopalan show, $\Phi_{\text{CO}} - \Phi_{\text{H}_2}$ may become quite large. However, the thermal stability of CH_3O (or CH_2OH) and the effect of the higher temperatures on the ratio k_6/k_7 may tend to lessen the importance of the aldehyde reduction relative to chain decomposition. At high intensities and lower temperatures, such as used by McQuigg, and in the high-intensity experiments used in the one phase of this work, radical-radical reactions should predominate. Thus reaction 8 is favored as the usual fate of H and HCO radicals, and a hydrogen-carbon monoxide balance is observed at high intensities.

A possible alternative in the mechanism given is the inclusion of the primary process III as a contributor to the carbon monoxide excess observed. Such a primary process alone cannot lead to $\Phi_{\text{CO}} - \Phi_{\text{H}_2}$ values greater than unity. Since the data of Kutschke and Venugopalan show that this difference can be greater than unity, this reaction cannot account for all of the effect, but its possible small contribution cannot be excluded from the facts at hand. Indeed, in view of the evidence for energy limitations on process I at 3660 Å, postulation of its occurrence at 3660 Å is attractive.

The quantitative mechanistic treatment of the carbon monoxide over hydrogen excess data for the propylene inhibition studies is impossible with the limited data at hand. However, some interesting observations can be made. In addition to the reaction sequence I, II, 5–9, reactions 11–14 are probably important. The



addition of the propyl radical to propylene, and subsequent addition steps, may also occur, and these would be followed by H-abstraction or chain-termination reactions analogous to eq 12 and 13–14, respectively.

It can be seen from the data of Tables I–III that propylene addition increases the quantum yield of carbon monoxide, although that for hydrogen is

(27) A. S. Gordon, *J. Chem. Phys.*, **36**, 1330 (1962).

suppressed to a limiting value. This probably results in part from the increased rate of reaction 5 with increasing gas concentration, but in addition the rate constant ratio $k_{12}/(k_{12} + k_{14})$ may be greater than $(k_6 + k_7)/k_8$; that is, the propyl radical may be more effective in propagating the chain decomposition of formaldehyde than is the hydrogen atom.

It is evident from the results described here that the photolysis of formaldehyde is a much more complex system than has been expected previously. Some of the details are clear from this work, but obviously further definitive experiments will be necessary to determine the extent of the process III in the creation of the carbon monoxide excess in the products.

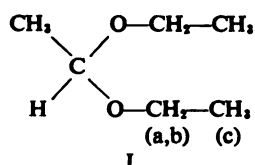
The ^{13}C -H Satellite Nuclear Magnetic Resonance Spectrum of Nonequivalent Protons in Acetal

Lana S. Rattet, L. Mandell, and J. H. Goldstein

Contribution from the Department of Chemistry, Emory University, Atlanta, Georgia 30322. Received December 22, 1966

Abstract: The nuclear magnetic resonance spectrum of the ethoxy protons in acetaldehyde diethyl acetal (acetal) has been investigated. By using, in addition to the normal proton spectrum, the data provided by the ^{13}C -H satellite spectrum, a unique set of spectral parameters has been obtained, eliminating the previously reported ambiguity in the solution of this problem. The ^{13}C -H coupling parameters of the two methylene protons are different, providing a new criterion of nonequivalence in structures of low symmetry.

The proton magnetic resonance spectrum of acetaldehyde diethyl acetal, or simply acetal (I), exhibits a much more complex structure in the methylene region



than is to be expected from a simple A_2B_2 spin system. Since there is no evidence of coupling through the oxygen atom, this complexity has been attributed to magnetic nonequivalence of the methylene protons.¹⁻³ Three analyses of the spectrum of acetal have been described, all of which treat the ethoxy group as an ABC_2 system, but leading to two markedly different sets of values of the proton-proton couplings. In the first approach Shafer, *et al.*,¹ and Waugh and Cotton² assumed J_{gem} to be of the same sign as the vicinal couplings (taken to be positive). Two different values of the vicinal couplings were then required to match the observed spectrum. The coupling values reported in these studies were: $J_{gem} = 9.4$ cps, $J_{vic} = 7.35, 6.68$ cps;¹ and $J_{gem} = 9.2$ cps, $J_{vic} = 7.2, 6.7$ cps.² Subsequently, however, Kaplan and Roberts reexamined the problem and reported an acceptable fit using $J_{gem} = -9.30$ cps, in which case the vicinal couplings are identical, $J_{ac} = J_{bc} = +7.03$ cps.³ Since both sets of values led to acceptable agreement with experiment, the outcome was described as indecisive, following the pattern of some other reported nonunique iterative analyses.⁴

In similar situations we have previously demonstrated that the requirement of simultaneously matching ^{13}C -H satellite patterns and normal proton spectra can yield unique sets of parameters.⁵ Several factors suggested the desirability of attempting to resolve the existing ambiguous situation in the case of acetal. Obviously, the occurrence of multiple solutions of the spectroscopic problem is, in general, a deterrent to efforts directed toward the interpretation of nmr parameters. There is, in addition, considerable intrinsic importance and interest in the origin and magnitude of the effects produced by nonequivalent environments such as those existing in acetal. Finally, successful analysis of the satellite patterns would provide still another and different kind of criterion of nonequivalence.

This communication describes the results obtained from such a simultaneous study of the proton and ^{13}C -H satellite spectra of the ethoxy region of acetal. The proton-proton couplings so obtained are in close agreement with the results of the last analysis cited above (J_{gem} and J_{vic} of opposite sign), and the alternative solution was found to be unacceptable. A small (~ 1.4 cps) but real difference in the ^{13}C -H couplings was observed for the two geminal protons. These results are discussed in relation to the other relevant nmr data and to the structural situation in acetal.

Experimental Section

The acetal used was the commercially available material, purified by fractional distillation over a range of $\sim 0.5^\circ$. All spectra were observed with a Varian Associates A-60-A spectrometer operating at 60 Mc/sec. Calibrations were performed by the side-band technique using a Hewlett-Packard Model 200J oscillator monitored with a Hewlett-Packard Model 5512A counter. All reported frequencies represent the average of at least four forward and four reverse sweeps. The neat liquid acetal was used throughout with

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(2) J. S. Waugh and F. A. Cotton, *J. Phys. Chem.*, **65**, 562 (1961).

(3) F. Kaplan and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 4666 (1961).

(4) S. Castellano and J. S. Waugh, *J. Chem. Phys.*, **34**, 295 (1961).

(5) R. T. Hobgood, Jr., R. E. Mayo, and J. H. Goldstein, *ibid.*, **39**, 2501 (1963).

a small amount of TMS (or benzene in one case) added to serve as the internal reference. Some difficulty was experienced because of the presence of two impurity lines in the satellite region. Since these lines diminished appreciably in relative intensity with purification, they were omitted from further consideration. Only nine lines of the low-field methylene satellite pattern were observable, as the other fifteen were masked by the quartet of the single hydrogen on the central carbon atom.

The average deviations of the measured frequencies (per peak) were: proton patterns, 0.065 cps; satellite patterns, 0.08 cps.

Results

The proton spectrum of I is essentially similar to that previously reported and will not be described here in detail. The satellite spectrum is given in Table I.

Table I. The ^{13}C -H Satellite Spectrum of the Ethoxy Protons of Neat Acetal^a

Observed	Calculated		Calculated intensity
	Methyl	Methylene	
Low-Field Methylene			
-301.02		-300.92	
-293.72		-293.69	
-291.41		-291.50	
-287.18		-287.13	
-277.12		-277.14	
-270.33		-270.15	
-266.26		-266.26	
-263.56		-263.67	
-256.78		-256.85	
High-Field Methylene and Low-Field Methyl			
-160.69		-160.61	0.17
-154.07		-154.00	0.21
-153.05		-153.07	0.44
-151.24		-151.26	1.31
-147.27		-147.29	1.35
...		-146.80	0.26
-145.78		-145.79	0.57
-144.80		-144.79	1.52
-143.68		-143.68	3.16
-141.04		-141.08	1.55
-140.18		-140.21	3.19
-138.80		-138.83	0.37
-138.11		-137.95	0.15
-137.57	-137.20	-137.64	3.67 1.83
-136.62	-136.61		7.14
-136.30	-136.08	-136.40	3.50 3.83
-134.36		-134.37	1.84
-133.41		-133.44	3.80
-132.24		-131.87	0.19
-131.16		-130.82	0.42
-129.86	-129.86		11.86
-129.49	-129.41	-129.54	11.86 2.33
-127.06		-127.06	2.25
-125.20		-125.21	0.26
-124.06		-124.05	0.59
-123.24	-123.26		2.55
-122.62	-122.65		5.00
-121.97	-121.91		2.44
-117.55		-117.78	0.42
High-Field Methyl			
...	-11.23		
-10.96	-10.98		
...	-10.77		
-3.96	-4.05		
...	-3.87		
...	+2.83		
+3.05	+3.06		
...	+3.33		

^a All frequencies are in cps at 60 Mc/sec, relative to TMS.

Each proton gives rise to two patterns displaced by $\pm 0.5J_{\text{H-C-H}}$ from its proton resonance position (except for a negligible isotopic effect on the proton shift).

The upper pattern of the methyl group and the lower methylene pattern are well isolated, but the two remaining patterns overlap very badly, as indicated in Table I. This complicated the assignments, and it was necessary in the analysis of the spectrum to proceed on a trial-and-error basis in this region until a consistent set of assignments was obtained for all the spectral lines in Table I.

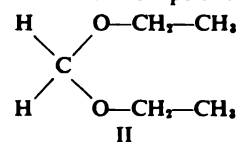
The final predicted frequencies and intensities are listed in the appropriate columns of Table I. Excluding overlapping lines, the predicted and observed frequencies agree to within ~ 0.05 cps. (The corresponding agreement for the proton pattern is ~ 0.02 cps.)

The above results were obtained using the final values for the nmr parameters shown in Table II. (The uncertainties shown in this table are those derived from the least-squares procedure used.) On the other hand, the couplings first reported by Shafer, *et al.*, clearly failed to reproduce the satellite spectra, and no reasonable variation of these values were found to improve the results. The isotope effect for the methylene proton shifts (not listed) were ~ 0.05 cps and were not considered to be significant; that for the methyl group is also quite small, but probably outside experimental error.

Discussion

The results described above establish that, to a very high degree of probability, the parameters of Table II constitute a unique set of values for the ethoxy group of acetal. Accordingly, the ambiguity in the solution referred to by Kaplan and Roberts can be considered as essentially resolved. The proton-proton couplings determined here do not vary significantly from those reported by Kaplan and Roberts, the differences being ~ 0.13 and ~ 0.01 cps for J_{gem} and J_{vic} , respectively. The difference in shifts for the methylene protons also agrees nicely in the two studies, 9.23 cps as against the value of 9.02 cps obtained here.

Waugh and Cotton were the first to correctly identify the origins of the nonequivalence of the methylene protons in structures such as acetal.² They pointed out that, although nonequivalence could arise from rotational isomers of different stability, it would still persist in the case of free internal rotation because of the low degree of symmetry of the acetal molecule. These workers also commented that the pmr spectrum of ethylal (II) exhibited an uncomplicated pattern indica-



tive of equivalent methylene protons. We have confirmed this observation by examining the ^{13}C -H satellite patterns of II, which turns out to correspond qualitatively to an A_2B_3 ethoxy system. Frankiss has also reported values of 140.5 ± 1.0 and 126.0 ± 0.3 cps for the two ^{13}C -H couplings of the ethoxy system in ethylal.⁶ These results were quite similar to those obtained here for acetal. More recently, Elvidge and Foster, in their nmr studies of various acetals, have restated the conclusions of Waugh and Cotton regard-

(6) S. G. Frankiss, *J. Phys. Chem.*, **67**, 752 (1963).

Table II. Nmr Parameters for the Ethoxy Protons in Neat Acetal^a

	Methylene		Methyl
	H _a	H _b	H _c
ν	-212.88 \pm 0.03	-203.855 \pm 0.03	-67.165 \pm 0.03
J_{13C-H}	141.01 \pm 0.06	139.64 \pm 0.08	125.86 \pm 0.07
J_{vic}	+7.043 \pm 0.018		
J_{gem}	-9.427 \pm 0.034		
Isotope shift			+0.155

^a All values are in cps. The shifts are relative to internal TMS, at 60 Mc/sec.

ing the source of nonequivalence.⁷ The present evidence does not permit an assignment of the relative importance of inherent asymmetry and restricted rotation, and it is likely that detailed temperature studies will be required to clarify the problem. (Shafer, *et al.*, reported the proton pattern of acetal is not significantly changed at temperatures as low as -80° .)

Whatever the origin of the environmental nonequivalence may be, any interpretation of the chemical shift difference, $\nu_b - \nu_a$, is complicated by the difficulty of separating magnetic and inductive contributions. Conceivably, a significant fraction of the 9 cps difference could be attributed, for example, to neighboring-group anisotropy effects. Hence, it is problematical whether, on the basis of the shift data, a significant difference in the character of the two methylene C-H bonds can be inferred.

The $^{13}C-H$ coupling values, again, reflect very decisively the nonequivalence of the two methylene protons. The difference of ~ 1.3 cps, while small, is nevertheless approximately 10% of the total substituent effect produced by an oxygen atom.⁸ (It is worthwhile to point out this difference could not possibly be determined by the simple procedure of calibrating the centers of the satellite patterns, if for no other reason, because of the overlapping of the two systems of peaks.) The occurrence of two distinct $^{13}C-H$ couplings in the methylene group means that the nonequivalence can actually be localized in the two corresponding C-H bonds. By contrast in the case of the shifts, it is possible, as pointed out above, that part or all of the difference resides in the environment and is of largely magnetic origin.

It has been established that $^{13}C-H$ couplings are, in at least some cases, affected by the medium.^{9,10} How-

ever, such affects do not appear to be of magnetic origin, but rather to arise from factors, either specific or general, which influence the charge distribution in the C-H bonds. For chloroform⁹ and for several dihaloethylenes and halomethanes¹⁰ it has been found that increasing J_{13C-H} was associated with the displacement of the shifts to the lower field. In the latter compounds, in fact, a plot of J vs. ν (as concentration is varied) turns out to be quite linear. Any interaction which displaces charge from the proton to its bonded C atom would be expected to produce at least the observed trend, and it can be tentatively assumed that in acetal also the methylene C-H bonds have been polarized in this manner. (It is observed that in acetal the larger J_{13C-H} is associated with the lower shift value.) However, the factors responsible for this polarization cannot be reliably assigned on the basis of the presently available evidence.

To the extent that these arguments are valid and applicable here, it seems likely that the $^{13}C-H$ coupling parameter provides a new criterion of nonequivalence, which has the advantage of not being significantly affected by the magnetic contributions which complicate the interpretation of chemical shifts. Further, use of this criterion in similar stereochemical situations appears to be warranted.

Acknowledgments. This research was supported by grants from the National Institutes of Health and the Corn Industries Research Foundation. One of us (L. S. R.) is the recipient of a National Science Foundation Predoctoral Traineeship. We wish to acknowledge several helpful discussions with Dr. D. J. Goldsmith.

(9) D. F. Evans, *J. Chem. Soc.*, 5575 (1963).

(10) V. S. Watts, J. E. Loemker, and J. H. Goldstein, *J. Mol. Spectry.*, 17, 348 (1965); V. S. Watts and J. H. Goldstein, *J. Phys. Chem.*, 70, 3887 (1966).

(7) J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 981 (1964).

(8) N. Muller and P. I. Rose, *J. Am. Chem. Soc.*, 84, 3973 (1962).

Ligand Effects on the Rate of Metal-Ion-Catalyzed Decarboxylation of Dimethyloxaloacetic Acid

John V. Rund and Kenneth G. Claus

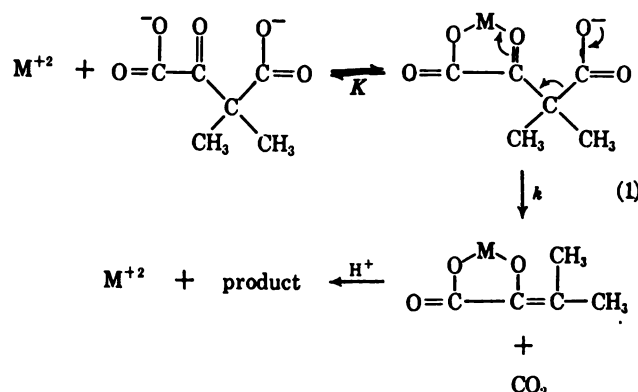
Contribution from the Department of Chemistry, The University of Arizona, Tucson, Arizona. Received August 26, 1966

Abstract: The rate of decarboxylation of dimethyloxaloacetic acid catalyzed by metal ions is shown to be sensitive to the ligands attached to the metal. The Mn(phen)^{2+} complex (phen = 1,10-phenanthroline) is a more effective catalyst than aqueous manganese, and Mn(phen)_2^{2+} is still more active. Catalysis by zinc and magnesium ions is unaffected by coordinated phenanthroline. Substitution of the hydrogens on the phenanthroline with various groups affects the rates of catalysis of both manganese and zinc. Some substituents appear to cause a change in which step of the reaction is rate determining. The authors suggest that conjugation between the phenanthroline and the acid through the metal occurs, and that there is also another influence on the rate.

Many reactions are known during the course of which the reacting molecules are coordinated to metal ions.¹ The effect of the other ligands associated with the metal on the reaction has also been studied.^{2,3} This is particularly interesting in the case of metallo enzymes. Enzyme proteins are often said to be activated by metal ions. In some simple cases, at least, the converse seems to be true: metal ions by themselves can carry out a reaction, but the addition of enzyme protein considerably speeds it up. One ligand (the protein) is acting upon the reaction rate of another (the substrate) while both are coordinated to a common metal ion. More elaborate effects, such as substrate discrimination by the enzyme and influence on the steric path of the reaction, are also known, but these will not be considered here. Even for simple protein-induced increases in rate, a number of mechanisms can be envisioned by which the substrate-protein interactions may result. (1) The protein by coordination may change the electron distribution or density of the metal in such a way as to modify the electronic environment of the substrate. (2) The large protein molecule may create a local disruption of the solvent structure and decrease the solvent-rearrangement contribution to the activation energy. (3) The protein may have a functional group which is situated near the site of coordination and assists in the reaction. (4) The metal may change the configuration of the protein in such a way as to unfold an active catalytic site from the interior.

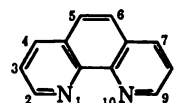
This paper reports an attempt to discover whether electronic influences can be transferred by one ligand to another through a metal ion. The investigation was carried out on an enzyme-like model system. The reaction studied was the decarboxylation of the β -keto acid, dimethyloxaloacetic acid. Oxaloacetic acid is decarboxylated enzymatically in certain biological systems,⁴ and the two methyl groups simplify the kinetics by preventing enolization. The metals studied were manganese, zinc, and magnesium. 1,10-Phenanthroline derivatives were used in place of the enzyme protein. It had been shown⁵ that when these molecules

were coordinated to a +2 metal ion, they acted in a fashion somewhat similar to real enzymes. The course of the reaction for a hydrated metal ion in aqueous solution is⁶



The metal acts as a positive center which attracts electrons and facilitates the rupture of the bond between the carboxyl group and the rest of the molecule. The same mechanism occurs with the metal-phenanthroline complex. In the enzyme, there is evidence that an amine group is involved at some point in the reaction,⁷ but the same sequence of substrate association, decarboxylation, and dissociation undoubtedly occurs.

In order to test the transference of electronic effects from one ligand to another through the metal, a number of derivatives of 1,10-phenanthroline were prepared, most substituted in the 4 and 7 positions. Groups in



1,10-phenanthroline

these positions influence the electron density of the nitrogens *para* to them. Not only are the metal-nitrogen σ bonds affected, but it has been shown by nmr that there is significant mixing between the orbitals of the paramagnetic metal ion and the π system of the phenanthroline.⁸ Withdrawal of electron density from

(1) For example, see "Reactions of Coordinated Ligands," *Advances in Chemistry Series*, No. 37, American Chemical Society, Washington, D. C., 1963.

(2) W. F. Little and R. Eisenthal, *J. Org. Chem.*, **26**, 3609 (1961).

(3) W. F. Little and R. Eisenthal, *J. Am. Chem. Soc.*, **83**, 4936 (1961).

(4) B. Vennesland, M. G. Gollub, and J. F. Speck, *J. Biol. Chem.*, **178**, 301 (1949).

(5) J. V. Rund and R. A. Plane, *J. Am. Chem. Soc.*, **86**, 367 (1964).

(6) R. Steinberger and F. H. Westheimer, *ibid.*, **73**, 429 (1951).

(7) I. Fridovich and F. H. Westheimer, *ibid.*, **84**, 3208 (1962).

(8) M. W. Dietrich and A. C. Wahl, *J. Chem. Phys.*, **27**, 1591 (1963).

the metal should increase k and K (see eq 1), while electron donation should decrease them; π interactions among the ligands must be transferred through the d orbitals of the metal. In zinc and magnesium these are of too high an energy to play a significant role. σ -Bond effects may occur with any of the metals, possibly through the rehybridization mechanism suggested to explain the *trans* effect in transition metal complexes.⁹

Experimental Section

Chemicals. Metal catalysts were made up from reagent grade salts and their concentrations determined by standard volumetric and gravimetric techniques. Water was distilled before use in kinetic runs. The following phenanthroline compounds were purchased from the G. Frederick Smith Chemical Co. and used without further purification: the 4,7-dimethyl, 2,9-dimethyl, 4,7-diphenyl, and 4,7-diphenyl sodium sulfonate derivatives. Others were prepared by published procedures listed below.

1,10-Phenanthroline¹⁰ had mp 118°, lit. 117°; 5-nitro-1,10-phenanthroline,¹¹ mp 200°, lit. 199°; 3,8-dicarboxy-4,7-dihydroxy-1,10-phenanthroline, 3,8-dicarboxy-4,7-dihydroxy-1,10-phenanthroline, and 4,7-dihydroxy-1,10-phenanthroline¹² are not readily purified to give analytical samples. 4,7-Dichloro-1,10-phenanthroline¹³ had mp 248°, lit. 249–250°; subsequent recrystallizations raised the melting point to 262°. 4,7-Dibromo-1,10-phenanthroline¹³ had mp 233°, lit. 236°. A reported method¹⁴ for 4,7-dimethoxy-1,10-phenanthroline involving a sealed tube reaction with a copper catalyst did not give satisfactory results. Instead, 2.0 g of 4,7-dichloro-1,10-phenanthroline and 65 ml of methanol were warmed on a steam bath; 35 ml of 10% sodium methoxide in methanol was added, and the solution refluxed for about 20 hr. The precipitated sodium chloride was filtered off, and the solvent was evaporated. The residue was recrystallized from aqueous ethanol, then benzene, and then 20% aqueous methanol with decolorizing charcoal. The final product is white and melts at 205°. *Anal.* Calcd for $C_{14}H_{10}N_2O_2$: C, 70.00; H, 5.00; N, 11.66. Found: C, 70.23; H, 4.99; N, 11.67.

All kinetic measurements were made on reactions in glutarate buffer. Matheson Coleman and Bell glutaric acid was recrystallized from chloroform to give a material melting at 98–99°. A weighed amount of acid was mixed with a measured volume of standardized sodium hydroxide and diluted to an appropriate volume. The measured pH was 5.3.

The preparation of dimethyloxaloacetic acid has already been described.⁴

Kinetic Runs. The rate of evolution of carbon dioxide was measured by a simple manometer under conditions of partial vacuum in a vessel resembling a Warburg flask.⁴ Five or six runs were made for each set of concentrations, and four to eight different concentrations of catalyst were used for each phenanthroline.

The reactions generally gave good pseudo-first-order plots in CO_2 pressure. Some deviations occurred at the beginning of the reactions, but the pressures began to fall on a straight line within a small fraction of a half-life. First-order kinetics was observed over three or four half-lives in a number of cases, but routine runs were normally carried out for only one or two. A precipitate was observed in some of the reactions, particularly near completion. No change in kinetics seemed to accompany precipitation, and the reactions were not otherwise anomalous.

Calculations. The association constant between the catalyst and substrate and the rate constant for decarboxylation of this complex (K and k in reaction 1) were calculated using an IBM 7072 computer. A program written by one of the authors calculated the concentrations of all the species present and then corrected the observed rate constant for effects of substrate autodecarboxylation and catalysis due to metal ions not coordinated to phenanthroline. The best straight line fitting the corrected data was determined by a weighted-least-squares method. Weighting factors were calculated from the standard deviation of rates of several identical runs.

(9) See F. Basolo and R. G. Pearson, *Progr. Inorg. Chem.*, **4**, 381 (1962), and references contained therein.

(10) K. Madeja, *J. Prakt. Chem.*, **17**, 104 (1962).

(11) G. F. Smith and F. W. Cagle, *J. Org. Chem.*, **12**, 781 (1947).

(12) H. R. Snyder and H. E. Freier, *J. Am. Chem. Soc.*, **68**, 1320 (1946).

(13) F. H. Case, *J. Org. Chem.*, **16**, 941 (1951).

(14) D. E. Zacharias and F. H. Case, *ibid.*, **27**, 3878 (1962).

The values of K and k were calculated from the resulting straight line.

Treatment of Kinetic Data. The method of calculating the intrinsic rate constant, k , and the intrinsic equilibrium constant, K , may be most easily explained by illustrating the calculation for the hydrated-metal-ion catalyst. The reactions of consequence are



S is the dianion of the substrate dimethyloxaloacetic acid, M is the metal ion, and P is the decarboxylated acid. For a rate-determining decarboxylation step, the mechanism requires that

$$\frac{d[CO_2]}{dt} = k[MS] \quad (6)$$

Experimentally, the observed rate constant is defined by

$$\frac{d[CO_2]}{dt} = k_o S_t \quad (7)$$

where S_t is the total amount of substrate present, and where the rate has been corrected for a small amount of autodecarboxylation of the substrate. Combining these equations, one obtains

$$\frac{1}{k_o} = \frac{S_t}{k[MS]} \quad (8)$$

Expanding S_t gives

$$\frac{1}{k_o} = \frac{[S] + [HS^+] + [MS]}{k[MS]} = \frac{[S]}{k[MS]} + \frac{[HS^+]}{k[MS]} + \frac{1}{k} \quad (9)$$

Substituting $[H^+][S]/K_a$ for $[HS^+]$

$$\frac{1}{k_o} = \frac{[S]}{k[MS]} + \frac{[H^+][S]}{k[MS]K_a} + \frac{1}{k} \quad (10)$$

$1/K[M]$ is substituted for $[S]/[MS]$ and terms are combined to give

$$\frac{1}{k_o} = \frac{1 + [H^+]/K_a}{kK[M]} + \frac{1}{k} \quad (11)$$

At very high metal-ion concentrations (where all the substrate is in the form of the MS complex), the observed rate will approach as a limit the rate of the decarboxylation step, and the observed and intrinsic rate constants will become equal. Equation 11 shows that a plot of $1/k_o$ against $1/[M]$ will be a straight line. The limit is best found by extrapolating the plot back to $1/[M] = 0$ to find the intrinsic rate constant, k . Plots of this kind are shown in Figure 4.

The calculation is more complicated, however, since $[M]$ may not be found until K is known. It is possible to change the variable into known total metal concentration. Consider two points, $(1/[M]_1, 1/k_1)$ and $(1/[M]_2, 1/k_2)$, on the straight line which fits the plot of $1/[M]$ against $1/k_o$. Equation 11 indicates that

$$\frac{1}{k} = \frac{1}{k_2} - \frac{1}{[M]_2} \left(\frac{1/k_1 - 1/k_2}{1/[M]_1 - 1/[M]_2} \right) \quad (12)$$

that is, the extrapolation of $1/k_o$ to $1/[M] = 0$ gives $1/k$. The equilibrium metal concentration may be expressed as

$$[M] = M_t - [MS] \quad (13)$$

where M_t is the total metal concentration. Using relation 8 for $[MS]$, one obtains

$$[M] = M_t - \frac{k_o S_t}{k} \quad (14)$$

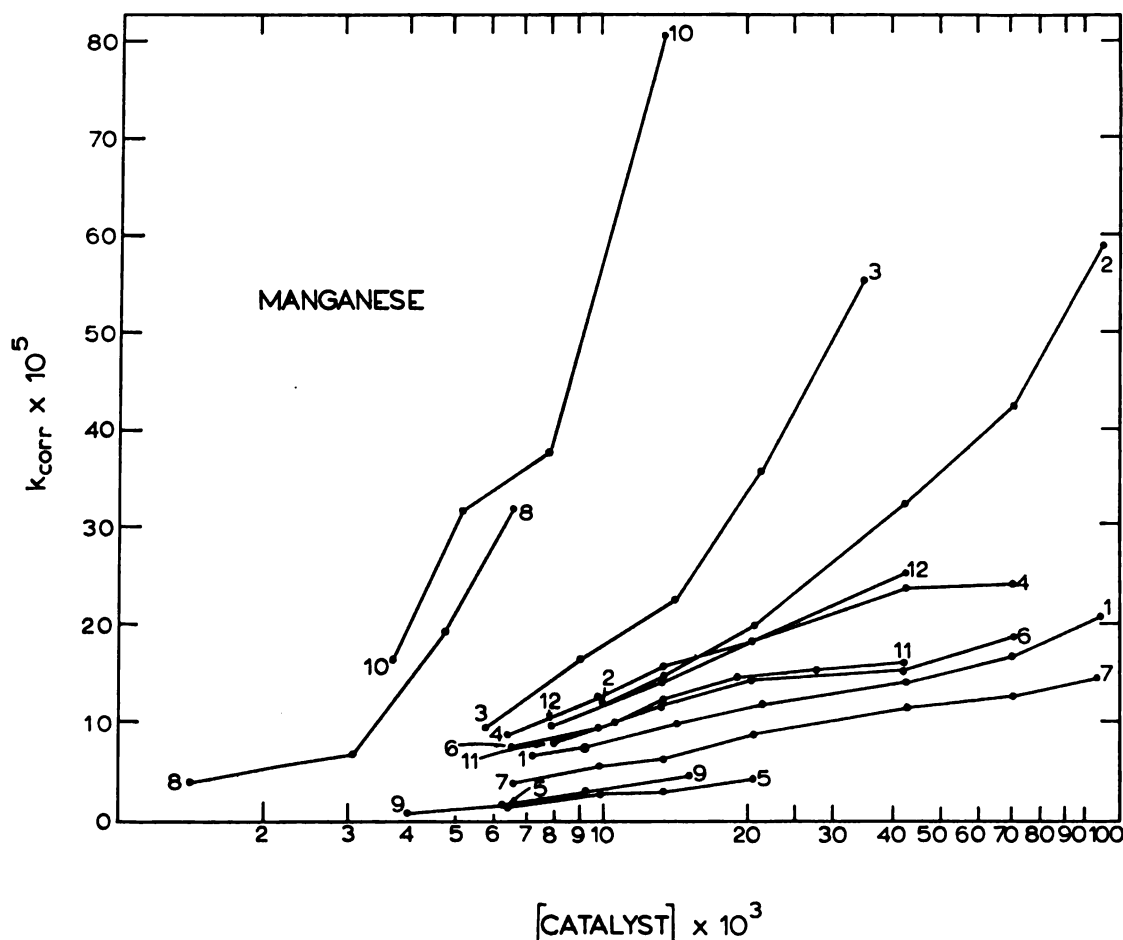


Figure 1. Corrected rate constants as a function of catalyst concentration for manganese catalysts. Numbers refer to Table I.

Substitution of (14) into (12) gives

$$\frac{1}{k} = \frac{1}{k_2} - \left(\frac{1}{M_2 - \frac{k_2}{k} S_t} \right) \left(\frac{1/k_1 - 1/k_2}{1/(M_1 - \frac{k_1}{k} S_t) - 1/(M_2 - \frac{k_2}{k} S_t)} \right) \quad (15)$$

where M_1 and M_2 are total metal concentrations corresponding to $[M]_1$ and $[M]_2$. Rearrangement of this equation gives a quadratic in k

$$k^2[(M_1 k_2/k_1) - M_2] + k[k_2(M_2 - M_1)] + [(k_2 k_1 - k_2^2) S_t] = 0 \quad (16)$$

The value of k which is calculated from this equation is inserted into eq 11 to calculate K .

When the catalyst is a metal-phenanthroline complex, additional corrections must be made as a result of the incomplete association between the metal and the ligand. Relatively few association constants between metals and substituted phenanthrolines have been measured. The constants which are known are not very different from that of 1,10-phenanthroline itself. Since the corrections involving these constants are minor, the value of the association constant for a metal with 1,10-phenanthroline is used for the value of the association constant for the same metal with substituted phenanthrolines. An exception is made in the case of 2,9-dimethyl-1,10-phenanthroline, where some association data are available. We are led to assume the relatively small value of 300 for its association constant with manganese.

The range in the values for constants K and k was estimated by moving the line best fitting $1/k$ vs. $1/[\text{catalyst}]$ within the confines of the standard deviations of k . It is important to test the results in this way, since the intercepts of the lines are often near zero on the

reciprocal plot, and even small deviations can cause large fluctuations in the values of the constants.

Results and Discussion

Table I presents the data and calculated results. M_t in the first column is the total concentration of metal ion in the reaction, $[\text{cat}]$ is the calculated concentration of metal-phenanthroline catalyst, k_o is the observed rate constant, σ is its standard deviation, k_c is the rate constant from which the contributions from other reactions have been subtracted, and K and k are the intrinsic reaction constants of eq 1. Figures 1 and 2 show the corrected rate constants, k_c , as functions of the catalyst concentrations for manganese and zinc. For clarity the rate constants are plotted without indicating the standard deviations, and the concentrations are placed on a logarithmic scale. Generally speaking, when the data are plotted with their standard deviations on a linear scale, they can be fit by a smooth, monotonic curve. At high concentrations of catalyst, the curve will level off as the corrected rate constant approaches the intrinsic rate constant of decarboxylation, k . It has been pointed out above that k can also be determined by extrapolation of the linear plot of $1/k$ against $1/[M]$, and this method is considerably more accurate.

Electronic Effects. The activation of aqueous manganese by one and two coordinated molecules of phenanthroline can be seen in Figure 1 (data numbered 2 and 3, respectively). That there is no activation of zinc

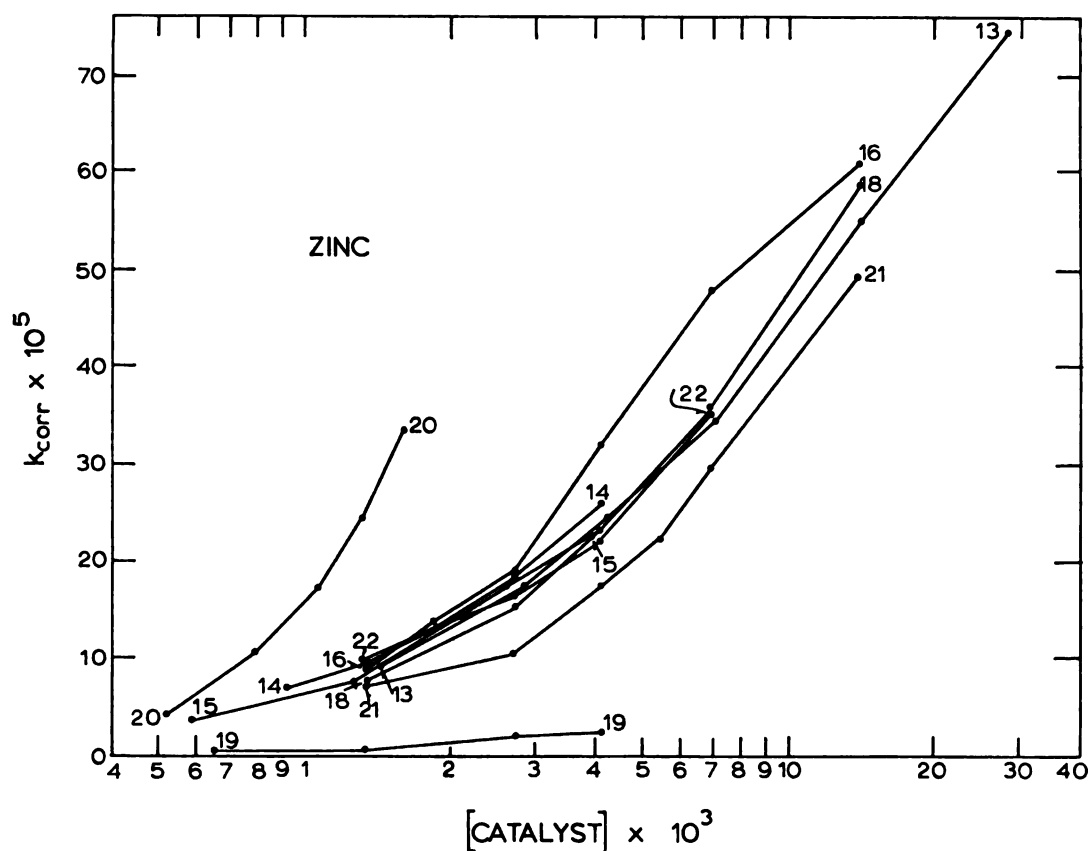


Figure 2. Corrected rate constants as a function of catalyst concentration for zinc catalysts. Numbers refer to Table I.

by phenanthroline is shown in Figure 2, in which the three catalysts, Zn(aq)^{2+} , Zn(phen)^{2+} , and Zn(phen)_2^{2+} have nearly the same catalytic activity. This result is consistent with the explanation that the function of the metal is to accept electron density from the substrate, and that coordination to a phenanthroline molecule increases the metal's ability to act in this way by an interaction with its d orbitals to delocalize the substrate electron density over a greater volume of space. Manganese(II) interacts readily, but the d orbitals of zinc(II) are of too high an energy to mix extensively with the substrate or phenanthroline π orbitals. To use the terminology developed in physical organic chemistry, the substrate and the phenanthroline are conjugated through the manganese, but not through zinc because of the absence of an appropriate π orbital. If this were the only influence operating on the decarboxylation rate, one would expect that upon substitution of the phenanthrolines at the 4 and 7 positions additional changes in rate would occur for the manganese catalyst but not for the zinc, as a result of the resonance effect. Many of the zinc catalysts in fact have quite similar rates, but at least the dichloro and dimethoxy derivatives show marked differences. Some other influence must also be operating on the substrate as a result of the substitution of remote positions on the phenanthroline. It should be noted that the resonance effect can be made to correlate a considerable amount of the data. Ligands may be picked out which seem to be affected to the same extent by whatever influence is operative beyond the resonance effect. These are the aqueous catalyst, the phenanthroline complex, the bis(phenanthroline) complex, and the complexes of

4,7-dihydroxy and 4,7-dibromo derivatives, which all have the same rates for zinc, where resonance does not operate. Examining the rates of the corresponding manganese complexes, one finds them in an order consistent with resonance activation. The aqueous catalyst is slow, Mn(phen)^{2+} is faster, and Mn(phen)_2^{2+} is still faster. The bromo derivative seems a little slower and the dihydroxy derivative much slower than the unsubstituted phenanthroline.

Some other cause must be invoked to help account for the results. The inductive effect, which could operate in both the zinc and manganese catalysts, seems to be a logical complement to the resonance effect. The methoxy group attracts electrons inductively, and this might be responsible for its activation of the catalyst. The apparently contradictory inhibiting effect of hydroxide substitution may be due to partial ionization of the protons on the hydroxide, which would lower the positive charge on the catalyst.

Another possible cause of activation is the disruption of the solvent structure in the region of the metal ion. Reorientation of the water molecules during decarboxylation may contribute to the activation energy of the reaction, and the exclusion of water by phenanthrolines may lower the activation energy. Large substituents on the phenanthrolines should increase water exclusion. The two most effective zinc catalysts do in fact contain the largest substituents, methoxy and phenyl groups. Neither of these arguments, however, will explain the results of methyl substitution at the 4 and 7 positions, which increases the catalytic activity of the manganese complex and decreases that of the zinc complex. It may be that the 4,7-dimethyl-

Table I. Decarboxylation Rates and Rate Constants for Various Catalysts^a

M_i $\times 10^3$	[cat] $\times 10^3$	k_o $\times 10^5$ sec ⁻¹	σ $\times 10^5$ sec ⁻¹	k_e $\times 10^5$ sec ⁻¹	k $\times 10^5$ sec ⁻¹	K	M_i $\times 10^3$	[cat] $\times 10^3$	k_o $\times 10^5$ sec ⁻¹	σ $\times 10^5$ sec ⁻¹	k_e $\times 10^5$ sec ⁻¹	k $\times 10^5$ sec ⁻¹
1. Aqueous Manganese							11. Manganese-4,7-Dichloro-1,10-phenanthroline					
7.25	7.25	8.0	0.39	6.5	19	116	9.01	7.98	11.1	0.44	8.0	21
9.48	9.48	8.6	0.38	7.5	± 1	± 13	12.0	10.8	12.7	0.65	9.9	± 1
14.5	14.5	10.3	0.97	9.6			15.0	13.7	14.8	0.21	12.2	
21.7	21.7	12.1	1.00	11.7			21.0	19.4	16.5	0.08	14.1	
43.4	43.4	14.2	1.12	14.0			30.0	28.1	17.6	0.37	15.1	
72.5	72.5	16.7	0.23	16.6			45.0	42.7	18.9	0.51	16.0	
108.6	108.6	18.8	0.76	18.7			12. Manganese-4,7-Dibromo-1,10-phenanthroline					
2. Manganese-1,10-Phenanthroline							9.01	7.98	12.3	0.56	9.21	44
11.3	10.1	14.0	0.62	11.5	84	18	15.0	13.7	16.8	0.73	14.3	± 13
15.0	13.7	16.9	0.84	14.6	± 8	± 3	22.5	20.8	20.5	2.52	18.1	
22.5	20.9	22.3	1.19	19.9			45.0	42.7	29.2	6.27	26.3	
45.0	42.7	34.9	1.44	32.1			13. Aqueous Zinc					
75.1	72.0	45.9	2.78	42.5			0.431		6.3	0.14		111
112.6	108.8	62.8	2.30	58.8			0.718		8.0	0.19		± 10
3. Manganese-2(1,10-Phenanthroline)							1.44	1.44	12.6	0.20	9.2	
7.90	5.88	13.5	0.85	9.3	1650 ^b		2.87	2.87	20.3	0.98	17.6	
11.8	9.31	20.6	0.32	16.4			4.31	4.31	26.7	0.90	24.6	
17.8	14.6	26.9	0.89	22.4			7.18	7.18	35.8	1.84	34.7	
25.7	21.8	40.9	1.74	35.8			14.4	14.4	55.3	2.95	55.0	
39.5	34.6	62.5	2.07	56.4			28.7	28.7	74.7	4.52	74.6	
4. Manganese-4,7-Diphenyl-1,10-phenanthroline							14. Zinc-1,10-Phenanthroline					
7.50	6.57	11.8	1.00	8.8	30	107	0.718		9.7	0.33		
11.3	10.1	14.6	0.69	12.2	± 4	± 40	1.01	0.94	11.6	0.20	7.2	119
15.0	13.7	17.7	1.41	15.4			1.44	1.36	14.0	0.18	9.7	± 30
22.5	20.8	20.5	3.03	18.1			2.01	1.92	17.6	0.29	13.5	
45.0	42.7	26.5	3.42	23.7			2.87	2.76	22.8	0.46	19.0	
75.1	72.0	27.6	3.60	24.2			4.31	4.18	29.9	1.20	26.6	
5. Manganese-3,8-Dicarboxy-4,7-dihydroxy-1,10-phenanthroline							15. Zinc-2(1,10-Phenanthroline)					
7.50	6.57	14.36	0.09	1.45	23	12	0.718	0.601	8.8	0.20	3.8	350
11.3	10.1	14.94	0.16	2.49	+22	+7	1.44	1.27	12.8	1.34	7.7	
15.0	13.7	5.22	0.37	2.93	-8		2.87	2.63	22.1	1.40	17.2	
22.5	20.8	6.18	0.14	4.16			4.31	4.00	27.9	0.91	23.1	
6. Manganese-5-Nitro-1,10-phenanthroline							16. Zinc-4,7-Diphenyl-1,10-phenanthroline					
7.50	6.57	10.8	0.75	7.5	27	82	1.44	1.36	13.4	0.31	9.1	164
11.3	10.1	12.3	0.35	9.5	± 2	± 19	2.87	2.76	22.9	0.83	19.1	± 18
15.0	13.7	14.2	0.57	11.7			4.31	4.18	35.3	4.25	32.0	
22.5	20.9	16.8	0.91	14.4			7.18	7.01	50.5	5.10	48.0	
45.0	42.7	23.1	0.97	20.2			14.4	14.1	63.0	11.67	61.0	
75.1	72.0	27.0	1.60	23.6			17. Zinc-4,7-Diphenyl-1,10-phenanthroline, Sulfonated, Sodium Salt					
7. Manganese-4,7-Dihydroxy-1,10-phenanthroline							1.44	1.36	12.61	1.33	8.3	
7.50	6.57	6.6	0.19	3.7	16	67	2.01	1.92	15.31	1.69	11.2	
11.3	10.1	7.8	0.22	5.4	± 1	± 10	2.87	2.76	14.21	0.96	10.4	
15.0	13.7	8.5	0.16	6.2			3.44	3.33	15.18	0.17	11.6	<i>d</i>
22.5	20.8	10.7	0.45	8.4			4.31	4.18	16.13	1.68	12.8	
45.0	42.7	14.0	0.51	11.2			5.74	5.59	18.81	2.68	16.0	
75.0	72.0	16.0	0.92	12.6			18. Zinc-4,7-Dihydroxy-1,10-phenanthroline					
112.6	108.8	18.3	0.65	14.3			1.44	1.36	12.2	0.74	7.9	250
8. Manganese-4,7-Dimethyl-1,10-phenanthroline							2.87	2.76	19.1	0.41	15.3	+325
1.88	1.44	7.9	0.03	3.6			4.31	4.17	26.8	0.64	23.5	-100
2.81	2.26	9.6	0.71	5.6			7.18	7.01	38.3	2.09	35.9	
3.75	3.11	10.3	2.21	6.5	<i>c</i>		14.35	14.1	60.8	10.25	58.8	
5.63	4.83	22.5	3.15	19.2			19. Zinc-4,7-Dimethyl-1,10-phenanthroline					
7.50	6.57	34.8	5.07	31.8			0.718	0.665	5.9	0.31	0.1	
9. Manganese-2,9-Dimethyl-1,10-phenanthroline							1.44	1.36	6.1	0.23	0.7	<i>d</i>
7.50	3.89	6.0	0.51	0.3	280 ^b		2.87	2.76	6.8	1.18	2.1	
10.5	6.28	7.3	0.22	1.6			4.31	4.18	6.7	1.28	2.7	
15.0	9.40	8.9	0.31	2.7			20. Zinc-4,7-Dimethoxy-1,10-phenanthroline					
22.5	15.3	11.1	0.15	4.4			0.574	0.528	10.0	0.78	4.3	
10. Manganese-4,7-Dimethoxy-1,10-phenanthroline							0.861	0.804	16.3	1.56	10.7	
4.50	3.79	21.0	1.00	16.5			1.15	1.08	22.8	0.28	17.3	<i>c</i>
6.00	5.17	35.5	3.17	31.6			1.44	1.36	30.8	4.92	25.4	
9.01	7.98	40.7	2.10	37.6	<i>c</i>		1.72	1.64	39.0	5.36	33.8	
12.0	10.8	62.9	7.84	60.2								
15.0	13.7	83.0	8.45	80.5								

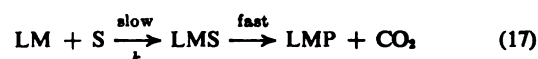
	[cat] × 10 ³	k_o × 10 ⁵ sec ⁻¹	σ × 10 ⁵ sec ⁻¹	k_o × 10 ⁵ sec ⁻¹	k × 10 ⁵ sec ⁻¹	K
21. Zinc-4,7-Dichloro-1,10-phenanthroline						
44	1.36	12.0	0.73	7.7	112	71
87	2.76	14.7	0.79	10.9	±21	±22
31	4.18	21.0	0.73	17.7		
74	5.59	25.6	1.18	22.7		
18	7.01	31.8	1.47	29.3		
4	14.1	51.9	1.46	49.8		
22. Zinc-4,7-Dibromo-1,10-phenanthroline						
44	1.36	14.2	0.42	9.9	80	196
37	2.76	20.6	0.71	16.8	±7	±35
31	4.18	25.8	1.08	22.5		
18	7.01	37.7	0.71	35.3		

M_i × 10 ³	[cat] × 10 ³	k_o × 10 ⁵ sec ⁻¹	σ × 10 ⁵ sec ⁻¹	k_o × 10 ⁵ sec ⁻¹	k × 10 ⁵ sec ⁻¹	K
23. Aqueous Magnesium						
10.0	10.0	5.1	0.12	3.1	8.5	93
15.0	15.0	5.7	0.27	4.2	±0.3	±10
22.5	22.5	6.3	0.24	5.2		
45.0	45.0	6.8	0.20	6.2		
75.0	75.0	7.6	0.28	7.3		
150.0	150.0	8.6	0.25	8.4		
24. Magnesium-1,10-Phenanthroline						
45.0		6.7	0.16			
75.0		7.8	0.29	<i>e</i>		

e initial concentration of dimethyloxaloacetic acid was $7.81 \times 10^{-3} M$ in every case. Metals were introduced as solutions of the salts. ^b Calculated on the assumption of an association-limited mechanism. ^c Mechanism is dissociation limited. ^d Results erratic for a meaningful calculation. ^e Compare with aqueous magnesium rates at the same catalyst concentrations.

phenanthroline-zinc catalyst is a very effective boxylating agent, but that its affinity for the boxylated product is large enough to prevent a or extensive regeneration of the catalyst. The sponding manganese catalyst would be more easily erated because of the larger size of the metal ion. ore compelling conclusion will have to await denation of the rate-determining step by the mass- ometric method.

Rate-Determining Step. In the cycle of decar- ation catalysis, any of three steps may limit the the association of the substrate and the catalyst, ecarboxylation of the complex, or the dissociation e catalyst and the decarboxylated substrate. In ystem under study, the rate-determining reaction usually be distinguished. A rate-limiting associa- will be first order in catalyst concentration and a of k_o vs. [catalyst] (or of $1/k_o$ vs. $1/[\text{catalyst}]$) will

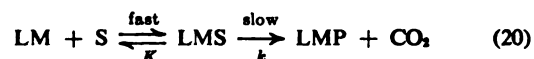


$$\text{rate} = k[LM][S] = k_{\text{obsd}}[S] \quad (18)$$

$$k_{\text{obsd}} = k[LM] \quad (19)$$

straight line going through the origin. This would when association was for some reason very un- able, for example, due to steric effects.

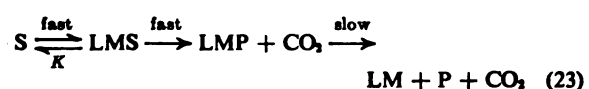
When decarboxylation is rate-determining, the graph vs. [catalyst] will be curved. This is indicated by which results from [LM] being a function of [S],



$$\text{rate} = k[LMS] = kK[LM][S] \quad (21)$$

$$k_{\text{obsd}} \neq kK[LM] \quad (22)$$

prevents eq 21 from being integrated as a first- equation in [S]. The graph of $1/k_o$ vs. $1/[\text{catalyst}]$ e a straight line with a nonzero intercept. Deriv- of the proper equation has already been dealt with. the dissociation step, which regenerates the /st, should become rate determining, a rapid l decarboxylation will occur until the catalyst is ated with decarboxylated substrate. The rate will decrease as it becomes limited by catalyst regenera-



tion. This initial fast rate would be expected to be visible when the catalyst is at a concentration which is smaller, but not a great deal smaller, than the substrate.

Caution must be exercised in the interpretation of the rate-determining step. In particular, a fast rate-determining decarboxylation will have a very small intercept on the plot of $1/k_o$ vs. $1/[\text{catalyst}]$, and may thus be confused with a rate-determining association. Generally speaking, the latter should be slow and the former fast, if an appropriate standard of "normal" speed can be found.

Rate-Determining Association. One catalyst seems to have its activity limited by the rate at which the substrate can coordinate to the metal ion: the 2,9-dimethyl-1,10-phenanthroline-manganese complex. Its rate is plotted in Figure 3 and may be seen to fit the expected pattern fairly well. The rate is slowed by steric hindrance. The methyl groups project out beyond the metal and must considerably impede the approach of the substrate to the metal. The reaction is kinetically well behaved. Steric and neighboring-group effects will be treated in a later paper. The intrinsic constant for this catalyst is 0.00280 sec^{-1} . This number refers to k in eq 15. It can be compared to the product kK for a reaction with a rate-determining decarboxylation step and is seen to be much smaller than the rates of other mono(phen) derivatives. Another catalyst which may be in this category is the $Mn(\text{phen})_2^{2+}$ complex (see Figure 3). Its reaction rate is also first order in catalyst. Its reactions are fast, however, and its intrinsic rate constant, assuming this mechanism, is 0.0165 sec^{-1} . It is possible that this is a case of rate-determining decarboxylation which is fast enough that the intercept of the reciprocal plot is not distinguishable from zero. These two alternatives can be decided between using the kinetic isotope approach employed by Westheimer.¹⁵

Rate-Determining Decarboxylation. The aqueous metal ions and catalysts 2, 4-6, 7, 11, 12, 14-16, 18, 21, and 22 have rate-determining decarboxylation steps. Some reciprocal plots are illustrated in Figure 4. Coordination of the enzyme protein to a metal ion causes this step to become so much faster that it is no longer rate determining.¹⁵ Thus the factors which influence the rate of this step are of particular interest in under-

(15) S. Seltzer, G. A. Hamilton, and F. H. Westheimer, *J. Am. Chem. Soc.*, **81**, 4018 (1959).

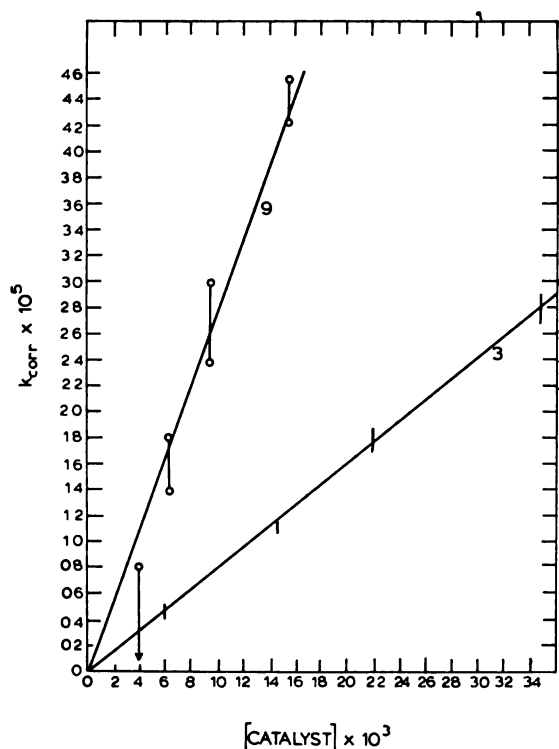


Figure 3. Catalysts conforming to the expected pattern for rate-determining association. Numbers refer to Table I. Units on the left ordinate refer to catalyst 9, and those on the right to 3.

standing the function of the protein. The intrinsic reaction constants are a disappointment in this regard because of their great sensitivity both to the exact fit of the line to the reciprocal plot and to the value chosen for the rate of the autodecarboxylation. The rate of autodecarboxylation was influenced by the addition of ligand, even when no metal ion was present. The error in this correction cannot have been large, but, in an unfavorable case, it might have made a considerable error in the intrinsic rate constants, larger than that indicated in Table I.

In examining the intrinsic rate constants for manganese, it may be seen that the Mn(phen)^{2+} catalyst has the largest k . Even the groups on the phenanthroline which are expected to be electron withdrawing, Br and Cl, seem to be slower than H. This may perhaps be explained on the basis of the high charge on the metal ion, which might polarize these groups more than it can the hydrogen and cause them to be relatively electron donating. The range for most of the constants is so great for zinc that no general statement about those catalysts is possible. The results are not readily explained.

The intrinsic equilibrium constants are smaller than the ones reported between these metals and similar β -keto acids.¹⁶ It has already been pointed out⁵ that this is a result of the difference in what is being measured. The kinetic method used here measured only coordination of the acid in the manner favorable for decarboxylation (see reaction 1), while the potentiometric method measured coordination through any atoms. The difference in the two equilibrium constants, which is about an order of magnitude, suggests that the substrate spends most of its time on the metal

(16) E. Gelles and R. W. Hay, *J. Chem. Soc.*, 3673 (1958).

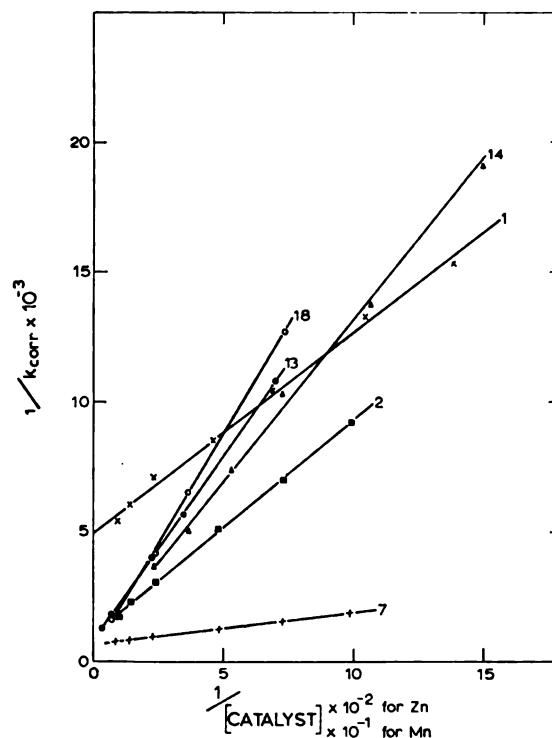


Figure 4. Some representative plots for catalysts with rate-determining decarboxylation steps. Numbers refer to Table I.

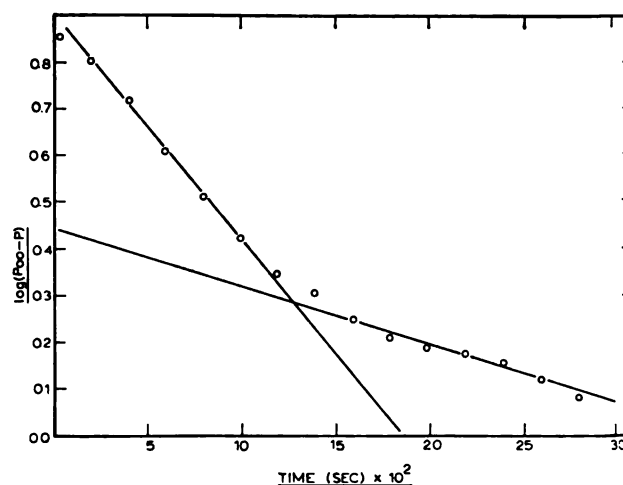


Figure 5. A kinetic run for manganese-4,7-dimethoxy-1,10-phenanthroline catalyst at a concentration of 0.00657 M . This illustrates the predicted pattern for a rate-determining dissociation step.

in a position in which it cannot be decarboxylated. If an enzyme protein were capable of causing the substrate to approach the metal only in a disposition favorable to reaction, the rate would be greatly enhanced.

Rate-Determining Dissociation. There are three mono(phen) catalysts which are much more active than any of the others. These are the 4,7-dimethoxyphenanthroline complexes of manganese and zinc and the 4,7-dimethyl complex of manganese. None of these fits either of the previous patterns of variation in rate as a function of catalyst concentration. An initial large rate, slowing as the catalyst becomes saturated

decarboxylated substrate, was observed for a number of the reactions. The effect was most pronounced where the catalyst was present to the extent of 60–80% of the substrate. Figure 5 illustrates a situation where this is occurring. Both manganese salts exhibited this behavior, but it was not observed for zinc, where the highest concentration of it was only 20% of the substrate. It may be that the initial fast reaction was over before any measurements were made. Certainly when the manganese salts were at this concentration, the fast initial part was difficult to see. The values given in Table I are for the slower part of the reaction. Initial rates were as much as five times this fast.

These complexes are the most like the enzyme, in that as they are the most efficient catalysts and apparently have the same rate-determining step. The other complexes at least do not derive their activation from the resonance effect, which does not occur for zinc and would be expected to deactivate the manganese complex.

Other Catalysts. At low concentrations, some of the complexes showed deviations from the expected patterns of behavior. The corrections for these were large relative to the rate constant itself. Their observed rates are reported in Table I, but the corrected constants are omitted. These data were not used to compute rate constants. The sodium salt of the sulfonated phenyl-1,10-phenanthroline complexes gave such results that computations based on them are meaningless.

Conclusions

It has been shown that when two ligands are coordinated to a single metal ion, changes in one can affect the reaction rate of the other, even when the changes in the first are remote from the second. Coordination of a manganese ion with a phenanthroline molecule greatly increases its ability to catalyze the decarboxylation of a β -keto acid. Catalysis by zinc, however, is unaffected by coordination with phenanthroline. Substitution of the phenanthroline at the 4 and 7 positions is also shown to change the rate. The resonance effect, which allows electron density from the acid to be delocalized into the system of the metal-phenanthroline complex, is suggested as a contributing influence. A second influence, the nature of which has not yet been determined, also affects the catalytic behavior of these compounds. The inductive effect is not usefully invoked to do this. Some very effective catalysts for decarboxylation have been found, and these are activated by the second influence. The data strongly suggest that they have the same rate-determining step as the decarboxylase enzyme. The enzyme protein does not activate the metal ion in the same way as phenanthroline itself does, but the second and unidentified influence, exerted for example by the methoxy phenanthrolines, may be a contributor to the activation by the enzyme.

Acknowledgment. This research was carried out under a grant from the National Institutes of Health, GM 11989.

Preparation and Characterization of New Fluoroxy Compounds. Bis(fluoroxy)perfluoroalkanes^{1,2}

Phillip G. Thompson and Julianne H. Prager

Contribution No. 394 from the Central Research Laboratories, Minnesota Mining and Manufacturing Company, Saint Paul, Minnesota 55119. Received August 1, 1966

Abstract: The synthesis and characterization of $\text{CF}_3\text{CF}(\text{OF})_2$ and $(\text{CF}_3)_2\text{C}(\text{OF})_2$, representing the new class of geminal bisfluoroxy compounds, are reported. Their formation from $(\text{CF}_3)_2\text{C}(\text{OH})\text{ONa}$ illustrates the unique behavior of salts in direct fluorination.

We have reported³ the preparation and reactions of the monofluoroxy compounds: $\text{CF}_3\text{CF}_2\text{OF}$, $\text{CF}_3\text{CF}_2\text{OF}$, $(\text{CF}_3)_2\text{CFOF}$, $(\text{CF}_3)_2\text{COF}$, $\text{NO}_2\text{CF}_2\text{OF}$, $\text{ClCF}_2\text{CF}_2\text{OF}$, $\text{Cl}_2\text{CFCF}_2\text{OF}$, and $\text{Cl}_3\text{CF}_2\text{OF}$, as well as⁴ $\text{FC}(\text{O})\text{CF}_2\text{CF}_2\text{OF}$ and $\text{FOCF}_2\text{CF}_2\text{OF}$.

Some of the material in this paper was included in the review "Oxygen Fluorides and Hypofluorites" by P. G. Thompson at the Symposium of the Inorganic Division of the American Chemical Society, Ann Arbor, Mich., June 27, 1966. (b) In accordance with the recommendations of the American Chemical Society Committee on Nomenclature of Highly Fluorinated Molecules, the term fluoroxy is used for the OF group. This research was supported by the Advanced Research Projects Agency under Contract NOrd 18688 and was monitored by the Bureau of Chemical Warfare.

H. Prager and P. G. Thompson, *J. Am. Chem. Soc.*, **87**, 230 (1965).

H. Prager, *J. Org. Chem.*, **31**, 392 (1966).

$\text{CF}_3\text{CF}_2\text{OF}$. Cady and co-workers previously described the synthesis of CF_3OF ⁵ and several unstable acyl OF compounds.⁶ In this paper the preparation of two members of a new class of compounds, the bis(fluoroxy)perfluoroalkanes, is reported. The characterization and certain reactions of these compounds, $\text{CF}_3\text{CF}(\text{OF})_2$ and $(\text{CF}_3)_2\text{C}(\text{OF})_2$, are also presented. In addition, an improved synthesis of $\text{C}_2\text{F}_5\text{OF}$ ³ is reported.

Discussion

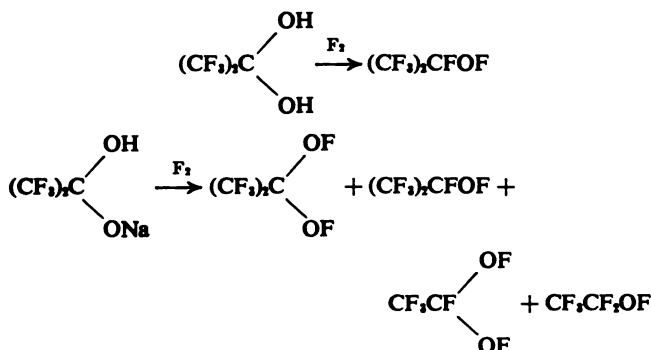
The direct fluorination of perfluoroacetone hydrate, $(\text{CF}_3)_2\text{C}(\text{OH})_2$, yields $(\text{CF}_3)_2\text{CFOF}$.³ We now report

(5) K. B. Kellogg and G. H. Cady, *J. Am. Chem. Soc.*, **70**, 3986 (1948).

(6) (a) G. H. Cady and K. B. Kellogg, *ibid.*, **75**, 2501 (1953); (b) A. Menefee and G. H. Cady, *ibid.*, **76**, 2020 (1954).

the direct fluorination of the monosodium salt of perfluoroacetone hydrate, $(\text{CF}_3)_2\text{C}(\text{OH})\text{ONa}$,⁷ to give $(\text{CF}_3)_2\text{C}(\text{OF})_2$ and $\text{CF}_3\text{CF}(\text{OF})_2$ in addition to the previously reported³ $(\text{CF}_3)_2\text{CFOF}$ and $\text{C}_2\text{F}_5\text{OF}$. The two compounds, 2,2-bis(fluoroxy)perfluoropropane and 1,1-bis(fluoroxy)perfluoroethane, represent the first examples of compounds containing two fluoroxy groups bonded to the same atom.⁸

The surprising difference in the products obtained from the direct fluorination of these two structurally similar materials illustrates the advantage of using salts to prepare fluoroxy compounds, particularly when bis-fluoroxy structures are desired.



A further demonstration of this point is found in a comparison of the fluorination products of trifluoroacetic acid and its salts.^{1,9} The acid affords rather low yields of the unstable hypofluorite, $\text{CF}_3\text{C}(\text{O})\text{OF}$,^{6a,10} whereas the salts give yields of up to 60% $\text{CF}_3\text{CF}(\text{OF})_2$. The combined yield of OF compounds obtained from the perfluoroacetate salts can approach 95% of theory.^{1,9}

It was earlier pointed out that OF-containing compounds are formed in best yield when starting materials low in C-H content are used.³ The compound $(\text{CF}_3)_2\text{COF}$, for example, is obtained in excellent yield from $(\text{CF}_3)_2\text{COH}$. The fluorination of nitrosyl perfluoroacetate, $\text{CF}_3\text{C}(\text{O})\text{ONO}$, described in this paper, gives $\text{CF}_3\text{CF}_2\text{OF}$ in approximately 20% yield, while $\text{CF}_3\text{CH}_2\text{OH}$ gives only about 10% of this product. The fluorination of a material high in C-H content, *i.e.*, $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{OC}(\text{O})\text{CCl}_3$, was shown to produce $\text{FOCF}_2\text{CF}_2\text{CF}_2\text{OF}$ only in very small amount.⁴

The direct fluorination of the monosodium salt of perfluoroacetone hydrate proceeds rapidly at room temperature. The products include CO_2 , COF_2 , and, in order of decreasing yield, the following OF-containing compounds: $(\text{CF}_3)_2\text{CFOF}$, $(\text{CF}_3)_2\text{C}(\text{OF})_2$, $\text{CF}_3\text{CF}_2\text{OF}$, and $\text{CF}_3\text{CF}(\text{OF})_2$. The combined yield of fluoroxy compounds obtained in this reaction is substantial, amounting to about 35% of the isolated product. It is interesting to note that under the conditions used in this fluorination reaction more of the three-carbon fluoroxy compounds were formed than of the two-carbon species. Although CO_2 and COF_2 were formed in rather large amounts, fluorination to CF_3OF apparently did not take place.

(7) The preparation of this compound is described for the first time in this paper. Additional reactions will be published later by J. H. Prager and P. H. Ogden.

(8) There is a marked contrast between hypofluorites containing normal fluoroxy groups and the extremely unstable, low-temperature oxygen fluoride, O_2F_2 , as discussed in ref 1.

(9) P. G. Thompson, to be published.

(10) G. L. Gard and G. H. Cady, *Inorg. Chem.*, **4**, 594 (1965).

These various fluoroxy compounds present an interesting contrast in properties. The perfluoroethylidene compound, $\text{CF}_3\text{CF}(\text{OF})_2$, is not especially susceptible to explosive decomposition, and it is considerably more stable thermally than $\text{CF}_3\text{CF}_2\text{OF}$. On the other hand, the perfluoropropylidene compound, $(\text{CF}_3)_2\text{C}(\text{OF})_2$, is very prone to explode and, in fact, is more difficult to handle than any of the other fluoroxyperfluoroalkyl compounds investigated in our laboratory. The reason for this sensitivity is not understood. It does not appear to be due to steric crowding since no such difficulties were observed with $(\text{CF}_3)_2\text{COF}$.³

The tendency of $(\text{CF}_3)_2\text{C}(\text{OF})_2$ to explode is so pronounced that a dilution technique was used in the work-up of these fluorination runs. The inert solvent, CFCl_3 , was condensed into the trap containing the mixture of volatile fluorination products, and only then was the separation of the products attempted. In general, no difficulty was experienced in isolating and purifying $\text{CF}_3\text{CF}_2\text{OF}$, $(\text{CF}_3)_2\text{CFOF}$, and $\text{CF}_3\text{CF}(\text{OF})_2$ by fractional distillation-condensation using vacuum-line techniques followed by gas chromatography. However, any operation which tended to concentrate $(\text{CF}_3)_2\text{C}(\text{OF})_2$ was found to be difficult and, in fact, many attempts were necessary before the infrared and nmr spectra of this compound were successfully obtained on the same sample. Because of this great sensitivity little information was obtained on the reactions of this material.

Results

1,1-Bis(fluoroxy)perfluoroethane, $\text{CF}_3\text{CF}(\text{OF})_2$. Isolation of pure $\text{CF}_3\text{CF}(\text{OF})_2$ was accomplished by gas chromatography. 1,1-Bis(fluoroxy)perfluoroethane is a colorless gas boiling at approximately -35° . The melting point of a sample of $\text{CF}_3\text{CF}(\text{OF})_2$ containing small amounts of SiF_4 and COF_2 was between -83 and -77° . The infrared spectrum of $\text{CF}_3\text{CF}(\text{OF})_2$ contains absorptions at 7.44 (m), 7.79 (w), 8.06 (vs), 8.30 (s), 8.73 (s), 9.24 (s), 10.83 (w), 11.17 (m), and 13.58 μ (m).¹¹ The peak at 11.17 μ is attributed to the OF group.

The diagram in Figure 1 shows the analysis of the splittings observed in the F^{19} nmr spectrum of $\text{CF}_3\text{CF}(\text{OF})_2$. The spectrum contains an absorption at $\phi^* -150.4$ which is assigned to the OF group. The CF_3 group signal is at $\phi^* 77.4$ and the CF at $\phi^* 111.9$. The coupling constant between CF_3 and CF is less than 1 cps; that between OF and CF_3 is 10.3 cps and that between OF and CF is 26.2 cps. The absorption of the CF_3 group is split into a triplet by the two equivalent OF groups; additional splitting from the CF was not resolved with our instrument (40.0 Mc). The CF signal is likewise split into a triplet by the two OF groups. The absorption of the OF groups is split into a doublet by the CF and each mode further split into a quadruplet by the three equivalent fluorine nuclei of the CF_3 group. The peak areas were found to be in the ratio of 2.0:1.0:3.0.

1,1-Bis(fluoroxy)perfluoroethane shows much greater thermal stability than fluoroxyperfluoroethane.³ Several samples, stored in sealed glass nmr tubes with

(11) The relative intensities of the absorptions are indicated by the symbols, vs, s, m, and w, standing for very strong, strong, medium, and weak, respectively.

CFCl₃, showed only minor decomposition after approximately 5 years at ambient temperatures. Differential thermal analysis indicated no decomposition up to 200°, at which temperature the sample underwent a very rapid exothermic reaction, probably exploding. In this case the CF₃CF(OF)₂ may have reacted with the metal cup in the dta apparatus; the products formed (as shown by infrared) were CF₄, COF₂, CO₂, and a trace of SiF₄. When CF₃CF(OF)₂ is flashed or ignited, quantitative analysis of the products formed indicates that thermal decomposition proceeds predominantly by



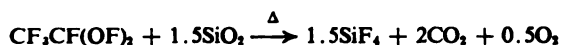
The results of additional stability tests (on rate of decomposition in glass) at elevated temperatures are given in Table I. An analysis of the products formed (SiF₄,

Table I. Thermal Stability Tests of CF₃CF(OF)₂^a

Temp, °C	Time, hr	% of CF ₃ CF(OF) ₂ recovered
150	6.5	95
175	15	70
190	12	32

^a Sealed in glass nmr tubes; 10–15 mole % solution in CFCl₃ as internal reference.

CO₂, O₂, trace of BF₃, no CF₄) indicated that the OF compound was reacting with the Pyrex glass tube



rather than undergoing thermal decomposition (expected products: CF₄, COF₂, and O₂). The activation energy for the observed reaction with glass was calculated to be 38 kcal/mole.

The polarographic half-wave potential of CF₃CF(OF)₂, measured by means of an indicating electrode vs. a saturated calomel electrode as reference, was found to be approximately 0.5 v, which is consistent with our earlier reported values³ for CF₃OF and C₂F₅OF. Since the electrochemical reduction of these OF compounds is not reversible, oxidation potentials are not readily obtainable from the polarographic half-wave potential. However, as with other OF-containing compounds, 1,1-bis(fluoroxo)perfluoroethane is strongly oxidizing toward substances such as mercury, ferrocene, potassium iodide, and sodium hydroxide.

Reduction of CF₃CF(OF)₂ has been found to occur both by (1) normal reductive defluorination with a two-electron change per OF group, and by (2) reductive decomposition wherein oxidation–reduction occurs within the molecule *via* the fragmentation of CF₃CF(OF)₂, resulting in cleavage of the carbon–carbon bond. The mechanism for reductive decomposition is apparently not so straightforward as in the case of the monofluoroxo compounds discussed previously,³ and it has not been determined whether a chain mechanism is involved.

The predominant mode of reduction appears to depend upon the effective contact of the OF compound with the reducing agent. With mercury, unless the reaction vessel is agitated, the film of mercurous fluoride hinders the reductive defluorination mode, and con-

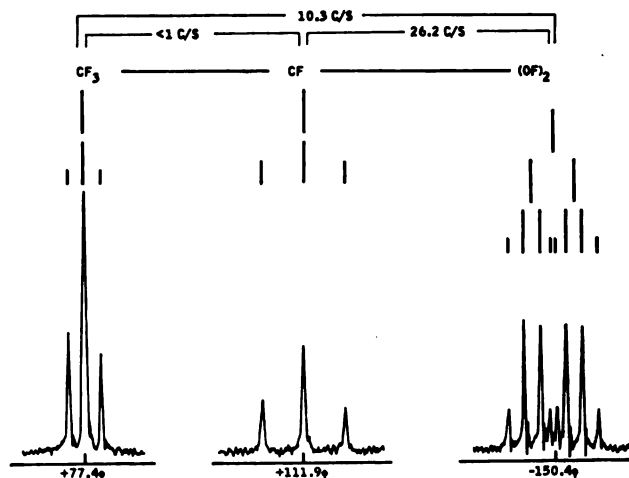
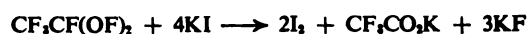


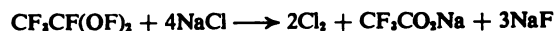
Figure 1. Nmr spectrum of CF₃CF(OF)₂.

siderable CF₄ and CO₂ are formed, together with smaller amounts of CF₃CFO, (CF₃CO₂)₂Hg, and C₂F₆. The reaction with ferrocene also proceeds predominantly by the reductive decomposition path, CF₄ and CO₂ being the principal products in addition to ferrocenium fluoride. With excess potassium iodide (in water or in acetonitrile–water media) the two-electron (per OF group) reductive defluorination mode takes place almost exclusively. The over-all reaction can be expressed by

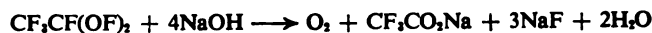


Since this oxidation of iodide to iodine occurs rapidly and without appreciable side reactions, the process can be used for a quantitative measure of the oxidizing power of the fluoroxy compound. Determination of the oxidizing power of a sample of chromatographed CF₃CF(OF)₂¹² by this reaction gave a value of 22.0 mequiv of iodine per gram of sample (calculated for two-electron change per OF group, 23.0).

An attempt to follow the mode of decomposition in an infrared gas cell equipped with NaCl windows led to the formation of considerable CF₃CO₂Na on the windows after several days. The products detected indicate that the following reaction, analogous to that above with KI, occurred.



1,1-Bis(fluoroxo)perfluoroethane reacts only very slowly with water or acidic media, but rapidly oxidizes aqueous base, liberating oxygen³ according to the following equation.



The reaction is essentially stoichiometric. Oxygen was determined by gas chromatographic analysis, fluoride by conventional thorium nitrate titration, and sodium trifluoroacetate by infrared analysis of the solids. It should be noted that the reaction between the fluoroxy compound and aqueous base is a redox reaction, also analogous to the reaction of CF₃CF(OF)₂ with aqueous potassium iodide, and does not involve

(12) A value of 21.1 mequiv of I₂/g was initially obtained; upon standing overnight a value of 22.0 mequiv of I₂/g (after possible air oxidation was corrected by a blank) was obtained. Apparently approximately 4% of the CF₃CF(OF)₂ undergoes side reactions under the conditions employed.

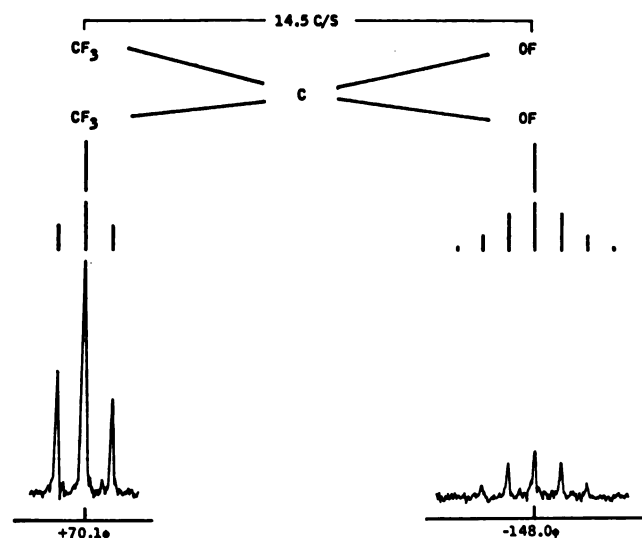


Figure 2. Nmr spectrum of $(\text{CF}_3)_2\text{C}(\text{OF})_2$.

hydrolysis. Thus, the oxygen formed in this reaction would be expected to come from the NaOH and not from the OF compound.

2,2-Bis(fluoroxy)perfluoropropane, $(\text{CF}_3)_2\text{C}(\text{OF})_2$. 2,2-Bis(fluoroxy)perfluoropropane is a colorless gas which is strongly oxidizing and shows a pronounced tendency to explode. After considerable difficulty, infrared and nmr spectra were successfully obtained on the same sample of this material. The infrared spectrum shows peaks at 7.77 (vs), 7.92 (vs), 8.14 (sh), 8.89 (s), 9.28 (s), 9.79 (s), 11.26 (m), and 13.50 μ (m).¹¹ It is interesting to observe how closely the spectrum of $(\text{CF}_3)_2\text{C}(\text{OF})_2$ resembles the spectra of $(\text{CF}_3)_2\text{CFOF}$ ⁸ and $(\text{CF}_3)_2\text{CF}_2$.¹² However, C_2F_6 shows no absorption in the 11- μ region, whereas the spectrum of $(\text{CF}_3)_2\text{CFOF}$ shows medium intensity absorption at 11.3 μ and $(\text{CF}_3)_2\text{C}(\text{OF})_2$ shows a relatively stronger absorption at 11.26 μ . Infrared spectra of fluoroxy compounds have been shown to have absorption in this region.^{8,14} Thus the infrared spectrum of this compound is reasonable for $(\text{CF}_3)_2\text{C}(\text{OF})_2$.

The F^{19} nmr spectrum (Figure 2) shows an absorption at $\phi^* -148.0$, which is assigned to the OF groups; it is split into a sevenfold peak¹⁵ by the six equivalent fluorine nuclei of the two CF_3 groups. The absorption at $\phi^* 70.1$ is a triplet assigned to the CF_3 groups. The coupling constant is 14.5 cps. The peak areas were found to be in the ratio of 1.0:3.2.

Because of the extreme tendency to explode exhibited by the samples of undiluted 2,2-bis(fluoroxy)perfluoropropane prepared in this work, additional characterization of this compound was not done. Although some may feel that the structure of 2,2-bis(fluoroxy)perfluoropropane is thus tentative, it is the opinion of the authors that the identity of this compound is firmly established on the basis of straightforward analysis of the F^{19} nmr spectrum and additionally supported by the in-

(13) D. G. Weiblen, "The Infrared Spectra of Fluorocarbons and Related Compounds," "Fluorine Chemistry," Vol. II, J. H. Simons, Ed., Academic Press Inc., New York, N. Y., 1954, p 469.

(14) P. G. Thompson, *J. Am. Chem. Soc.*, **89**, 1811 (1967).

(15) Although Figure 2 only shows five peaks which are observed with certainty for the OF absorption, subsequent spectra at higher concentrations clearly show sevenfold splitting for the OF absorption. The intensity ratio for the splittings also indicates that the pattern is sevenfold rather than fivefold.

frared spectrum, oxidizing properties, gas chromatography retention time, synthesis route, and identity of the other products formed.

It is well known that nuclear magnetic resonance spectroscopy is a very useful method for determining molecular structures. For fluoroxyperfluoroalkanes it should be noted that F^{19} nmr spectroscopy is an exceptionally definitive method. There are two features of the spectra of both mono- and bis(fluoroxy)perfluoroalkanes which make them particularly valuable for structure assignment. (1) The values of the chemical shift for the fluorine of a fluoroxy group lie within a narrow range (approximately $\phi^* -140$ to -160) and are well outside the range of most other fluorine absorptions. (2) Furthermore, the OF group as well as other types of F in fluoroxyperfluoroalkanes give unusually clear, sharp, and well-resolved spectra (although for OF compounds containing longer perfluoroalkyl chains, the resolution becomes poorer because of the many rather similar coupling constants involved). Thus, consideration of the chemical shifts together with simple first-order analysis of the fine structure caused by spin-spin interaction as well as the relative area ratios permit an unequivocal assignment of structure to the OF compound in many instances. An extensive file of nmr spectra of related compounds has aided greatly in assigning specific positions to specific groups, of course. For all fluoroxy compounds reported by us to date, additional analytical data have merely served to confirm the structure as assigned from nmr data.

Obviously, molecular weight and elemental composition data, although useful, do not distinguish between compounds having the same molecular formula. Since F^{19} nmr spectra of simple molecules such as the fluoroxyperfluoroalkanes reported by us can often yield molecular structures directly, elemental composition and molecular weight of the compound are also indirectly obtained. Moreover, nmr has the extremely valuable advantage (especially for very reactive or unstable compounds) of not requiring completely pure samples. In a number of cases, only nmr spectroscopy has allowed a definite structure determination for several new compounds having the same molecular formula.^{1a,9}

Experimental Section

General Procedures. The direct fluorination reactions were carried out by a static bed procedure similar to that described previously.⁹ Fluorine (General Chemical Division, Allied Chemical Corp., about 95% pure), diluted with nitrogen to the desired concentration (mole per cent), was passed over the sample to be fluorinated, and the volatile products were condensed in a trap at -183° from the effluent gas stream. Because fluorination reactions occasionally proceed explosively, adequate shields were provided and safety equipment was worn.

Volatile fluorination products were worked up by slightly modified standard vacuum-line techniques; contact of the fluoroxy compounds with reducing agents such as mercury and hydrocarbon vacuum grease was avoided.

Gas chromatographic analyses were carried out with a Perkin-Elmer vapor fractometer (Model 154-D), which had been equipped with 3M Co. linear-type gas sampling and backflush valves. Perfluorotributylamine¹⁶ (33% on 30-60 mesh acid-washed Celite)¹⁷ gave the best results of all the stationary phases examined. The column temperature was usually maintained at -30° . For preparative scale separations 0.5-in. diameter columns of 10-ft and 8 ft, 7-in. length were employed. Helium, dried by passing through

(16) FC-43 (3M Co.).

(17) Chromosorb P (Johns-Manville).

4A Linde Molecular Sieves cooled in liquid nitrogen, was the carrier gas at flow rates of 150 to 320 cc/min.

red spectra were obtained on a Perkin-Elmer Model 21 beam instrument with a 2.5-cm gas cell with sodium chloride windows. Fluorine nuclear magnetic resonance spectra were obtained with a Varian V-4300-2 instrument operating at 40.0 Mc. Perfluoromethane was used as an internal standard for the determination of shielding values. The shielding values are in ϕ^{19} units at dilutions of about 15–30%, negative values for $\text{CF}_3\text{CF}(\text{OF})_2$. All precision measurements (chemical shifts and spin-littings) were made according to techniques described by

Side bands were produced by amplitude modulation of the frequency²⁰ for reasons discussed previously.³

Reactions of $\text{CF}_3\text{CF}(\text{OF})_2$ have been carried out for the most part in vacuum-line techniques. The course of reactions has been determined by appropriate methods such as infrared, nmr, and mass spectroscopy, powder X-ray, gas chromatography, and P - V - T measurements, as well as conventional volumetric analyses. Elemental analyses for carbon and fluorine were conducted according to standard microcombustion procedure for highly fluorinated compounds.²¹ Differential thermal analyses were carried out using apparatus and procedures developed in these laboratories for all highly explosive, fluorine-containing compounds.²²

Precautions. It should be noted that the OF-containing compounds described in this paper are potentially hazardous, although they have been handled, with the exception of 2,2-bis-(cyano)perfluoropropane, without great difficulty. However, explosions have occurred in the course of this work, and it is recommended that suitable protective equipment²³ be used when pre-treating, or storing these compounds. No detailed toxicity studies have been carried out on these substances, but it would be advisable to avoid exposure to any OF-containing compound of the known toxicity of OF₂.²⁴

Preparation of the Monosodium Salt of Perfluoroacetone Hydrate. A 1-g (0.038 mole) of perfluoroacetone hydrate was added with enough 1 *N* NaOH to bring the pH to 8.8. The amount of NaOH (38 ml) was close to the stoichiometric equivalent. The solution was evaporated to dryness in air and then in vacuum at room temperature. The white, crystalline solid thus obtained was found to be soluble in ether.

Calcd for $\text{C}_2\text{F}_5\text{HO}_2\text{Na}$: C, 17.5; Na, 11.2. Found: C, 17.5; Na, 11.2.

Elemental analysis and infrared spectrum are consistent with the molecular formula $(\text{CF}_3)_2\text{C}(\text{OH})\text{ONa}$. Absorptions at 4.1 and 5.2 μ appear to be due to a strongly associated OH structure. The infrared spectrum shows practically no carbonyl-type absorption.

Reaction of the Monosodium Salt of Perfluoroacetone Hydrate. A 7.3 mmole sample of the sodium salt of perfluoroacetone was treated with 0.42 mole of fluorine under the following conditions: 3% fluorine, 1 hr, -20° ; 15% fluorine, 1 hr, -20° ; 50% fluorine, 4 hr, temperature gradually increased from -20°

to 20° . The residual material in the reactor was found to weigh 0.47 g. The contents of the liquid oxygen trap were worked up as follows. The noncondensable gases were removed from the trap at liquid nitrogen temperatures under vacuum, and about 0.5 ml of CFCl_3 was condensed into the trap. (This dilution technique was found to eliminate explosions during this part of the work-up.) The mixed condensate was then allowed to warm gradually and was passed at about 40 mm pressure through traps at -78° , -119° , and -196° . The -119° fraction contained $(\text{CF}_3)_2\text{CFOF}$ in major amount and $(\text{CF}_3)_2\text{C}(\text{OF})_2$, $\text{C}_2\text{F}_5\text{OF}$, and $\text{CF}_3\text{CF}(\text{OF})_2$ in smaller amounts. The -196° fraction also contained small amounts of the latter two compounds. Because of the large incidence of explosions in these runs, little reliable data regarding yields are available. In a run carried out before the dilution technique was used, a total of 4.05 mmole of volatile products was isolated from 7.3 mmole of starting material. It was estimated that 1.5 mmole or about 35% of the isolated product consisted of OF-containing compounds. A typical product distribution was estimated by means of F^{19} nmr and infrared spectroscopy to consist of approximately 20–25% $(\text{CF}_3)_2\text{CFOF}$, 5% $(\text{CF}_3)_2\text{C}(\text{OF})_2$, 5% $\text{C}_2\text{F}_5\text{OF}$, and 3% $\text{CF}_3\text{CF}(\text{OF})_2$. The major by-products were generally CO_2 and COF_2 .

Fluorination of Nitrosyl Trifluoroacetate. Nitrosyl perfluoroacetate was kindly supplied by Dr. C. W. Taylor of our Central Research Laboratories. It was prepared by treating silver perfluoroacetate with excess nitrosyl chloride.^{25,26} A 1-g (7.0 mmole) sample of this compound, contained in a stainless-steel boat in the reactor, was treated with 0.16 mole of fluorine (2%) at -15° over a 6-hr period. The trapped gases were fractionated on the vacuum line through traps at -111° and -196° . The lower boiling fraction consisted of 2.1 mmole of products, which included $\text{C}_2\text{F}_5\text{OF}$. The over-all yield of this compound was 19%. Perfluoroacetyl fluoride, COF_2 , and NO_2OF were the major by-products.

1,1-Bis(fluoroxy)perfluoroethane. 1,1-Bis(fluoroxy)perfluoroethane was purified by gas chromatography at -30° . Its retention time was found to be 92 relative to fluorotrichloromethane. It is a colorless gas with an estimated boiling point of -35° ; its melting point lies between -83° and -77° . Elemental analyses were obtained on a sample of chromatographed $\text{CF}_3\text{CF}(\text{OF})_2$. A molecular weight determination (vapor density) on this material gave a value of 164 (calculated 170).

Anal. Calcd for $\text{C}_2\text{F}_4\text{O}_2$: C, 14.1; F, 67.0. Found: C, 14.1; F, 65.5.

2,2-Bis(fluoroxy)perfluoropropane. 2,2-Bis(fluoroxy)perfluoropropane was purified by gas chromatography at -30° . Its retention time was found to be 217 relative to fluorotrichloromethane. It is a colorless gas, which is rather prone to explode.

Acknowledgments. The authors are indebted to Dr. Robert L. Bohon for data measurements, to Dr. Robert L. Rebertus for checking the stoichiometry of several reactions, and to Dr. John J. McBrady and Mr. Rudd A. Meiklejohn for their help and counsel in regard to the interpretation of the nmr spectra. We also wish to thank the Analytical Section of our Central Research Laboratories for their expert support, and Mr. Richard B. Castle and Mr. Larry A. Fletcher for their fine experimental assistance.

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We have operated without injury within a quantity limit of 1 g. 25-in. poly(methyl methacrylate) shielding and wearing heavy-duty shields, leather coats, and leather gloves. Nonflammable materials are, of course, preferred.

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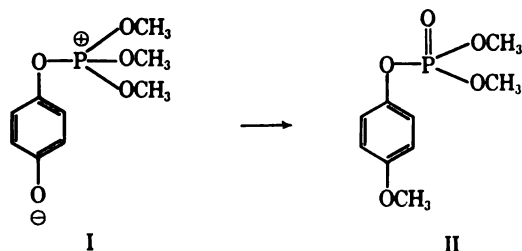
Crystal and Molecular Structures of Pentacoordinated Group V Compounds. I. 2,2,2-Triisopropoxy-4,5-(2',2''-biphenyleno)-1,3,2-dioxaphospholene. Orthorhombic^{1,2}

Walter C. Hamilton, Sam J. LaPlaca, Fausto Ramirez, and C. P. Smith

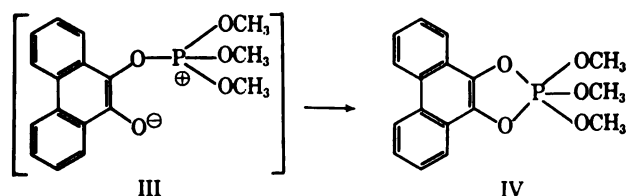
Contribution from the Departments of Chemistry, Brookhaven National Laboratory, Upton, New York 11973, and the State University of New York, Stony Brook, New York. Received December 5, 1966

Abstract: The reaction of triisopropyl phosphite with phenanthrenequinone forms a 1:1 adduct, 2,2,2-triisopropoxy-4,5-(2',2''-biphenyleno)-1,3,2-dioxaphospholene. This cyclic unsaturated pentaoxyphosphorane crystallizes in two allotropic forms. The preparation of these forms and the crystal structure of the orthorhombic form are described in this paper. The space group is *Pbca* with eight molecules in a cell of dimensions $a = 18.18 \pm 0.01$ Å, $b = 25.03 \pm 0.01$ Å, and $c = 10.14 \pm 0.01$ Å. The phosphorus atom is at the center of a PO_4 trigonal bipyramid, with two isopropoxy groups in equatorial positions and one in an apical position. The phenanthrenequinone moiety forms a bridge between one apical and one equatorial position as it forms a C_2O_2P five-membered ring. The apical P-O bond length in the ring is 1.76 ± 0.02 Å. The apical bond length to the isopropoxy group is 1.66 ± 0.02 Å. The equatorial bond lengths have an average value of 1.61 Å. The C-C bond length in the five-membered ring is considerably shorter than the corresponding bond in phenanthrene. More accurate values for the geometrical parameters were obtained for the monoclinic form, discussed in paper II of this series.

The reaction of trialkyl phosphites with *p*-quinones involves an attack by phosphorus on oxygen. The product seems to be a 1:1 dipolar adduct (I), which undergoes a very rapid alkyl group translocation to a stable alkyl ether of a *p*-quinol monoposphate (II).³

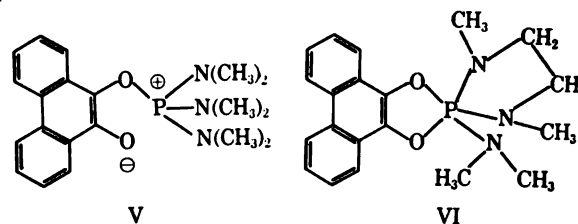


When this reaction was investigated in the series of *o*-quinones, a different and new type of structure was isolated.⁴ The product, again, was a 1:1 adduct of the phosphite and the quinone, in which the phosphorus had attacked an oxygen atom of the latter. However, no alkyl group translocation was observed in this case. The product was formulated as a cyclic unsaturated pentaoxyphosphorane (IV), a derivative of the 1,3,2-dioxaphospholene ring system.



The oxyphosphorane structure IV was originally based on the relatively large positive shift of the P^{31} nmr signal of these adducts relative to H_3PO_4 . For instance, the trimethyl phosphite adduct has $\delta P^{31} = +44.7$ ppm, and the triphenyl phosphite adduct has $\delta P^{31} = +58.7$ ppm. These positive P shifts, indicative of a rather effective shielding of the phosphorus nucleus by electrons, seem to favor the cyclic structure IV over the open-chain dipolar structure III. Moreover, the adducts are remarkably soluble in hexane and in benzene, a behavior not expected for dipolar structures like III. The infrared spectrum also favors the phospholene formulation IV.

More recently,⁵ dipolar structures like V have been made from *o*-quinones and tris(dimethylamino)phosphine; they give negative P shifts; for example, $\delta P^{31} = -38.6$ ppm for V. On the other hand, the cyclic *spiro*triaminodioxaphosphoranes (VI), made from cyclic triaminophosphines, have positive shifts; $\delta P^{31} = +29.8$ ppm.



The behavior of α -diketones, $RCOCOR$, toward tertiary phosphite esters was found to be analogous to the behavior of *o*-quinones. These results were reported by three independent groups of investigators.^{4,6,7}

(1) Research supported by the U. S. Atomic Energy Commission, by Public Health Service Research Grant CA-04769-07 from the National Cancer Institute, and by the National Science Foundation, Grant GP-3341.

(2) A preliminary account of this work is given by W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *J. Am. Chem. Soc.*, **87**, 127 (1965).

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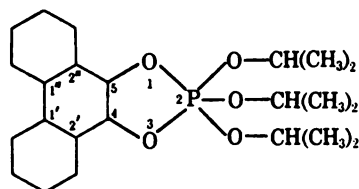
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is paper describes the initial investigation of the al and molecular structure of the adduct made phenanthrenequinone and triisopropyl phosphite, triisopropoxy-4,5-(2',2''-biphenylene)-1,3,2-dioxapholene (VII). This adduct was obtained in crystalline forms, monoclinic and orthorhombic. discuss here the crystal structure of the orthorhombic form; the preliminary results have already reported.² The following paper⁸ describes the ture of the monoclinic form and compares the



VII

e reaction of the quinone with the phosphite was d out in the absence of solvent. The reaction xothermic and the heat of the reaction raised the erature of the mixture to 120°. The melt crystal- in the monoclinic form. Recrystallization from e gave the monoclinic form if the crystallization arried out very slowly and without disturbances. : hexane solution was cooled rapidly and crystal- on was induced by scratching, the orthorhombic resulted. Both forms had the same P³¹ and H¹ spectra and the same infrared spectra in solutions. crystal data for C₂₂H₁₈O₅P, mol wt 416.45, showed e orthorhombic form probable space group Pbca: 18.18 ± 0.01 Å, b = 25.03 ± 0.01 Å, c = 10.14 ± Å, Z = 8, ρ_{X-ray} = 1.20 g cm⁻³. The monoclinic showed probable space group P2₁/c: a = 25.997 Å, b = 8.894 ± 0.001 Å, c = 9.880 ± 0.001 Å, 94.25 ± 0.01°, Z = 4, ρ_{X-ray} = 1.213 g cm⁻³.

Experimental Section

paration of the Phenanthrenequinone-Triisopropyl Phosphite adduct, 2,2,2-Triisopropoxy-4,5-(2',2''-biphenylene)-1,3,2-dioxapholene. The quinone was recrystallized from benzene, e phosphite ester was kept over sodium wire, decanted from 1 distilled with protection against moisture. isopropyl phosphite (6.5 ml, 25.5 mmoles) was added to nthrenequinone (5.3 g, 25 mmoles) at 20°. The temperature : mixture began to rise within 2 min; when it reached 37°, action became strongly exothermic and the temperature rose ° in 1 min. The resulting reddish brown thick oil became solid ; this material proved to be the *monoclinic form* of the 1:1 t. The crystals were dissolved in 20 ml of boiling hexane. ough the 1:1 adduct is pale yellow, this solution was red and ed traces of undissolved phenanthrenequinone; these of quinone can be removed by filtration, but they do not subsequent steps in the purification of the adduct. The red seems to be due to a very deeply colored complex between 1 adduct as donor and the quinone as acceptor.)

hexane solution was allowed to cool to 20°, very slowly (12 hr) ithout any disturbances. The first crop of reddish crystals , 60% of the theory) proved to be the *monoclinic form* of the t. The same monoclinic form is obtained by recrystallization monoclinic crystals, using 2 ml of hexane/g of adduct, pro- that the solution is allowed to cool to 20° very slowly as ted above. However, if cooling is rapid and if the crystal- n process is disturbed, the crystals that result have the *ortho- ic form*. It has not been possible to obtain the monoclinic is by recrystallization of the orthorhombic crystals from e by slow cooling.⁹

R. D. Spratley, W. C. Hamilton, and J. Ladell, *J. Am. Chem. Soc.*, 72 (1967).

The *monoclinic form* of the 1:1 adduct had a softening point of 97–98°, but it melted completely at 107–108° (in an open capillary tube). The *orthorhombic form*, made by dissolving monoclinic crystals in hexane and cooling rapidly while scratching the sides of the flask with a glass rod, had a sharp melting point of 107–108°. The P³¹ and the H¹ nmr spectra of both forms were indistinguishable in CCl₄ solution. The infrared spectra of both forms in CCl₄ solution were also identical.

The infrared spectrum was taken in a Perkin-Elmer Model 21 spectrometer and had the following bands (in cm⁻¹; w, weak; m, medium; s, strong; with respect to the C–H stretching at 2960 cm⁻¹ regarded as medium): 1650 (m), 1600 (w), 1505 (w), 1455 (m), 1380 (s), 1330 (w), 1170 (m), 1135 (w), 1105 (ms), 1060 (mw); 1015 (vs), 980 (m), 890 (w), 875 (w), and 865 (w).

The H¹ nmr spectrum, in CCl₄ solution, was taken at 60 Mcps. The spectrum examined at a 500-cps sweep width showed an 8 H¹ multiplet centered at τ 2.2 (aromatic H¹) (τ = shift in ppm from tetramethylsilane taken as 10); the methine H¹ gave a 3 H¹ multiplet at τ 5.40 (*vide infra*); the methyl H¹ gave an 18 H¹ doublet, J_{HCC} = 6.1 cps, centered at τ 8.75. When the spectrum was examined at a 50-cps sweep width, the methine H¹ gave a doublet, J_{HCOF} = 8.2 cps, of septets, J_{HCC} = 6.2 cps; the methyl H¹ gave a doublet, J_{HCC} = 6.2 cps, of doublets, J_{HCOF} = 0.7 cps. Examination of the methine region at 100 Mcps gave the couplings, J_{HCOF} = 8.4 and J_{HCC} = 6.4 cps; there was no indication of further fine structure and no indication of nonequivalence of the three isopropoxy groups at 30°.

The P³¹ nmr data are summarized in Table I.

Table I

Crystalline form	Solvent	δP ³¹ , ppm vs. H ₃ PO ₄
Monoclinic	Benzene	+49.2
Monoclinic	CDCl ₃	+48.6
Monoclinic	Dimethylformamide	+49.0
Monoclinic	Benzene-methanol (1:1)	+49.2
Monoclinic	Chloroform-methanol (1:9)	+49.0
Orthorhombic	CDCl ₃	+48.6

The adduct, in both crystalline forms, is sparingly soluble in methanol, but quite soluble in hexane, benzene, methylene chloride, carbon tetrachloride, and chloroform.

Anal. Calcd for C₂₂H₁₈O₅P: C, 66.4; H, 6.9; P, 7.4. Found: C, 66.0; H, 6.8; P, 7.3.

When the hexane filtrate (from which about 60% of the monoclinic form had been removed by the slow crystallization described above) was concentrated under vacuum until crystals appeared, an additional 20% of adduct resulted; this crop proved to be the orthorhombic form by X-ray examination.

Crystal Structure Determination

A sealed vial containing orthorhombic crystals was opened in a dry nitrogen atmosphere, and single crystals suitable for X-ray photography were sealed in glass capillaries with a wall thickness of 0.01 mm. The needle-like crystals were approximately 0.2 mm in diameter and 0.4 mm long. The c axis of the crystal was in each case parallel to the capillary axis. The unit cell and space group were determined from precession and Weissenberg photographs. The systematic absences, h0l for l odd, 0kl for k odd, and hk0 for h odd, are consistent with the assigned space group.

Intensities of 754 reflections were visually estimated from integrated Weissenberg photographs of the hk0, hk1, hk2, hk3, hk4, hk6, and hk7 reciprocal lattice layers.

(9) This curious behavior is undoubtedly due to the presence of seeds of the orthorhombic form being present. Clearly, there can be no difference between solutions prepared from the two crystalline forms.

Table II. Final Positional Parameters and R.m.s Displacements*

Atom	x	y	z	$\langle \delta r^2 \rangle^{1/2}$, Å
P	0.1365 (3)	0.1545 (2)	0.1462 (4)	0.43 (4)
O ₁	0.2135 (5)	0.1491 (4)	0.0671 (8)	0.44
O ₂	0.1005 (5)	0.1026 (4)	0.0485 (8)	0.45
O ₃	0.0731 (5)	0.1945 (4)	0.0958 (8)	0.45
C ₄₁	0.0096 (7)	0.1865 (6)	0.0137 (15)	0.45
C ₄₂	-0.0062 (11)	0.2448 (8)	-0.0441 (19)	0.65
C ₄₃	-0.0528 (9)	0.1639 (7)	0.0915 (17)	0.58
O ₄	0.1189 (6)	0.1161 (4)	0.2662 (8)	0.47
C ₅₁	0.1362 (9)	0.1257 (6)	0.4069 (14)	0.46
C ₅₂	0.0778 (11)	0.0926 (7)	0.4808 (13)	0.57
C ₅₃	0.2148 (10)	0.1049 (7)	0.4256 (16)	0.54
O ₅	0.1755 (6)	0.2019 (4)	0.2322 (8)	0.48
C ₆₁	0.2085 (12)	0.2513 (6)	0.1800 (15)	0.56
C ₆₂	0.2912 (11)	0.2510 (10)	0.2124 (23)	0.71
C ₆₃	0.1595 (11)	0.2963 (6)	0.2415 (15)	0.56
C ₁	0.1487 (9)	0.0837 (6)	-0.0367 (13)	0.44
C ₂	0.2112 (11)	0.1054 (6)	-0.0310 (14)	0.46
C ₃	0.2774 (9)	0.0982 (7)	-0.1109 (15)	0.47
C ₄	0.3454 (9)	0.1270 (6)	-0.1029 (13)	0.45
C ₅	0.4009 (11)	0.1156 (9)	-0.1889 (21)	0.64
C ₆	0.3973 (15)	0.0763 (11)	-0.2801 (25)	0.76
C ₇	0.3323 (15)	0.0456 (9)	-0.2954 (17)	0.69
C ₈	0.2684 (12)	0.0557 (7)	-0.2088 (17)	0.56
C ₉	0.2005 (11)	0.0299 (6)	-0.2150 (12)	0.53
C ₁₀	0.1823 (11)	-0.0159 (8)	-0.3069 (15)	0.56
C ₁₁	0.1096 (11)	-0.0354 (7)	-0.3063 (18)	0.57
C ₁₂	0.0511 (11)	-0.0244 (7)	-0.2255 (15)	0.58
C ₁₃	0.0685 (10)	0.0180 (6)	-0.1332 (14)	0.52
C ₁₄	0.1390 (11)	0.0402 (6)	-0.1340 (13)	0.47

* Standard deviations for x, y, and z are those obtained from the least-squares analysis as described in the text and are indicated in parentheses in terms of the least significant figure in the parameter value. The atoms are identified in Figure 1.

Structure factors were derived in the usual way by application of Lorentz and polarization factors. No absorption correction was applied; the linear absorption coefficient for Cu K α radiation is 12.96 cm⁻¹. The structure was solved by location of the phosphorus atom from a three-dimensional Patterson function and by a series of difference electron density syntheses. No attempt was made to locate the hydrogen atoms.

A separate isotropic temperature factor was applied to each atom, and a series of least-squares refinements reduced the value of

$$R = \frac{\sum |F_o| - |F_c|}{\sum |F_o|}$$

to 0.13. We had hoped for better agreement at this stage of the refinement. This fact together with the fact that the estimated errors of the bond lengths in the phenanthrene ring were rather large led us to collect a complete new set of data, this time using a scintillation counter and a 2θ - θ -scan technique with the crystal mounted on a General Electric single crystal orienter.¹⁰ Nickel-filtered Cu K α radiation was again used. Refinement of the structure based on this data set resulted in parameter values substantially the same as those obtained previously and an agreement factor R which was no better. It now seemed probable that the lack of agreement at this stage was due to the fact that the relatively large thermal motions were not being accounted for properly by the individual isotropic temperature factors. The final series of refinements was

(10) T. Furnas, "Single Crystal Orienter Instruction Manual," General Electric Co., Milwaukee, Wis., 1966.

Table III. Observed (FO) and Calculated (FC) Structure Factors in Electrons for Orthorhombic Crystals (all values have been multiplied by 10)

h	k	l	FO	FC	h	k	l	FO	FC	h	k	l	FO	FC	h	k	l	FO	FC	h	k	l	FO	FC
0	0	0	15000	2	4	5	370	395	0	4	2	629	391	2	0	0	991	948	0	0	4	334	397	
0	0	1	1637	2	4	6	101	102	0	4	2	235	141	2	0	0	330	330	0	0	4	134	107	
0	0	2	502	2	4	7	1510	1406	0	4	2	507	733	0	0	0	363	313	0	0	10	1	207	
0	0	3	107	2	4	8	1070	936	0	4	2	801	634	0	0	0	276	266	0	0	10	0	872	
0	0	4	927	2	4	9	1070	936	0	4	2	801	634	0	0	0	276	266	0	0	10	0	872	
0	0	5	1040	2	4	10	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	6	1279	2	4	11	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	7	2	2	4	12	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	8	2	2	4	13	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	9	2	2	4	14	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	10	2	2	4	15	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	11	2	2	4	16	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	12	2	2	4	17	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	13	2	2	4	18	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	14	2	2	4	19	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	15	2	2	4	20	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	16	2	2	4	21	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	17	2	2	4	22	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	18	2	2	4	23	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	19	2	2	4	24	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	20	2	2	4	25	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	21	2	2	4	26	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	22	2	2	4	27	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	23	2	2	4	28	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	24	2	2	4	29	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	25	2	2	4	30	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	26	2	2	4	31	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	27	2	2	4	32	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	28	2	2	4	33	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	29	2	2	4	34	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	30	2	2	4	35	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	31	2	2	4	36	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	32	2	2	4	37	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	33	2	2	4	38	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	34	2	2	4	39	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	35	2	2	4	40	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	36	2	2	4	41	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	37	2	2	4	42	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	38	2	2	4	43	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	39	2	2	4	44	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	40	2	2	4	45	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	41	2	2	4	46	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	42	2	2	4	47	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	43	2	2	4	48	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	44	2	2	4	49	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	45	2	2	4	50	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	46	2	2	4	51	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	47	2	2	4	52	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	48	2	2	4	53	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	49	2	2	4	54	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	50	2	2	4	55	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	51	2	2	4	56	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	52	2	2	4	57	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	53	2	2	4	58	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	54	2	2	4	59	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	55	2	2	4	60	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	56	2	2	4	61	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	57	2	2	4	62	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	58	2	2	4	63	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	59	2	2	4	64	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	60	2	2	4	65	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	61	2	2	4	66	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	62	2	2	4	67	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	63	2	2	4	68	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	64	2	2	4	69	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	65	2	2	4	70	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	66	2	2	4	71	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	67	2	2	4	72	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	68	2	2	4	73	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	69	2	2	4	74	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	70	2	2	4	75	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	71	2	2	4	76	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	72	2	2	4	77	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0	73	2	2	4	78	973	793	0	4	2	181	220	0	0	0	938	950	0	0	11	1	246	
0	0																							

Table IV. Some Bond Distances in Angstroms and Angles in Degrees in Orthorhombic Phenanthrenequinone-Triisopropylphosphite*

Bond		Angle		Bond		Angle	
PO ₅ Trigonal Bipyramid				Five-Membered Ring			
P-O ₁	1.76	O ₁ -P-O ₂	89	C ₁ -O ₁	1.32	C ₁ -O ₁ -P	113
P-O ₂	1.62	O ₂ -P-O ₃	87	C ₂ -O ₂	1.48	C ₂ -O ₂ -P	112
P-O ₃	1.63	O ₁ -P-O ₃	85	C ₁ -C ₂	1.26	O ₂ -C ₂ -C ₁	112
P-O ₄	1.60	O ₃ -P-O ₄	97	P-O ₁	1.76	O ₁ -C ₁ -C ₂	114
P-O ₅	1.58	O ₁ -P-O ₄	91	P-O ₂	1.62	O ₁ -P-O ₂	89
		O ₄ -P-O ₃	92				
		O ₂ -P-O ₅	120				
		O ₃ -P-O ₄	121				
		O ₅ -P-O ₃	119				
Phenanthrene Ring							
C ₁ -C ₂ , 1.26 (σ = 0.04); mean of 15 other C-C, 1.42 (σ = 0.05); C-C-C angles, 109-132; mean, 120 (σ = 6)							
Isopropoxy Groups (Mean Values)							
O-C 1.47 (σ = 0.02)				P-O-C 128 (σ = 3)			
C-C 1.54 (σ = 0.04)				O-C-C 106 (σ = 3)			
				C-C-C 115 (σ = 2)			

* These values are not as accurate as those for the monoclinic allotrope.⁸ The standard deviations of P-O, O-C, and C-C distances are about 0.02, 0.03, and 0.04 Å, respectively. The standard deviations of the bond angles range from 1° for O-P-O angles to 5° for some of C-C-C angles. The atoms are labeled as in Figure 1.

factors, one for each of the Weissenberg layers and one for the counter data, were also included as parameters in the least-squares refinements. The least-squares refinement was carried out on the structure amplitudes, with the counter data being weighted by $w = (\sigma^2 + 0.0025F^2)^{-1}$, where σ^2 is the estimated variance of F based on the Poisson counting statistics, and the visual photographic data by $w = (0.01F^2)^{-1}$, except that reflections with intensities lying below a preassigned minimum value were given constant weight. As the least-squares program used did not permit simultaneous refinement of the 269 parameters, the final refinement consisted of alternating cycles of refinement of partial parameter sets as shown in tabular form below.

Cycle	Parameters refined
N-3	Scale and 14 atoms in phenanthrene ring
N-2	15 other atoms
N-1	3 × 29 position parameters
N	6 × 29 thermal parameters

The value of R had converged at this point to 0.088 for calculated structure amplitudes based on the positional parameters in Table II and the anisotropic thermal parameters which are not quoted. The standard deviations are those estimated by the usual methods from the least-squares refinements on cycles N and N-1. These will be underestimates of the marginal standard deviations if there is any correlation between the two parameter sets refined as blocks.

A final difference Fourier synthesis, $\rho_{\text{obsd}} - \rho_{\text{calcd}}$, was calculated. The maximum electron density in this synthesis was 0.463 e Å⁻³, indicating that no atoms other than hydrogen remain to be located.

The observed and calculated structure factors are presented in Table III.

Description of the Molecular Structure

Interesting interatomic distances and angles are presented in Table IV. These are not as accurate as those for the monoclinic form,⁸ to which reference should be made for definitive bond lengths.

As shown in Figure 1, the phosphorus atom lies at the center of a trigonal bipyramid of the five oxygen

atoms which are covalently bound to the phosphorus. The distortions from the ideal O-P-O angles of 90 and 120° are slight. Two of the isopropoxy groups are bound to the phosphorus in equatorial positions and one in an apical position. The phenanthrenequinone

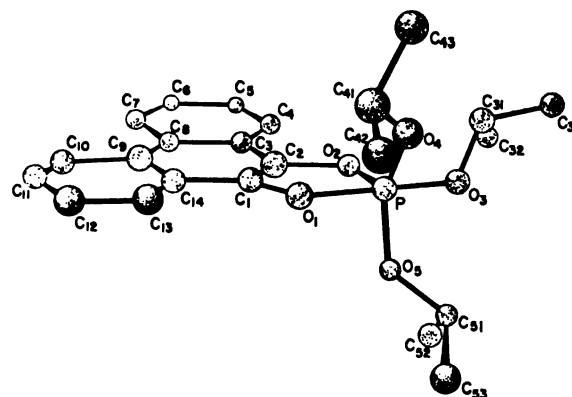


Figure 1. Molecular structure of orthorhombic phenanthrenequinone-triisopropyl phosphite 1:1 adduct.

thus forms with the phosphorus a five-membered ring which bridges the remaining equatorial and apical positions.¹¹ The bonding in this compound is discussed in the following paper.⁸ We remark here only that the apical bonds are lengthened relative to the equatorial bonds, as is typical of pentacoordinated phosphorus compounds, and that, further, the bonds to the phenanthrene ring are longer than equivalent bonds to the isopropoxy groups.

The phenanthrene ring, the phosphorus atom, and three of the oxygen atoms lie within 0.07 Å of the plane

$$5.904x - 16.753y + 6.7784z = -0.7855$$

where x , y , and z are the fractional coordinates of the atoms in question.

(11) In a discussion of the possible geometries of the transition states in the acid-catalyzed hydrolysis of ethylene hydrogen phosphate, and in the exchange of oxygen between the latter and the water solvent, P. C. Haake and F. H. Westheimer (*J. Am. Chem. Soc.*, **83**, 1102 (1961)) suggested structures in which the five-membered ring is in an apical-equatorial position, found here.

The large amplitudes of thermal motion and the size of the molecule with the attendant complexity of possible vibrations, librations, and other motions would make any detailed discussion of the thermal motion somewhat pretentious. Since the accuracy of these parameters is quite low, we have not quoted the individual values but have given only the root-mean-square displacements in Table II. There are significant anisotropies, and the amplitudes of motion are in general larger as the distance from the P atom increases.

The intermolecular packing is apparently determined entirely by interactions between carbon atoms or the hydrogens attached to them. There are six independent distances less than 4.0 Å between carbon atoms of phenanthrene groups in adjacent molecules: 3.55, 3.73, 3.77, 3.78, 3.79, 3.87. There are two such distances between carbon atoms of isopropyl groups: 3.86, 3.90. The remaining eleven distances are between phenanthrene carbon and isopropyl carbon:

3.50, 3.72, 3.72, 3.75, 3.75, 3.76, 3.89, 3.89, 3.94, 3.95, 3.97. There is nothing singular to be noted about these distances. Any detailed discussion of the intermolecular forces would require knowledge of the hydrogen-atom positions—which were not determined.

The intramolecular nonbonded distances are normal except for the four short distances between oxygen atoms and the central carbon atom of neighboring isopropyl groups. These are (in Å) O₂-C₃₁, 2.804; O₁-C₄₁, 2.695; O₄-C₃₁, 2.960; O₅-C₅₁, 2.700. This represents what must be an extreme overcrowding of the molecule, a factor which perhaps explains the relative instability of these kinds of molecules and perhaps the advantage derived from having a five-membered ring involving two of the oxygen atoms which may minimize such interactions. Intramolecular overcrowding might be, at least partially, responsible for the differences in molecular structure observed among adducts of phenanthrenequinone with tris(dialkylamino)phosphines, for example, V and VI.

Crystal and Molecular Structures of Pentacoordinated Group V Compounds. II. 2,2,2-Triisopropoxy-4,5-(2',2''-biphenyleno)-1,3,2-dioxaphospholene. Monoclinic^{1a}

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Contribution from the Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973, and Philips Laboratories, Briarcliff Manor, New York. Received December 5, 1966

Abstract: The crystal and molecular structures of the monoclinic allotrope of the phenanthrenequinone-triisopropyl phosphite 1:1 adduct have been determined by single crystal X-ray diffraction techniques. The space group is P2₁/c with four molecules in a unit cell of dimensions $a = 25.997 \pm 0.001$ Å, $b = 8.894 \pm 0.001$ Å, $c = 9.880 \pm 0.001$ Å, and $\beta = 94.25 \pm 0.01^\circ$. The final R factor for 2183 independent reflections is 0.109. The molecular structure is a trigonal bipyramid of oxygen atoms around the phosphorus with two isopropoxy groups in equatorial positions and one in an apical position. The phenanthrenequinone moiety bridges one apical and one equatorial position, thereby forming a C₂O₂P five-membered ring. The apical P-O bonds show the lengthening (relative to the equatorial bonds) commonly observed in PX₅ structures. In addition, P-O bonds in the five-membered ring are further lengthened, an effect that can be attributed to molecular π bonding.

A preliminary account of the molecular and crystal structures of the phenanthrenequinone-triisopropyl phosphite 1:1 adduct (PQTP), orthorhombic form, has been given.² A fuller account of this work including details of the preparative chemistry is in paper I of this series.³ This paper reports the results of a single crystal X-ray investigation of a second crystal modification of this species. Although the work reported in paper I established the molecular geometry in the compound beyond any doubt, the present study has resulted in bond lengths of much greater accuracy. The crystal data show a monoclinic form of probable space group P2₁/c; $a = 25.997 \pm 0.001$ Å, $b = 8.894 \pm 0.001$ Å, $c = 9.880 \pm 0.001$ Å, $\beta = 94.25 \pm 0.01^\circ$, $\rho_{X\text{-ray}} = 1.213$ g cm⁻³.

(1) (a) This work supported in part by the U. S. Atomic Energy Commission; (b) Brookhaven National Laboratory; (c) Philips Laboratories.

(2) W. C. Hamilton, S. J. LaPlaca, and C. P. Smith, *J. Am. Chem. Soc.*, **87**, 127 (1965).

(3) Paper I: W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *ibid.*, **89**, 2268 (1967).

Experimental Section

A suitable crystal prepared as described in I was ground into a sphere of diameter 0.432 mm and mounted in a Lindemann glass capillary; the intensities of 2817 reflections were measured on the automatic single crystal X-ray diffractometer FAIRRED⁴ using monochromatized copper K α radiation. The following reciprocal lattice layers were investigated: $hk0$, $hk1$, $hk2$, $hk3$, $hk4$, $hk5$, $hk6$, $hk7$, $0kl$, $2kl$, $3kl$, $4kl$, and $5kl$. Structure factors were derived in the usual way by application of Lorentz and polarization factors and an absorption correction. The absorption correction was calculated by the expression

$$A = K_0 + K_1\theta + K_2\theta^2 + K_3\theta^3$$

where the expansion coefficients K_i were obtained from a least-squares fit to values tabulated for a spherical specimen.⁵ The observed intensities were placed on approximate absolute scales by Wilson's method⁶ and the resulting 14 scale factors reduced to a

(4) See, for example, J. Ladell, *Trans. Am. Cryst. Assoc.*, **1**, 86 (1965).

(5) "International Tables for X-Ray Crystallography," Vol. II, The Kynoch Press, Birmingham, 1959.

(6) A. J. C. Wilson, *Nature*, **150**, 152 (1942).

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Anisotropic temperature factors for each atom and a single scale factor were used in a series of least-squares refinements. The data were first weighted by the function

$$w = (\sigma^2 + 0.0009F^2)^{-1}$$

Table II. Positional and Thermal Parameters* in Monoclinic PQTIP

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	0.35646 (7)	0.17295 (18)	0.27456 (18)	0.00119 (3)	0.0092 (2)	0.0063 (2)	0.0005 (1)	0.0006 (1)	0.0004 (2)
O ₁	0.40686 (19)	0.0783 (5)	0.2040 (5)	0.0014 (1)	0.0105 (6)	0.0063 (5)	0.0006 (2)	0.0006 (2)	0.0017 (5)
O ₂	0.37326 (19)	0.0948 (5)	0.4202 (5)	0.0017 (1)	0.0111 (6)	0.0070 (6)	0.0016 (2)	0.0009 (2)	0.0008 (5)
O ₃	0.31302 (18)	0.2690 (5)	0.3486 (5)	0.0013 (1)	0.0113 (6)	0.0111 (6)	0.0006 (2)	0.0015 (2)	-0.0002 (5)
O ₄	0.31346 (18)	0.0904 (6)	0.1800 (5)	0.0011 (1)	0.0146 (7)	0.0092 (6)	0.0003 (2)	0.0000 (2)	-0.0021 (5)
O ₅	0.38136 (18)	0.3181 (5)	0.2165 (5)	0.0016 (1)	0.0084 (6)	0.0116 (7)	0.0004 (2)	0.0008 (2)	0.0018 (5)
C ₁	0.4306 (3)	-0.0185 (7)	0.2923 (7)	0.0013 (1)	0.0094 (8)	0.0069 (8)	0.0003 (3)	0.0008 (3)	0.0005 (6)
C ₂	0.4138 (3)	-0.0128 (7)	0.4161 (7)	0.0013 (1)	0.0100 (9)	0.0073 (8)	-0.0002 (3)	0.0010 (3)	-0.0009 (7)
C ₃	0.4313 (3)	-0.1002 (7)	0.5278 (7)	0.0013 (1)	0.0106 (8)	0.0062 (8)	-0.0010 (3)	0.0003 (3)	-0.0013 (7)
C ₄	0.4109 (3)	-0.910 (9)	0.6574 (8)	0.0019 (1)	0.0143 (11)	0.0069 (8)	-0.0011 (3)	0.0003 (3)	0.0018 (8)
C ₅	0.4301 (4)	-0.1830 (9)	0.7603 (8)	0.0022 (2)	0.0162 (12)	0.0084 (9)	-0.0005 (4)	0.0005 (3)	-0.0000 (9)
C ₆	0.4707 (4)	-0.2810 (10)	0.7376 (9)	0.0022 (2)	0.0179 (14)	0.0122 (12)	-0.0011 (4)	-0.0007 (4)	0.0045 (10)
C ₇	0.4916 (3)	-0.2916 (9)	0.6148 (8)	0.0020 (1)	0.0145 (11)	0.0092 (10)	-0.0002 (3)	0.0001 (3)	0.0020 (8)
C ₈	0.4729 (3)	-0.2015 (7)	0.5054 (7)	0.0016 (1)	0.0100 (9)	0.0078 (8)	-0.0003 (3)	-0.0000 (3)	0.0008 (7)
C ₉	0.4935 (3)	-0.2084 (7)	0.3717 (7)	0.0014 (1)	0.0089 (8)	0.0083 (8)	-0.0001 (3)	0.0001 (3)	-0.0014 (7)
C ₁₀	0.5351 (3)	-0.3009 (8)	0.3436 (9)	0.0019 (1)	0.0111 (10)	0.0141 (12)	0.0007 (3)	0.0007 (4)	0.0015 (9)
C ₁₁	0.5519 (3)	-0.3105 (9)	0.2151 (10)	0.0022 (2)	0.0150 (13)	0.0146 (12)	0.0016 (4)	0.0033 (4)	0.0008 (10)
C ₁₂	0.5300 (3)	-0.2262 (9)	0.1085 (9)	0.0020 (2)	0.0139 (11)	0.0128 (11)	0.0001 (4)	0.0010 (4)	-0.0003 (10)
C ₁₃	0.4879 (3)	-0.1300 (8)	0.1315 (8)	0.0015 (1)	0.0110 (9)	0.0101 (9)	-0.0001 (3)	0.0016 (3)	0.0006 (7)
C ₁₄	0.4714 (3)	-0.1202 (7)	0.2618 (7)	0.0010 (1)	0.0098 (8)	0.0069 (8)	-0.0007 (2)	0.0006 (3)	-0.0001 (6)
C ₁₅	0.2741 (3)	0.1953 (9)	0.4245 (8)	0.0017 (1)	0.0166 (13)	0.0103 (10)	0.0010 (3)	0.0018 (3)	0.0026 (9)
C ₁₆	0.2820 (5)	0.2418 (14)	0.5717 (10)	0.0033 (2)	0.0272 (20)	0.0113 (12)	0.0028 (6)	0.0026 (5)	0.0013 (13)
C ₁₇	0.2221 (4)	0.2414 (17)	0.3596 (14)	0.0015 (2)	0.0388 (26)	0.0277 (22)	0.0030 (6)	0.0027 (5)	0.0113 (22)
C ₁₈	0.3185 (3)	-0.0212 (8)	0.0737 (8)	0.0019 (2)	0.0124 (10)	0.0103 (10)	-0.0005 (3)	0.0004 (3)	-0.0043 (8)
C ₁₉	0.2678 (5)	-0.1067 (15)	0.0640 (12)	0.0024 (2)	0.0319 (23)	0.0199 (17)	-0.0047 (6)	0.0011 (5)	-0.0094 (17)
C ₂₀	0.3300 (4)	0.0588 (12)	-0.0580 (9)	0.0028 (2)	0.0262 (19)	0.0095 (11)	-0.0000 (5)	0.0022 (4)	-0.0019 (12)
C ₂₁	0.3592 (3)	0.4709 (8)	0.2069 (9)	0.0021 (2)	0.0088 (9)	0.0144 (12)	0.0006 (3)	0.0017 (4)	0.0015 (8)
C ₂₂	0.3757 (5)	0.5586 (11)	0.3333 (13)	0.0032 (3)	0.0138 (13)	0.0248 (20)	0.0000 (5)	-0.0003 (6)	-0.0069 (14)
C ₂₃	0.3813 (5)	0.5355 (10)	0.0774 (13)	0.0036 (3)	0.0140 (13)	0.0259 (20)	0.0019 (5)	0.0043 (6)	0.0077 (13)

* Thermal parameters are those in the expression $\exp\{-\sum_{i,j} \beta_{ij} h_i h_j\}$. Estimated standard deviations in parentheses.

where σ is the estimated variance of F^2 based on the Poisson counting statistics. An analysis of variance with the reflections sorted into intensity classes indicated that this weighting scheme still assigned too much weight to the more intense reflections. The final weighting scheme was chosen so that the mean value of



Figure 1. Molecular structure of phenanthrenequinone-triisopropyl phosphite 1:1 adduct. The numbering of the atoms corresponds to that in the tables and is not an official numbering.

$w\Delta(F^2)$ was independent of the intensity class. This weighting scheme resulted in substantially improved estimated standard deviations on the parameters and to a final value of

$$R = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|} = 0.109$$

Since the least-squares program used did not permit simultaneous refinement of the 262 parameters, the final refinement consisted of alternating cycles of refinement of partial parameter sets as shown in tabular form below.

The standard deviations on the parameters given in the next section are those estimated by the usual methods⁸ from the least-

Cycle	Parameters refined
N-3	14 atoms in phenanthrene ring (all parameters) + scale
N-2	15 other atoms (all parameters) + scale
N-1	6 × 29 thermal parameters
N	3 × 29 position parameters + scale

squares refinements on cycles N and N-1. These will be underestimates of the marginal standard deviations if there is any correlation between the two parameter sets refined as blocks. Various considerations suggested that conservative estimates of the marginal standard deviations in the derived bond lengths and angles could be taken as 1.5 times those estimated from the least-squares refinement, and the errors for the *derived* functions in the following sections include this factor of 1.5. The error estimates obtained in this way for the C-C bond lengths in the isopropoxy groups are in agreement with those obtained by considering the agreement between the six such distances which should be equal.

A final difference Fourier synthesis ($\rho_o - \rho_c$) was calculated. The maximum electron density in this synthesis was less than 0.5 \AA^{-3} , showing that only hydrogen atoms remained to be located. No serious attempt was made to determine the hydrogen positions.

The observed and calculated structure factors are given in Table I.

Description of the Structure

The final positional and thermal parameters are given in Table II with the least-squares estimates of their standard deviations. A model of the molecule is shown in Figure 1.⁹ Tables III-VI present the bond distances and angles for the monoclinic crystal. The precision and general quality of the data are better for the monoclinic form, and these should be taken in preference to those for the orthorhombic crystal as the standard values for this compound. It should be noted, however, that there are no differences between the two which the authors consider to be significant.

(8) W. C. Hamilton, "Statistics in Physical Science," The Ronald Press Co., New York, N. Y., 1964.

(9) A standard numbering system is not used. The IUC name of the compound is 2,2,2-triisopropoxy-4,5-(2',2''-biphenylene)-1,3,2-dioxaphospholene.

Trigonal Bipyramid. Distances and angles in the trigonal bipyramid are given in Table III. The phosphorus atom lies almost exactly at the center of the equatorial plane of the trigonal bipyramid composed of the five oxygen atoms covalently bound to the phosphorus. As the bond angles indicate, the distortions from ideal O-P-O angles of 90 and 120° are slight. Two of the isopropoxy groups are bound to phosphorus equatorial positions, and one is in an apical position. The P-O bond lengths show large differences which are well outside the limits of experimental error and which depend in a systematic way on the position of the bond in the trigonal bipyramid. Of the three bonds in the equatorial plane, that which is also in the five-membered ring is 0.057 Å longer than the average of the other two bond lengths. Similarly, the apical bond in the five-membered ring is longer than the other apical bond, which is in turn longer than the average length of the two equatorial bonds to isopropoxy oxygens. In short, the variation in bond lengths may be regarded as a superposition of two effects: the first, the tendency of apical bonds to be longer than equatorial bonds in pentacoordinated phosphorus compounds; and second, a lengthening of the bonds joining the phosphorus to the phenanthrene ring system. Possible explanations will be discussed in a following section.

Table III. Bond Lengths and Angles in PO₅ Trigonal Bipyramid

Bond	Bond length		Bond	Bond angle, deg
	length, Å	corrected for thermal motion, Å		
P-O ₁	1.751 (7)	1.753 (7)	O ₁ -P-O ₃	89.3 (3)
P-O ₂	1.633 (7)	1.641 (7)	O ₂ -P-O ₃	88.6 (4)
P-O ₃	1.638 (6)	1.649 (7)	O ₂ -P-O ₄	91.3 (4)
P-O ₄	1.588 (8)	1.601 (8)	O ₂ -P-O ₅	93.1 (5)
P-O ₅	1.574 (7)	1.586 (7)	O ₂ -P-O ₄	117.2 (4)
			O ₄ -P-O ₅	117.2 (4)
			O ₅ -P-O ₃	125.5 (4)

Five-Membered Ring. The phenanthrenequinone moiety bridges an apical and an equatorial position, thus forming a PO₂C₂ five-membered ring. The bond lengths and angles are summarized in Table IV. The

Table IV. Bond Lengths and Angles in C₂PO₂ Five-Membered Ring

Bond length, Å		Bond angle, deg	
P-O ₁	1.751 (7)	O ₂ -P-O ₁	89.3 (3)
P-O ₂	1.633 (7)	P-O ₁ -C ₁	111.9 (6)
O ₁ -C ₁	1.347 (11)	O ₁ -C ₁ -C ₂	113.9 (9)
O ₂ -C ₂	1.433 (12)	C ₁ -C ₂ -O ₂	110.3 (9)
C ₁ -C ₂	1.333 (14)	C ₂ -O ₂ -P	114.2 (6)

P-O bonds have been discussed. The C-C distance is short (1.33 Å), and, although a correction for thermal motion might slightly increase this apparent bond length, it seems unlikely that it is much longer than the normal C=C double-bond length of 1.33 Å. It is significantly shorter than the corresponding distance in phenanthrene itself, 1.37 Å,¹⁰ and in agreement with

(10) J. Trotter, *Acta Cryst.*, **16**, 605 (1963).

the observed rather high infrared frequency of 1650 cm⁻¹ (I). This distance was also very short in the orthorhombic crystal.

Phenanthrene Ring. Distances and angles in the phenanthrene ring are given in Table V. The variation

Table V. Bond Lengths and Angles in Phenanthrene Ring

Bond length, Å		Bond angle, deg	
C ₁ -C ₂	1.333 (14)	C ₁ -C ₃ -C ₂	126.5 (9)
C ₂ -C ₃	1.402 (15)	C ₂ -C ₃ -C ₄	115.5 (9)
C ₃ -C ₄	1.429 (16)	C ₃ -C ₄ -C ₅	120.7 (10)
C ₄ -C ₅	1.373 (16)	C ₄ -C ₅ -C ₆	119.5 (12)
C ₅ -C ₆	1.403 (19)	C ₅ -C ₆ -C ₇	119.4 (12)
C ₆ -C ₇	1.373 (18)	C ₆ -C ₇ -C ₈	122.6 (12)
C ₇ -C ₈	1.406 (15)	C ₇ -C ₈ -C ₉	120.5 (12)
C ₈ -C ₉	1.441 (15)	C ₈ -C ₉ -C ₁₀	117.4 (10)
C ₉ -C ₁₀	1.467 (15)	C ₉ -C ₁₀ -C ₁₁	119.7 (9)
C ₁₀ -C ₁₁	1.428 (14)	C ₁₀ -C ₁₁ -C ₁₂	120.8 (9)
C ₁₁ -C ₁₂	1.409 (15)	C ₁₁ -C ₁₂ -C ₁₃	116.5 (9)
C ₁₂ -C ₁₃	1.379 (15)	C ₁₂ -C ₁₃ -C ₁₄	120.9 (9)
C ₁₃ -C ₁₄	1.384 (19)	C ₁₃ -C ₁₄ -C ₁₅	116.3 (9)
C ₁₄ -C ₁₅	1.425 (19)	C ₁₄ -C ₁₅ -C ₁₆	121.4 (11)
C ₁₅ -C ₁₆	1.395 (17)	C ₁₅ -C ₁₆ -C ₁₇	122.0 (11)
C ₁₆ -C ₁₇	1.448 (15)	C ₁₆ -C ₁₇ -C ₁₈	118.9 (11)
		C ₁₇ -C ₁₈ -C ₁₉	118.7 (11)
		C ₁₈ -C ₁₉ -C ₂₀	122.5 (10)

in bond distances shows a qualitative agreement with Trotter's results; however, the large standard deviations on the bond lengths in both studies make it difficult to attach much meaning to the differences. The phenanthrene ring, the phosphorus atom, and three oxygen atoms lie nearly in a single plane. The best least-squares plane through these atoms is given by

$$16.677x + 6.4125y + 2.1108z = 7.6559$$

where x , y , and z are the fractional coordinates of the atoms. The maximum distance from this plane is 0.07 Å.

Isopropoxy Groups. Distances and angles in the isopropoxy groups are presented in Table VI and are normal.

Table VI. Bond Lengths and Angles in Isopropoxy Groups

Bond length, Å		Bond angle, deg	
C ₃₁ -O ₃	1.463 (13)	C ₃₁ -O ₃ -P	121.8 (6)
C ₃₂ -C ₃₁	1.515 (21)	C ₃₂ -C ₃₁ -O ₃	108.8 (11)
C ₃₃ -C ₃₁	1.515 (19)	C ₃₂ -C ₃₁ -O ₃	107.2 (10)
		C ₃₂ -C ₃₁ -C ₃₃	112.8 (13)
C ₄₁ -O ₄	1.461 (13)	C ₄₁ -O ₄ -P	129.9 (7)
		C ₄₂ -C ₄₁ -O ₄	105.1 (11)
C ₄₃ -C ₄₁	1.537 (19)	C ₄₂ -C ₄₁ -O ₄	109.3 (9)
C ₄₄ -C ₄₁	1.525 (18)	C ₄₂ -C ₄₁ -C ₄₃	113.6 (12)
C ₅₁ -O ₅	1.478 (12)	C ₅₁ -O ₅ -P	127.5 (7)
C ₅₂ -C ₅₁	1.511 (20)	C ₅₂ -C ₅₁ -O ₅	109.6 (10)
C ₅₃ -C ₅₁	1.556 (19)	C ₅₂ -C ₅₁ -O ₅	103.0 (9)
		C ₅₂ -C ₅₁ -C ₅₃	113.1 (13)

Thermal Motion. Root-mean-square components of the thermal motion along principal axes of the vibrational ellipsoids are presented in Table VII. The errors quoted are those estimated from the least-squares refinement. A stereo view of the molecule is shown in Figure 2 in which these ellipsoids of thermal motion

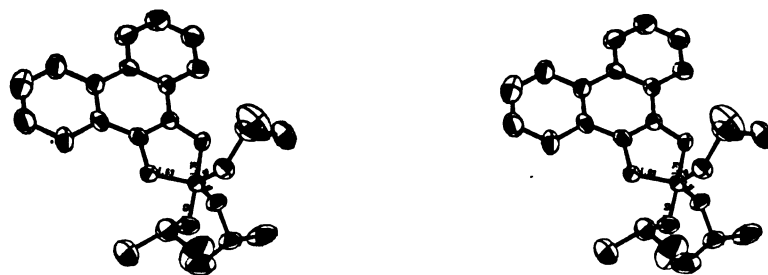


Figure 2. The molecular structure of phenanthrenequinone-triisopropyl phosphite 1:1 adduct found in the monoclinic crystal. The equiprobability ellipsoids illustrate the thermal motion of the atoms. This is a stereo pair and may be viewed by a hand-held stereoscope. Note especially the large amplitudes of vibration for the end carbons of the isopropyl groups.

can be observed. In this view, the ellipsoid boundaries are drawn at 50% probability. The increased thermal motion at the extremities of the molecule is quite obvious. The motions are undoubtedly complex, and, although the accuracy here is high, no attempt will be made to give a detailed analysis of these motions.

Molecular Packing. A comparison of the packing in the two crystalline modifications of PQTP is shown in

2.86 Å) which must represent a severe internal overcrowding of the molecule, as in the orthorhombic form.

Discussion of the Bonding

It has become well known, as observed in the present molecule, that apical bonds in pentacoordinated phosphorus compounds are longer and weaker than equatorial bonds.¹²⁻¹⁵ Qualitative molecular orbital descriptions of the bonding in these molecules have been given by several authors,^{12,15,16} and recent calculations on bonding in phosphorus chlorfluorides¹⁷ have shown these descriptions to be reasonable. The essence of the approach is to consider the X-P-X apical bonds to be formed from three p orbitals forming the type of three-center, four-electron bond that so successfully describes the bonding in interhalogen ions and rare gas halides.¹⁵ It is not necessary to invoke the use of higher energy phosphorus d orbitals. This method accounts well for the σ bonding in PQTP and will not be discussed further.

π Bonding

Cruickshank¹⁸ has used the concept of $pd-\pi$ bonding to explain observed bond lengths in tetrahedral XO_4^{n-} ions ($X = Si, P, S, Cl$). He found that X-O bond lengths were consistently shorter than those predicted for single bonds by the Schomaker-Stevenson rule.¹⁹ In the case of phosphorus compounds, he defines the following bond lengths as representative: P-O single bond (predicted), 1.76 Å; P-O(R), 1.62-1.63 Å; P-O (free PO_4^{3-}), 1.4 Å. An examination of the P-O bond lengths in PQTP suggests that, if Cruickshank's approach is justified, a considerable amount of double-bond character is present in the PO_5 group.

The ten oxygen 2p orbitals available for π bonding yield, on group-theoretical analysis assuming D_{3h} symmetry, orbitals which may be designated $a_1' + a_2'' + 2e' + 2e''$. Phosphorus 3d orbitals of suitable symmetry for interaction with these oxygen symmetry orbitals are $(d_{x^2-y^2}, d_{xy})e''$ and $(d_{xz}, d_{yz})e'$. Although these 3d orbitals are quite diffuse in the free ion,²⁰ it is conceivable that the highly electronegative oxygen

Table VII. Rms Displacements (in Å) along Principal Axes

Atom	Rmsd 1	Rmsd 2	Rmsd 3
P	0.166(3)	0.182(2)	0.216(2)
O ₁	0.164(8)	0.198(6)	0.239(6)
O ₂	0.170(8)	0.185(7)	0.272(7)
O ₃	0.171(7)	0.218(6)	0.257(7)
O ₄	0.196(7)	0.202(7)	0.254(6)
O ₅	0.175(7)	0.221(7)	0.256(7)
C ₁	0.172(13)	0.191(9)	0.228(9)
C ₂	0.167(13)	0.197(9)	0.229(9)
C ₃	0.166(11)	0.185(10)	0.241(9)
C ₄	0.175(12)	0.226(10)	0.279(10)
C ₅	0.203(12)	0.250(10)	0.281(10)
C ₆	0.212(11)	0.247(11)	0.322(12)
C ₇	0.203(11)	0.247(10)	0.267(10)
C ₈	0.189(10)	0.203(10)	0.243(9)
C ₉	0.175(10)	0.197(10)	0.236(10)
C ₁₀	0.201(10)	0.253(12)	0.275(11)
C ₁₁	0.175(13)	0.244(11)	0.339(12)
C ₁₂	0.232(11)	0.241(11)	0.274(11)
C ₁₃	0.180(12)	0.209(9)	0.264(10)
C ₁₄	0.164(11)	0.188(10)	0.218(9)
C ₁₅	0.181(12)	0.232(10)	0.295(11)
C ₁₆	0.203(11)	0.290(13)	0.387(14)
C ₁₇	0.195(12)	0.308(14)	0.456(16)
C ₁₈	0.176(11)	0.252(11)	0.272(11)
C ₁₉	0.203(14)	0.292(14)	0.426(16)
C ₂₀	0.185(15)	0.318(12)	0.330(13)
C ₂₁	0.183(10)	0.233(11)	0.302(11)
C ₂₂	0.208(12)	0.328(13)	0.376(14)
C ₂₃	0.205(12)	0.277(13)	0.428(14)

the stereo views of Figure 3 (monoclinic) and Figure 4 (orthorhombic). Both modifications exhibit alternating layers of phenanthrene rings and isopropyl groups. In the orthorhombic crystal the phenanthrene rings occur in perpendicular pairs, while in the monoclinic case the pairs are parallel with a separation between planes of about 3.5 Å (agreeing well with Pauling's estimate of the half-thickness of an aromatic molecule of 1.85 Å¹¹). There are four intramolecular nonbonded oxygen-carbon distances less than 3 Å (2.63, 2.70, 2.74,

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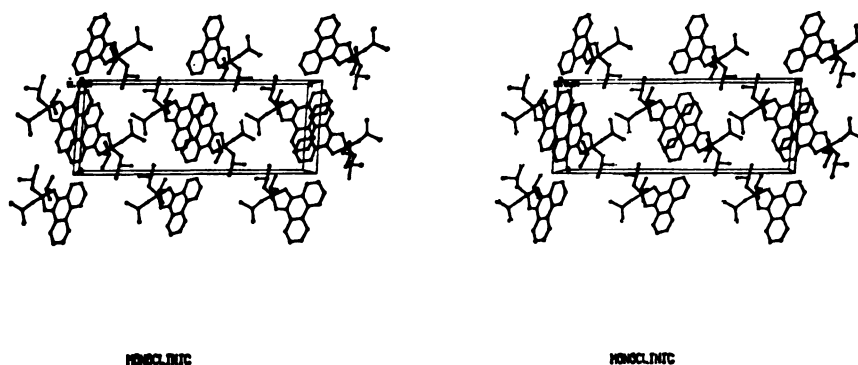


Figure 3. Stereo drawing of the packing in the monoclinic crystals. Note the planar packing of pairs of phenanthrene rings.

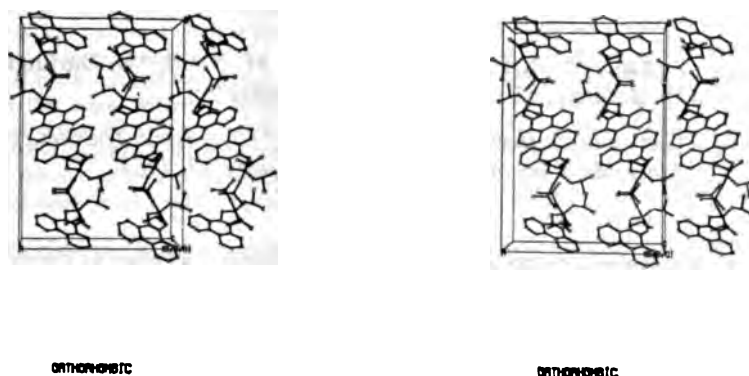


Figure 4. Stereo drawing of the packing of the orthorhombic crystals. Note that here the phenanthrene rings are nearly perpendicular at their point of closest approach. It is also interesting to observe the pronounced separation of the crystal into alternating horizontal layers of aromatic rings and isopropyl groups. The same effect exists in the monoclinic crystal, where the layers are vertical in the drawing in Figure 3.

ligands attract charge away from the phosphorus atom, causing contraction of the 3d orbitals.

The fact that the bonds to the phenanthrenequinone ring are longer than those to the isopropoxy groups in equivalent geometric positions ($\Delta r = 0.05$ Å for the equatorial bond and $\Delta r = 0.11$ Å for the apical bond) may be taken as firm evidence of P–O π – π bonding in these and similar compounds. In PQTP, there is the possibility of interaction of any PO_2 π system with that of the phenanthrene ring. The phenanthrene ring is a competitor for the π -bonding electrons of the oxygen atoms. These electrons are thus not as available for bonding to phosphorus, and the bonds to the ring thus do not show the π -bond-caused shortening, relative to the expected single bond distances, which is apparent for the isopropoxy groups. The apical bond to the ring has just the length of 1.76 Å suggested by Cruickshank for a P–O single bond. An apical single bond in a trigonal bipyramid would be expected to be somewhat longer; thus the π -bond character of this bond, although small, is not altogether zero.

Conclusions

The accurate molecular geometry of a pentacoordinated phosphorus–oxygen compound has been given. It is found that the PO_2 unit exhibits the lengthening of the apical bonds that is observed in other PX_5 species; this lengthening is due to the different character of the σ bonding. In addition, the bonds to the isopropoxy group are shortened considerably by π – π bonding between O and P. This shortening is considerably less for the bonds to the phenanthrenequinone system,

which acts as a competitor for the bonding power of the oxygen 2p π electrons.

Acknowledgments. We have profited from many valuable discussions with Professor F. Ramirez whose chemical work stimulated this investigation. The assistance of Dr. Paul Goldstein in the collection of the data is gratefully acknowledged. We thank Dr. D. F. Koenig for solving the structure by the symbolic addition method.

Appendix

Phase Determination by the Symbolic Addition Method.²¹ The symbolic addition method²² was used to determine signs of 362 structure factors. The distribution of magnitudes of quasi-normalized structure factors agreed well with the theoretical distribution for centrosymmetric structures. The signs of six reflections having E 's greater than 2.5 were designated by letters. (To permit later correlation with early stages of a parallel attempt to determine the structure by Patterson methods, the origin was not specified.) Symbolic phase determination was first restricted to the 92 reflections having E 's not less than 2.35 until 60 of the signs were determined in three cycles of an IBM 7094 program. The lower limit of E was then reduced to 2.00, and the symbolic signs of 139 of the 169 reflections were determined at the fourth cycle. Within two further cycles, signs of 362 of the 369 reflections having E 's not less than 1.60 were determined. After the fourth

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cycle, it was clear that $c = 0^\circ$ and $b = 180^\circ$. After the fifth and final cycle, it was certain that $a = d + e$. Thus only symbols d , e , and f remained and could be chosen at will to fix the origin; they were all chosen equal to 0° . The first Fourier synthesis (E map), using 367 reflections with all E 's taken as 2.0, clearly showed

23 of the 29 nonhydrogen atoms and several more probable atoms. The subsequent difference Fourier synthesis (electron density difference map) computed from these 23 atoms revealed the remaining 6 carbon atoms as well as indicating moderate shifts in the positions of the 23 input atoms.

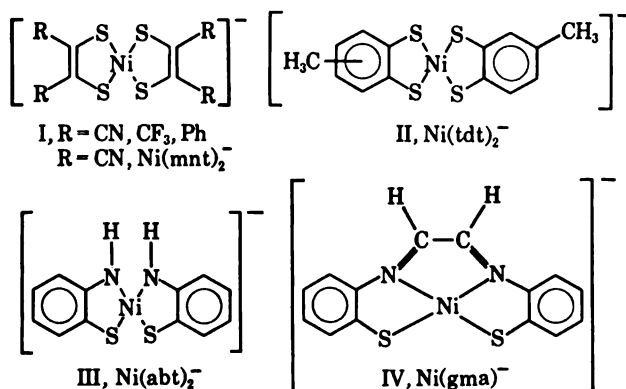
Identification of Two Reduction Products of Glyoxal Bis(2-mercaptoanil)nickel. Characterization of the One-Electron Reduction Product and the Partially Hydrogenated Anion

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Abstract: Two different paramagnetic monoanions have been previously identified as the one-electron reduction product of glyoxal bis(2-mercaptoanil)nickel, Ni(gma). These anions result from (a) the initial borohydride reduction of Ni(gma), and (b) the sodium amalgam reduction of Ni(gma). These ions differ in their physical properties. The ion resulting from (a) has a green color, with $\langle g \rangle = 2.051$, $g_1 = 2.009$, $g_2 = 2.027$, and $g_3 = 2.119$, while the ion resulting from (b) is red-brown, with $\langle g \rangle = 2.0042$, $g_1 = 1.979$, $g_2 = 2.006$, and $g_3 = 2.028$ in 2-methyltetrahydrofuran. In this communication, we demonstrate that the product from (b) is identical in its properties with the one-electron electroreduction product of Ni(gma) in dimethylformamide and, since the reduction wave is reversible, is identified as the monoanion of Ni(gma). The green anion from (a) is shown to result from hydrogen addition across the conjugated bridge and is identified as Ni(H₂gma)⁻.

The characterization of stable, square-planar nickel complexes in unusual formal oxidation states has opened an area of discussion concerning their electronic formulation.²⁻⁵ Four types of complexes have played a key role in the discussion and are shown below (I-IV).



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As an example of the problem, the paramagnetic ($S = 1/2$) Ni(mnt)₂⁻ complex has been described in two different ways: as an effectively d⁷ Ni(III) complex, [Ni^{III}(mnt)₂]⁴⁻,²⁻⁵ and as an effectively d⁸ Ni(II)-stabilized radical ligand [Ni(II) srl] system, [Ni^{II}(mnt)₂]³⁻.^{3,4}

In many cases the same polarographic and esr results have been interpreted as supporting the Ni(III) or the Ni(II) srl picture, depending on the relative emphasis placed on various details of these experiments. A particularly unfortunate controversy has arisen concerning the interpretation of polarographic and esr experiments on various reduction products of Ni(gma).^{4,5} Specifically, the borohydride⁴ and sodium amalgam⁵ reduction products are clearly different, and this has led to considerable confusion about the identity of the authentic Ni(gma)⁻ complex. We have now thoroughly characterized the monoanionic borohydride reduction product of Ni(gma) as a partially hydrogenated species designated Ni(H₂gma)⁻ (V).

On the other hand, the sodium amalgam reduction product of Ni(gma)⁵ has been shown to be the actual anion, Ni(gma)⁻. These results should give added impetus to the total resolution of the outstanding problems.

It is also our view that in a number of situations the Ni(III) and Ni(II) srl descriptions approach each other. On careful examination of the allegedly opposed formulations,^{4,5} it is apparent that there is no significant basis for controversy. Therefore, it is the purpose of this paper to present the characterization of the Ni(H₂gma)⁻

Ni(gma)^- complexes and to attempt to resolve as of the controversial electronic structural issues as e.

Experimental Section

Preparation of $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ from $(n\text{-Bu}_4\text{N})(\text{BH}_4)$ and Ni . All solvents used in this synthesis were degassed by four freeze-drying cycles on the high-vacuum line unless noted e. All operations were conducted in the drybox in a dry atmosphere. Ethanol used was USP Grade Absolute. F was dried (prior to degassing) by distilling from LiAlH_4 .

Suspended Ni(gma) , (0.8 g, 0.0024 mole) in 150 ml of THF, solution of $(n\text{-Bu}_4\text{N})(\text{BH}_4)$ (1.4 g, 0.0054 mole) in 50 ml of is added. The Ni(gma) rapidly dissolved, giving a green solution. A sample withdrawn at this stage in a flat quartz cell measurement revealed the presence of two signals. The g had $g = 2.004$, while the other had $g = 2.048$. These were observed to decay in intensity while in the spectrometer. An esr measurement was made initially before the decay was observed. Comparison with the signal intensity of a standard Ni(mnt)_2 solution revealed that the spin concentration in the sample could account only for about 6% of the Ni atoms in the solution. A second sample withdrawn from the reaction after 0.5 hr of stirring showed no trace of esr absorption.

Reaction of 1.0 g of $(n\text{-Bu}_4\text{N})\text{Br}$ in 150 ml of absolute EtOH, resulting in an immediate discharge of the green color and evolution of gas. A sample of the grayish black solution showed no esr absorption. We next bubbled a small quantity of O_2 into the solution. A brilliant green color was observed immediately and increased in intensity as more O_2 was added. Monitoring the solution with esr indicated that the formation of the green color was associated with the development of an g value with $g = 2.047$. An intensity measurement gave the number of spins in the line equivalent to $81 \pm 10\%$ of the number of spins in the reaction mixture. Addition of excess O_2 to a reaction of the reaction mixture resulted in a decrease in the intensity of the line at $g = 2.047$ and the development of a new g value $g = 2.0043$.

A microcrystalline $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ was obtained by adding the O_2 -treated mixture to about half its volume and with a large volume of n -hexane (Matheson Coleman and Bell, high purity, not degassed). The precipitate was washed with n -hexane and dried *in vacuo* over P_2O_5 . The infrared spectrum was recorded as mulls in Nujol and Fluorolube.

Acceptable analyses on samples from different preparations of $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ were obtained. The best analysis was:

Calcd for $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$: C, 62.81; H, 8.45; S, 11.18. Found: C, 62.56; H, 8.56; N, 7.25; S, 11.10.

Preparation of $(n\text{-Bu}_4\text{H})[\text{Ni}(\text{HDgma})]$ from $(n\text{-Bu}_4\text{N})(\text{BD}_4)$ and Ni .

We prepared the complex as described above, using (BD_4) instead of $(n\text{-Bu}_4\text{N})(\text{BH}_4)$. An infrared spectrum of $(n\text{-Bu}_4\text{H})[\text{Ni}(\text{HDgma})]$ as a Fluorolube mull when compared to that of $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ prepared with $(n\text{-Bu}_4\text{N})(\text{BH}_4)$ showed the absence of one of the weak C-H stretching bands (cm^{-1}) and the presence of a new band at 2130 cm^{-1} due to C-D stretching indicating the incorporation of at least one D atom into the gma structure. Neither sample showed evidence of a band attributable to an N-H stretching vibration. The sample of $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{HDgma})]$ prepared with $(n\text{-Bu}_4\text{N})$ was completely burned in O_2 , the water of combustion was collected and frozen, all volatiles were pumped off *in vacuo*, and the residue was introduced into a mass spectrometer. The ratio of peaks $\text{HOD}/\text{H}_2\text{O}$ was determined. The calculated ratio for natural abundance of D for one D atom/mole is 1 for two D atoms/mole is 0.088. Two successive determinations yielded 0.043 and 0.044, establishing unequivocally that the reaction of Ni(gma) with BD_4^- involves the incorporation of one deuterium atom per molecule of Ni(gma) .

Preparation of $(n\text{-Bu}_4\text{N})[\text{Ni(gma)}]$. All solvents were dried and degassed as described in an earlier section, and all operations were conducted in a drybox.

A sample (3.29 g, 0.01 mole) was suspended in 50 ml of THF and with 0.20 g (0.0087 g-atom) of sodium in 20 ml of Hg. The complex dissolved rapidly on shaking to form a deep red solution.

Addition of 3.22 g of $(n\text{-Bu}_4\text{N})\text{Br}$ in 100 ml of ethanol to the filtered solution gave a brown crystalline precipitate which was filtered and dried *in vacuo* over P_2O_5 . The $(n\text{-Bu}_4\text{N})[\text{Ni(gma)}]$ is extremely air sensitive and must be handled in an inert atmosphere.

Anal. Calcd for $(n\text{-Bu}_4\text{N})[\text{Ni(gma)}]$: C, 63.05; H, 8.11; N, 7.35; S, 11.22. Found: C, 61.93, 61.83; H, 7.65, 7.83; N, 7.22, 7.07; S, 11.36, 11.55.

Physical Measurements. Static susceptibility measurements on solid samples were made at room temperature by the Gouy method using $\text{Hg}[\text{Co}(\text{SCN})_4]$ as calibrant.⁶ Conductances were determined on an Industrial Instruments bridge, Model RC16B2, using a cell calibrated with 0.02 M KCl solution. Polarographic measurements were made in DMF solution with a dme in a three-electrode cell, using an electronic polarograph described elsewhere.⁷ Silver-silver perchlorate was used as the reference electrode ($\text{Ag}|\text{AgClO}_4$, 0.1 M; $(n\text{-Pr}_4\text{N})\text{ClO}_4$, 0.1 M). Solutions were approximately 10^{-3} M in complex and 10^{-1} M in $(n\text{-Pr}_4\text{N})\text{ClO}_4$. Cyclic voltammetry was employed, using a platinum indicator electrode and a $\text{Ag}|\text{AgCl}(1.0 \text{ M KCl})$ reference electrode. The same electrodes and scan rates were used for all comparative measurements. The DMF solvent for cyclic voltammetry and epr measurements was Baker Analyzed reagent, gc-spectrophotometric quality that had been fractionated under vacuum from K_2CO_3 on a spinning-band column and stored in the drybox until used. Sample preparation, cyclic voltammetry measurements, and the filling of epr sample cells were all done within the drybox. Solutions were about 10^{-1} M in $n\text{-Bu}_4\text{NClO}_4$ and 5×10^{-4} M in complex unless otherwise stated. Optical spectra were measured on a Cary Model 14 spectrophotometer in the wavelength range 350–700 m μ . ESR measurements were made on a Varian V-4502-12 spectrometer system operating at 9500 Mc/sec using 100-kc/sec field modulation. The microwave frequency was measured by means of a Hewlett-Packard Model 2590A frequency converter and Model 5245L frequency counter. The magnetic field was monitored with a proton resonance gaussmeter whose frequency was measured by the same frequency counter. g values were calculated by means of the equation⁸

$$g = 3.041997 \times 10^{-3} \nu_H / \nu_p$$

Results

The green crystalline $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ complex is a 1:1 electrolyte in nitromethane ($\Lambda = 64$). The esr spectrum of a polycrystalline sample of $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ shows three g values. The average g estimated from the polycrystalline spectrum is 2.050 ± 0.005 . The esr spectra in various carefully prepared solutions (under oxygen-free nitrogen from freshly distilled and degassed solvents), with DMF, DMSO, and THF as solvents, show g values in a small range near 2.051, with the lowest value being 2.048 ± 0.002 in THF solution. The complex has a magnetic moment of 1.95 BM in the solid state, in good agreement with the g value of 2.050 from the esr spectrum of a polycrystalline sample. In DMF- CHCl_3 , the $\text{Ni}(\text{H}_2\text{gma})^-$ ion has the following g values in the low-temperature glass:⁹ $g_1 = 2.009$, $g_2 = 2.027$, $g_3 = 2.119$. The $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ complex in DMF solution shows a reversible one-electron oxidation wave at -0.758 v and a reversible one-electron reduction wave at -1.591 v vs. $\text{Ag}|\text{AgClO}_4$. Under identical solvent and instrumental conditions, a pure sample of neutral Ni(gma) shows reversible one-electron reduction waves at -0.823 and -1.605 v . These differences in half-wave potentials for the Ni(gma) and $\text{Ni}(\text{H}_2\text{gma})^-$ systems are small, but are definitely outside of experimental error.

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The $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ complex is air sensitive (as would be expected from the polarographic results), and all operations which preserve its properties must be carried out under nitrogen. Upon exposure to air in any solvent the green color rapidly fades and a brown color develops. The compound is apparently being oxidized by air, but a pure sample of either $\text{Ni}(\text{H}_2\text{gma})$ or $\text{Ni}(\text{gma})$ could not be isolated by this route. A freshly prepared sample of analytically pure $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ was dissolved in freshly distilled THF under N_2 , giving a single strong signal at $\langle g \rangle = 2.048$. The sample was then allowed to stand in air until it appeared brownish. The signal at $\langle g \rangle = 2.048$ was still present but with greatly reduced intensity. In addition, a new and strong signal appeared at 2.004. An analogous experiment was then performed in DMF solution in the polarographic cell. After the brown color appeared, no reversible waves could be found, even when the cell was refilled with nitrogen. The nature of the reaction product with $\langle g \rangle = 2.004$ is still uncertain. This paramagnetic species is not the same as $\text{Ni}(\text{gma})^-$, resulting from the coulometric reduction of $\text{Ni}(\text{gma})$, although its $\langle g \rangle$ value is similar (*vide infra*).

Further confirmation of the identity of $\text{Ni}(\text{H}_2\text{gma})^-$ is provided by preliminary work on the crystal structure of the borohydride reduction product of dimethylglyoxal bis(2-mercaptoanil)nickel. It is found that the $\text{CH}_2\text{-C-C-CH}_2$ angles are consistent with a tetrahedral configuration around at least one of the carbon atoms in the bridge.⁹

Cyclic voltammetry measurements of $\text{Ni}(\text{gma})$ in DMF gave a one-electron reduction wave (checked by coulometry) with a peak potential of -0.322 v and an oxidation peak at -0.253 v vs. $\text{Ag}|\text{AgCl}$ on the reverse scan. The accuracy of these and subsequent values is estimated at ± 0.003 , unless otherwise stated, and was obtained as the average of two successive scans. Complete coulometric reduction of this solution was carried out at a constant potential of -0.5 v. Cyclic scans of this solution showed a reduction peak at -0.320 v and an oxidation peak at -0.250 v vs. $\text{Ag}|\text{AgCl}$. This agreement of potentials leaves little doubt that the product of this electroreduction of $\text{Ni}(\text{gma})$ is $\text{Ni}(\text{gma})^-$. Cyclic voltammetry measurements on the sodium amalgam reduction product of $\text{Ni}(\text{gma})^6$ (as the analyzed $n\text{-Bu}_4\text{N}^+$ salt) showed a reduction peak at -0.321 v and an oxidation peak at -0.250 v vs. $\text{Ag}|\text{AgCl}$ in excellent agreement with $\text{Ni}(\text{gma})$ and $\text{Ni}(\text{gma})^-$ prepared by coulometric reduction. Cyclic voltammetry of $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{H}_2\text{gma})]$ showed a reduction peak at -0.226 v and an oxidation peak at -0.146 v vs. $\text{Ag}|\text{AgCl}$. These potentials are well outside of experimental error of the $\text{Ni}(\text{gma})$ potentials, as are the polarographic half-wave potentials reported above.

The second reduction peaks of $\text{Ni}(\text{gma})$ and $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{gma})]$ (sodium amalgam reduced) were also compared by sweeping both reduction peaks in the same scan. The second reduction and oxidation peaks occurred at -1.112 and -1.031 v for $\text{Ni}(\text{gma})$, and -1.097 and -1.036 v vs. $\text{Ag}|\text{AgCl}$ for $(n\text{-Bu}_4\text{N})[\text{Ni}(\text{gma})]$. The estimated accuracy in this case is ± 0.005 v because of the larger voltage scan. These solutions were about 3×10^{-3} M in complex.

In order further to confirm the identity of the sodium amalgam reduced $\text{Ni}(\text{gma})$ and coulometrically gener-

ated $\text{Ni}(\text{gma})^-$, we have made an accurate comparison of the $\langle g \rangle$ values of the two paramagnetic ions in DMF. The coulometrically reduced $\text{Ni}(\text{gma})^-$ solution contained 0.1 M $(n\text{-Bu}_4\text{N})\text{ClO}_4$ as supporting electrolyte. In order to avoid possible ionic strength effects on $\langle g \rangle$ values, the solution of the sodium amalgam reduced salt was also made up to 0.1 M in $(n\text{-Bu}_4\text{N})\text{ClO}_4$. With samples having $\langle g \rangle$ near the free spin value, the utmost precision must be employed to use this quantity as a qualitative analytical tool. This is because the region near $\langle g \rangle = 2.0023$ is thoroughly uncharacteristic, a large number of paramagnetic systems, including almost all of those described as free radicals, falling into this region. The principal uncertainty in our determination of absolute $\langle g \rangle$ values results from the difference in magnetic field at the sample and at the proton resonance probe, which must necessarily be placed in a different region of the magnetic pole gap. In order to avoid this error, we chose to measure the difference in $\langle g \rangle$ values of the two samples. Each sample was placed in a separate Varian flat cell, and the $\langle g \rangle$ value of each determined in turn in the same rectangular microwave cavity. The locations of the cavity and proton probe were disturbed as little as possible between the pair of determinations. The magnetic field was left on during a pair of determinations to avoid the small error due to a change in the field difference between sample and proton probe locations which is known to occur if the magnetic field is disturbed.⁸ Six pairs of determinations were made over a period of 3 days. In three of these the sample cells were exchanged to avoid any possible systematic error arising from this source.

The $\langle g \rangle$ values obtained from the six determinations were 2.004025 ± 0.000012 for coulometrically reduced $\text{Ni}(\text{gma})$ and 2.004052 ± 0.000012 for sodium amalgam reduced $\text{Ni}(\text{gma})$. It should be emphasized that these $\langle g \rangle$ values are not known absolutely to the precision quoted above, since no correction has been made for the systematic field difference between sample and proton probe locations. The estimate of precision applies when the two values are compared. We conclude that we cannot distinguish between the $\langle g \rangle$ values of the two samples within the precision of the determination. An evaluation of the absolute $\langle g \rangle$ value of both samples gives $\langle g \rangle = 2.0041 \pm 0.0001$. We previously reported⁸ $\langle g \rangle = 2.0527$ for coulometrically reduced $\text{Ni}(\text{gma})$ in $\text{CHCl}_3\text{-DMF}$. We now believe that the radical generated in this experiment resulted from a reaction product of $\text{Ni}(\text{gma})$ with impurities present in DMF; the radical is possibly III or V. This result emphasizes the extreme care which must be exercised when working with these systems. Scrupulously purified DMF leads only to $\text{Ni}(\text{gma})^-$ on electroreduction, as reported above.¹⁰

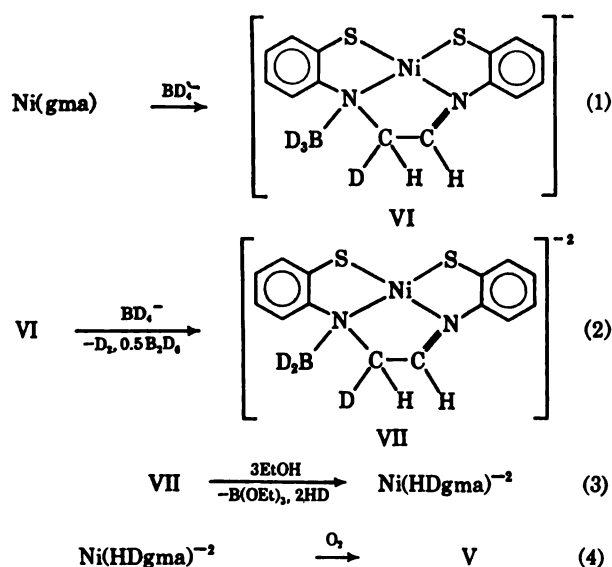
Optical absorption spectra of coulometrically reduced and sodium amalgam reduced $\text{Ni}(\text{gma})$ in DMF were identical in the observed region, $350\text{--}700$ m μ . Concentrations were about 10^{-4} M. Extinction coefficients were not measured. The main features of both spectra in this wavelength region are a strong absorption at 444 m μ which has three weak shoulders at 483 , 503 , and 539 m μ . A second, weaker absorption occurs at 589 m μ .

(10) Although $\text{Ni}(\text{gma})^-$ is stable for at least a week in scrupulously purified DMF, it undergoes decomposition within 5 days in the impure solvent leading to three new esr signals as reported in ref 5.

On the basis of the voltammetric measurements, esr, and the similarity of the optical spectra, we conclude that the sodium amalgam reduced Ni(gma) is correctly identified as Ni(gma)⁻.

Discussion

A Possible Reaction Sequence for the Synthesis of Ni(H₂gma)⁻. The data presented above show that borohydride reduction of Ni(gma) followed by treatment with a protic solvent and partial air oxidation leads to a substantial yield of the green complex designated as Ni(H₂gma)⁻, an anion in which the bridge is partially saturated. Substitution of borodeuteride in the reaction gives a product which must be formulated as Ni(HDgma)⁻. The infrared spectral evidence favors a C-D bond. A reaction sequence which is consistent with all of our observations may be formulated as shown in eq 1-4.



Ground-State Electronic Structure. One of the most interesting and desirable features to know in the mono-anionic complexes such as Ni(mnt)₂⁻ and Ni(gma)⁻ is the distribution of the unpaired electron between the metal and the ligand atoms. The Ni(II) srl and Ni(III) electronic structural formalisms imply different distributions for this unpaired electron. In the former case the unpaired electron is assumed to be in a molecular orbital of predominantly ligand composition, but metal d orbital participation is an important, if secondary, feature.^{2,4} That is, the term "Ni(II) stabilized" is meant to imply specific d orbital involvement in the appropriate molecular orbital, even though the ligands dominate in the electron distribution. The second point of view has been traditional when trying to describe the electron paramagnetic properties of "covalent" transition metal complexes. It begins from an appropriate d-orbital configuration on the metal and subsequently allows for mixing of metal and ligand orbitals of the appropriate symmetry. It is clear that properties of paramagnetic transition metal complexes

which depend upon the electron spin density near the metal atom (such as electron-metal nucleus hyperfine interaction, as well as large deviations of the *g* tensor from that of the free electron spin) are better handled from this point of view. The two viewpoints are, of course, complementary and fuse together in those complexes having roughly an equal distribution of spin density between metal and ligand orbitals.

Electron paramagnetic resonance should be of perhaps the greatest use in helping to decide matters of electron spin distribution in paramagnetic *S* = 1/2 complexes such as I-V. Particularly helpful would be the measurement of the anisotropic dipole-dipole contribution to the electron-metal nucleus hyperfine tensor. Since this property depends mostly on the ground state electron configuration, and to a much smaller extent on admixture of excited configurations through spin-orbit coupling (unless the *g* anisotropy is very large), it is most *directly* indicative of the wave function of the half-filled orbital in a molecular orbital description. The *g* tensor, on the other hand, depends not only on the ground-state configurational wave function, but on all the excited configurational wave functions and their degree of admixture by spin-orbit coupling. Measurement of the *g*-tensor is thus not as *directly useful* in leading to a quantitative description of the half-filled orbital, within the framework of existing molecular theory.

In the series of complexes under discussion, metal nucleus-electron hyperfine interaction thus far only has been measured for I, R = CN, using a sample enriched in ⁶¹Ni. The hyperfine tensor was interpreted to result from a ground-state configuration in which the half-filled *b*_{3g} orbital was approximately 50% delocalized over the ligand *π* system.^{2,11} This interpretation places Ni(mnt)₂⁻ directly in the overlap region between the two extreme descriptions (*vide supra*) of these complexes.

Care should be exercised in interpreting the *g*-tensor anisotropy in terms of the lowest energy configuration. This can be done only in the roughest, most qualitative way in this series of square-planar Ni complexes in the absence of detailed calculations and an adequate theory. Perhaps all that can be done at present is to define the behavior of the magnetic properties of the complex in the two extreme limits. In the limit of the d⁷ model, Ni(III), we would expect a metal nucleus-electron hyperfine tensor which is consistent with the value of *r*⁻³ given by a calculation on a properly self-consistent metal d orbital. In the limit of the Ni(II) srl model we would expect a very small anisotropy of the metal hyperfine tensor, as well as a *g* tensor which approaches that characteristic of the isolated ligand free radical.

Acknowledgment. We wish to thank Dr. Donald Young for mass spectral analyses. This project was partially supported by grants from the National Science Foundation (GP-3398, GP-4922, and GT623-IX).

(11) This symmetry for the half-filled orbital also has been obtained by a MO calculation: G. N. Schrauzer and V. P. Mayweg, *J. Am. Chem. Soc.*, **87**, 3585 (1965).

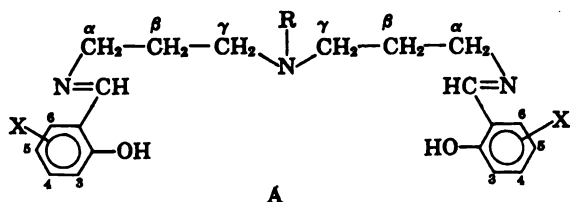
Proton Magnetic Resonance Studies of High-Spin Nickel(II) Complexes with Pentadentate Schiff Bases

Gerd N. La Mar and L. Sacconi

Contribution from the Physical Chemistry Institute, Swiss Federal Institute of Technology, Zurich, Switzerland, and Institute of General and Inorganic Chemistry, University of Florence, Florence, Italy. Received November 21, 1966

Abstract: The proton magnetic resonance spectra of two series of high-spin, five-coordinated nickel(II) complexes have been observed, where the pentadentate ligand is formed from substituted salicylaldehydes and bis(3-amino-propyl)amine or bis(3-aminopropyl)methylamine. Two sets of aromatic peaks are observed, which are interpreted as arising from the nonequivalence of the two aromatic fragments in the chelate. This extent of nonequivalence is found to depend markedly on the amino-nitrogen substituent, the solvent, and the temperature. This variable magnetic nonequivalence is related to small changes in the solution structure produced by steric effects of the amino-methyl group, with the extent of nonequivalence increasing as the structure tends toward a square pyramid with the salicylaldimine fragments bonded *cis* to each other. This tendency for these pentadentate ligands to take up a square structure with *cis* rather than *trans* aromatic rings is also evidenced for the pyridine solutions of the chelates, where some peak splitting is observed in spite of octahedral coordination. The shift patterns for the five-coordinated chelates indicate π delocalization, but other factors must be important. The shift distribution for the pyridine adducts is consistent with that of other related octahedral complexes.

Complexes of the pentadentate ligand of structure A have recently been shown¹ to produce five-coordinated 3d metal(II) complexes. Five coordination



in these high-spin nickel(II) complexes has been established^{1,2} only very recently, though some uncharacterized complexes of this ligand has been reported earlier.³ To date there are only a few documented examples of five-coordinated nickel(II).⁴⁻⁷

The five coordination has been established on the basis of absorption and reflectance spectra,¹ which are inconsistent with either octahedral or tetrahedral coordination, but closely resemble the spectra of $[5\text{-Cl-SALen}(\text{C}_2\text{H}_5)_2]_2\text{Ni}^{II}$ and $[\text{N-CH}_2\text{-SAL}]_2\text{Ni}^{II}$ in the lattice of its zinc analog, both of which have been shown to be five coordinated by X-ray analysis, the former in a distorted square pyramid⁸ and the latter in a trigonal bipyramid.⁴ The present complexes also form adducts with a single molecule of pyridine,¹ resulting in octahedral coordination, and molecular weight measurements reveal that there exist only discrete monomers in solution.

Results for a single crystal X-ray analysis on one of these complexes, NiSAL-MeDPT, carried out simul-

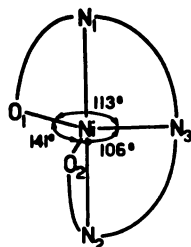
taneously with this work,² have proved five coordination, with a distorted trigonal bipyramidal arrangement of the five bonding atoms as shown in Figure 1. The great similarity of the reflectance and the solution absorption spectra indicates that the solution structure is essentially identical with that in the crystal.¹

Proton magnetic resonance studies have proved extremely useful in elucidating various magnetic and structural properties of nickel(II) complexes in solution.⁹⁻¹³ In view of the novel structure of these complexes, a pmr investigation was undertaken in order to determine what properties of the observed isotropic shifts can be related to their structure.

These complexes are fully paramagnetic,¹ $\mu_{\text{eff}} = \sim 3.34$ BM, and give no evidence of any paramagnetic \rightleftharpoons diamagnetic equilibrium in solution. Their solution pmr spectra can thus be expected to display large, isotropic resonance shifts^{9,10,14} for the protons from their position in the free ligand or diamagnetic zinc complex. Such shifts arise either from a proton-electron dipolar interaction or from the contact interaction resulting from the delocalization of unpaired spin onto the ligand.¹⁴ The character of the observed shifts can thus depend on both the magnetic anisotropy and on the type of orbital containing the unpaired electron. Such investigations for tetrahedral nickel complexes with substituted salicylaldehydes have demonstrated¹⁵ that their observed shifts originate in a contact interaction with spin in the highest filled ligand π orbital. From the temperature dependence of the shifts, the square-planar \rightleftharpoons tetrahedral solution equilib-

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X-Ray structure for coordinating atoms in NiSAL-

as characterized,¹⁵ as originally performed for oponeimines.^{9,16} More recently, pmr investigations have been extended to nickel chelates with N-tetrad salicylaldehydes, where the substituent is a site capable of bonding to the metal.^{12,13} This has resulted in a complicated mixture of in solution, either octahedral, tetrahedral, and planar¹² or octahedral, five-coordinated, and planar.¹³ The isotropic shift patterns for the NiSAL complexes differed significantly from those observed for the tetrahedral species,¹⁵ and the exact nature of the shifts is still in question, though π bonding is thought to be primarily responsible for the spin delocalization.

For the chelates giving rise to five-coordinated species in solution, as implied by their absorption spectra, the character of the observed shifts could not be directly related to the presence of the five-coordinated species, presumably because of the rapid equilibrium averaged over the shifts of the contributing species.

Reported here are the pmr spectra of two series of complexes with ligand A, where X = Cl, H, CH₃, the two differing in the R substituent. Those with R = H are designated X-NiSAL-DPT, while those with R = CH₃ are labeled X-NiSAL-MeDPT.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian A-100 spectrometer, using tetramethylsilane as internal reference. The spectra were run at 27°, unless noted otherwise. The spectra were obtained in both deuteriochloroform and pentamethylpyridine, at concentrations approximately 0.05 M, with the intensity to be concentration independent. The pmr spectra of NiSAL-DPT and NiSAL-MeDPT, and their two methyl ring-deuterated derivatives, were run over the temperature range -62 to +20°C, using a dewar probe and a liquid nitrogen cryostat described elsewhere.¹² The pmr spectra of 0.10 M CHCl₃ solutions of NiSAL-DPT and NiSAL-MeDPT were recorded as a function of added deuteriopyridine. The diamagnetic zinc complexes were run on a Varian A-100 spectrometer.¹⁷ The pmr spectra of 5-CH₃-NiSAL-MeDPT and 3-CH₃-NiSAL-MeDPT were also recorded in the following protonless or fully deuterated solvents: carbon disulfide, carbon tetrachloride, *d*₆-benzene, *d*₄-methanol, *d*₅-nitromethane, and *d*₇-acetonitrile. These chelates were only sparingly soluble in these solvents, 1 M, with the exception of CS₂. All other samples were insoluble to produce discernible spectra in more than two solvents, often in none, or produced cloudy solutions, which precipitated within a few hours. Their pmr spectra were characterized by broad, unidentifiable peaks. Only the pmr spectra reported here for which we are reasonably certain that no precipitation occurred. A few of the solutions were too dilute to give recognizable peaks on the DP-60 spectrometer and were

R. Eaton, W. D. Phillips, and D. J. Caldwell, *J. Am. Chem. Soc.* **85**, 197 (1963).
Organic Chemistry Department, Swiss Federal Institute of Technology.

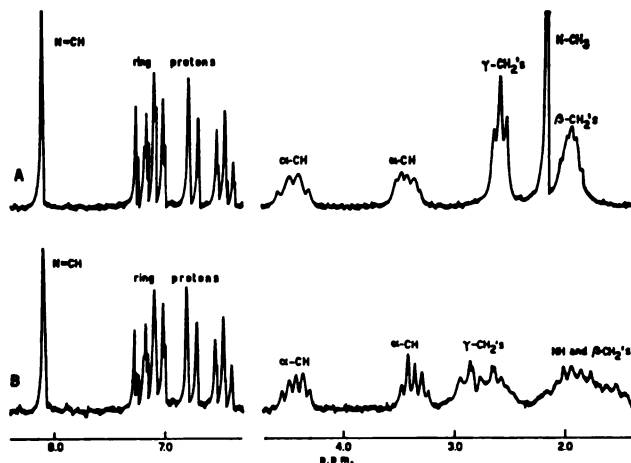


Figure 2. Pmr traces for (A) ZnSAL-MeDPT and (B) ZnSAL-DPT in CDCl₃.

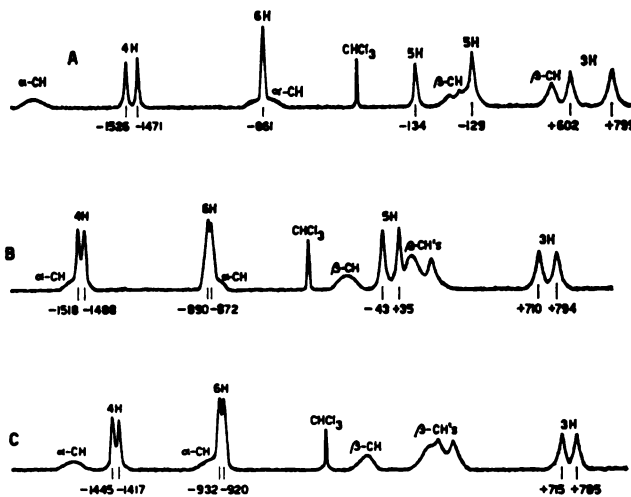


Figure 3. Pmr traces for ring protons of (A) NiSAL-DPT, (B) NiSAL-MeDPT, and (C) 5-Cl-NiSAL-MeDPT in CDCl₃.

thus run on the more sensitive HR-100 Varian spectrometer. A few test runs on both spectrometers verified that the observed shifts are proportional to field strength.

All shifts are reported as isotropic shifts, in cycles per second at 60 Mcps, defined as the difference in resonance position for a given proton in the paramagnetic chelate and the diamagnetic zinc complex, such that upfield shifts are considered positive.

The complexes used are those reported elsewhere.¹ The deuterated solvents were purchased from Fluka, AG, Buchs, Switzerland, except for *d*₅-nitromethane, *d*₇-acetonitrile, and *d*₄-methanol, which were obtained from E. Merck, Darmstadt, Germany.

An attempt was made to observe the electron spin resonance spectrum of a 0.1% solid solution of NiSAL-MeDPT in ZnSAL-MeDPT, using a Hilger & Watts X-Band spectrometer, in order to estimate the *g*-tensor anisotropy. However, no signal attributable to the sample was located down to liquid-nitrogen temperature.

Results

The pmr traces for ZnSAL-DPT and ZnSAL-MeDPT in *d*-chloroform are shown in Figure 2. The isotropic shifts for the ring protons of the complexes in *d*-chloroform are listed in Table I, and in Table II for the *d*₅-pyridine solutions. In both cases, the peaks are referenced against the zinc complexes. The pmr traces between -2000 and +1000 cps from TMS, the region over which all aromatic ring protons are observed, are recorded in Figure 3 for *d*-chloroform solu-

Table I. Isotropic Shifts for Ring Protons of X-NiSAL-RDPT in Deuteriochloroform^a

X	R	3		4		5		6		Δ_T
		ΔH	δ	ΔH	δ	ΔH	δ	ΔH	δ	
H	H	1204 1007	197	-1096 -1041	55	516 253	263	-439	0	515
3-Cl	H	...		-1279 -1225	54	396 244	152	-384	0	206
3-CH ₃	H	(-230) (-158)	(72)	-1374 -1296	78	475 272	203	-361	0	353
5-Cl	H	1211 1015	196	-1015 -966	49	-477	0	245
5-CH ₃	H	1268 1060	208	-1063 -1016	47	(-519) (-306)	(213)	-448	0	468
3,5-Cl ₂	H	-1216 -1146	70	-429 -404	25	95
H	CH ₃	1199 1115	84	-1088 -1058	30	421 344	77	-468 -450	18	209
3-Cl	CH ₃	-1273 -1231	42	348 348	0	-414 -368	46	86
3-CH ₃	CH ₃	(-188) (-179)	(9)	-1375 -1308	67	399 356	43	-395 -354	41	160
5-Cl	CH ₃	1190 1120	70	-1015 -987	28	-510 -498	12	110
5-CH ₃	CH ₃	1246 1151	95	-1015 -1033	22	(-422) (-350)	(70)	-470 -449	21	208
3,5-Cl ₂	CH ₃	-1201 -1155	46	-440 -386	54	100
4-CH ₃	CH ₃	-1190 1093	97	(552) (530)	(22)	457 385	72	-425	0	191

^a Shifts in cps at 60 Mcps, at 27°, referenced to the position for each proton in the diamagnetic zinc complex. Shifts in parentheses indicate methyl protons. δ denotes the splitting between two component peaks for position *i*. Δ_T denotes total ring splitting.

Table II. Isotropic Shifts for Ring Protons of X-NiSAL-RDPT in Pentadeuteriopyridine^a

X	R	3	4	5	6
H	H	449	-1050	37	-100
3-Cl	H	...	-1202	40	-126
3-CH ₃	H	(-77)	-1339	49	-83
			-1323		
5-Cl	H	439	-950	..	-108
5-CH ₃	H	448	-1037	(-66)	-74
3,5-Cl ₂	H	...	-1120	..	-113
H	CH ₃	462	-1072	20	-116
3-Cl	CH ₃	...	-1265	32	-108
3-CH ₃	CH ₃	(-91)	-1342	41	-99
5-Cl	CH ₃	444	-965	..	-108
5-CH ₃	CH ₃	454	-1030	(-55)	-95
3,5-Cl ₂	CH ₃	...	-1110	..	-109
4-CH ₃	CH ₃	465	(246)	36	-98

^a Shifts in cps at 60 Mcps, at 27°, referenced to the position in the diamagnetic zinc complex. Parentheses denote methyl protons.

tions of NiSAL-DPT, NiSAL-MeDPT, and 5-Cl-NiSAL-MeDPT. The temperature dependence of the two unsubstituted chelates is illustrated in Figure 4.

The dependence of the positions of the ring proton resonances in *d*-chloroform solution, as *d*₅-pyridine is added to NiSAL-DPT and NiSAL-MeDPT, appears in Figure 5. Table III and Table IV present the isotropic shifts for the ring protons of 5-CH₃-NiSAL-MeDPT and 3-CH₃-NiSAL-DPT, respectively, in the two inorganic and six fully deuterated solvents.

Discussion

Assignment of the Peaks. The peak at -8.1 ppm belongs to the azomethine proton, and the four peaks between -6.4 and -7.3 ppm arise from the four ring protons. For the ZnSAL-MeDPT complex, the signal at -2.2 ppm must arise from the aminomethyl group.

Table III. Isotropic Shifts for Ring Protons of 5-CH₃-NiSAL-MeDPT in Various Solvents^{a,b}

Solvent	3		4		5		6		Δ_T	ϵ^c
	ΔH	δ	ΔH	δ	ΔH	δ	ΔH	δ		
Carbon tetrachloride	1142	53	-1121	37	(-324)	19	-420	38	147	2.24
<i>d</i> ₆ -Benzene	1089		-1084		(-305)		-382			
	1144	69	-1091	41	(-364)	55	-430	29	194	2.28
	1075		-1050		(-309)		-401			
Carbon disulfide	1110	66	-1080	38	(-333)	46	-386	32	182	2.64
	1044		-1042		(-287)		-354			
<i>d</i> -Chloroform	1245	95	-1055	22	(-422)	70	-470	21	208	4.81
	1150		-1033		(-352)		-449			
<i>d</i> ₆ -Acetone	1296	102	-1046	42	(-409)	87	-480	29	260	20.7
	1194		-1004		(-322)		-451			
<i>d</i> ₄ -Methanol	1388	53	-965	73	(-520)	189	-527	0	315	32.6
	1335		-892		(-331)					
<i>d</i> ₅ -Nitromethane	1366	113	-1034	66	(-482)	150	-505	8	337	39
	1253		-968		(-332)		-497			
<i>d</i> ₃ -Acetonitrile	844	84	-988	194	(-470)	129	-269	0	407	39
	760		-794		(-241)					

^a See footnote a, Table I. ^b For 3-CH₃-NiSAL-MeDPT, Δ_T 's (cps) were observed as: carbon tetrachloride, 162; carbon disulfide, 160; acetone, 193; acetonitrile 440. ^c ϵ denotes dielectric constant, "Handbook of Chemistry and Physics," 45th ed, The Chemical Rubber Co., Cleveland, Ohio, 1964.

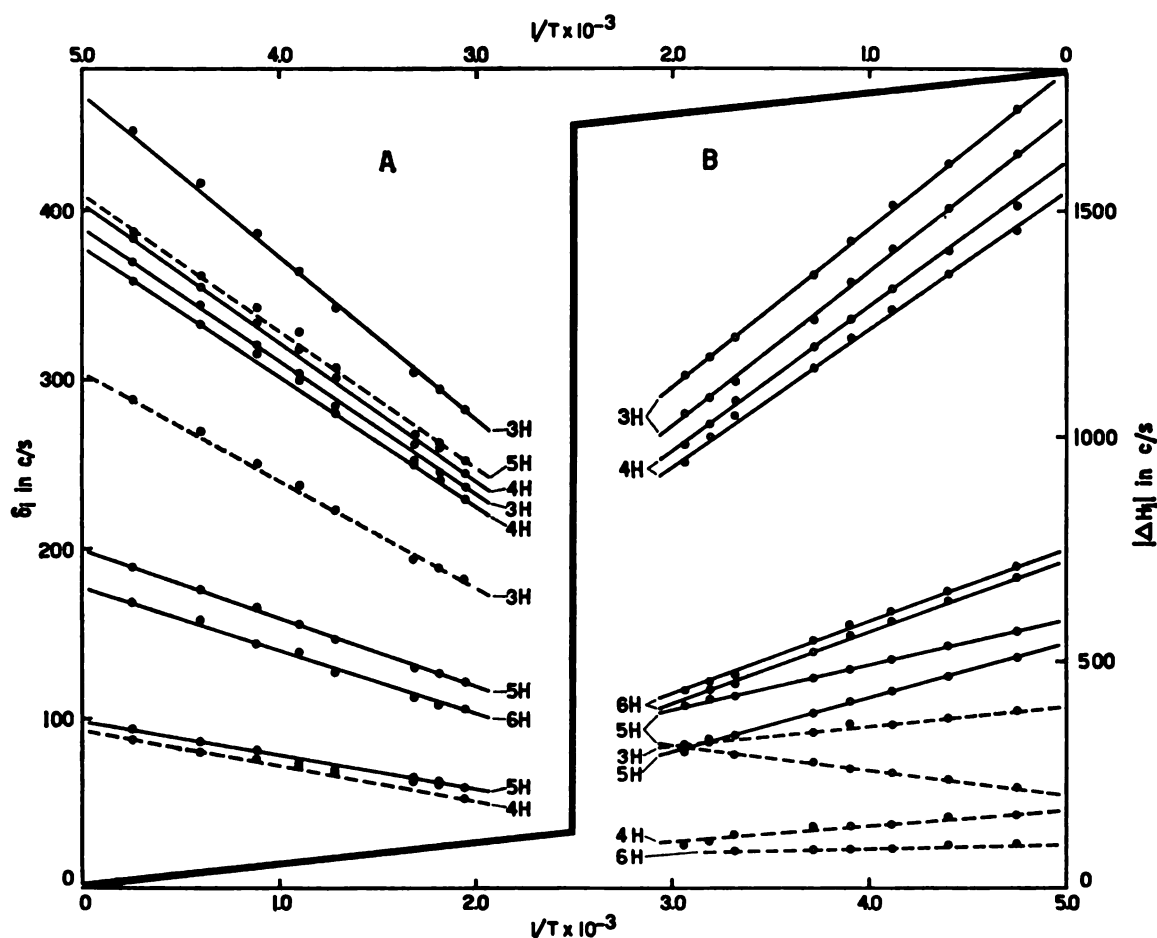


Figure 4. Temperature dependence for ring proton isotropic shifts, ΔH_i , —; and peak splittings, δ_i , ---, for (A) NiSAL-DPT and (B) NiSAL-MeDPT, in CDCl_3 .

Remaining are thus four peaks with relative areas 2:2:4:4 for ZnSAL-MeDPT, and with areas 2:2:4:5 for ZnSAL-DPT, going upfield with the

DPT. The fact that six-membered rings are formed upon coordination to the metal makes these splittings expected. The peak at -2.6 ppm is assigned to the

Table IV. Isotropic Shifts for the Ring Protons of 3- CH_2 -NiSAL-DPT in Various Solvents^{a,b}

Solvents	3		4		5		6		Δ_T	ϵ^c
	ΔH	δ	ΔH	δ	ΔH	δ	ΔH	δ		
Carbon tetra- chloride	(-258) (-184)	74	-1450 -1374	76	460 248	212	-361 -351	10	372	2.24
<i>d</i> ₆ -Benzene	(-252) (-179)	73	-1397 -1301	96	470 268	202	-366	0	371	2.28
Carbon disulfide	(-194) (-132)	62	-1326 -1240	86	524 379	145	-416	0	293	2.64
<i>d</i> -Chloroform	(-230) (-158)	72	-1374 -1296	78	475 272	203	-361	0	353	4.64
<i>d</i> ₆ -Acetone	(-244) (-182)	62	-1370 -1286	84	436 241	197	-326	0	343	20.7
<i>d</i> ₄ -Methanol	(-215) (-131)	84	-1218 -1153	65	502 406	96	-409 -369	40	285	32.6
<i>d</i> ₅ -Nitromethane	(-225) (-127)	98	-1338 -1226	112	592 391	201	-470	0	411	39
<i>d</i> ₃ -Acetonitrile	(-199) (-105)	94	-1124 -1003	121	394 287	107	-263 -170	93	415	39

^a See footnote a, Table I. ^b For 5- CH_2 -NiSAL-DPT, Δ_T 's (cps) were observed as: carbon disulfide, 375; acetone, 320; methanol, 432. ^c See footnote c, Table III.

azomethine proton peak taken as 2. For ZnSAL-MeDPT, these four peaks arise from the 12 methylene protons, while the amino proton is apparently included in the farthest upfield peak in this set for ZnSAL-

γ -CH's, on the basis that a triplet appears for the MeDPT case due to coupling with the β -CH's, while this peak is further split by coupling to the NH proton for the DPT complex. The peak at -1.9 ppm is assigned

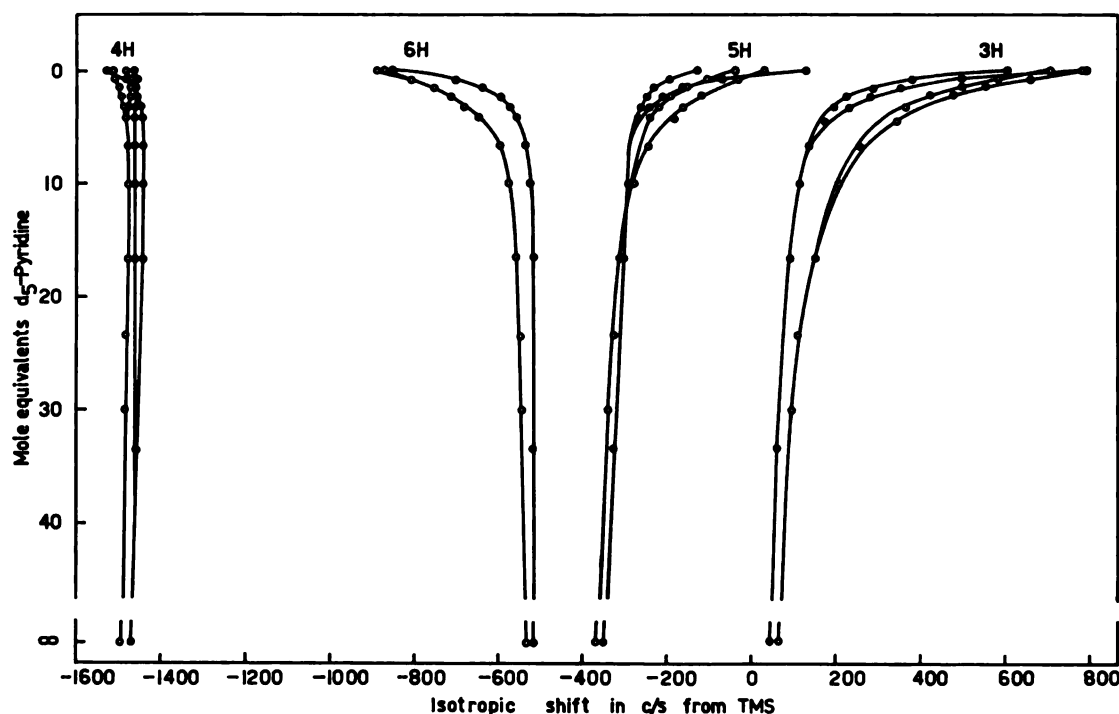


Figure 5. Plot of ring proton chemical shifts vs. excess molar equiv of deuteropyridine for NiSAL-DPT (●) and NiSAL-MeDPT (○) in CDCl_3 .

to the β -CH's, as it appears as a slightly broadened quintuplet indicating more or less equal coupling to the α -CH's and γ -CH's. This peak is again more complicated in ZnSAL-DPT, presumably because of further coupling with the NH. The two smaller peaks at -2.4 and -4.4 ppm thus belong to the α -CH's, since their multiplet structure is least affected by the amino nitrogen substituent. As this group of protons lie closest to the aromatic ring, the chemical shift difference for the axial and equatorial protons would be expected to be greatest,¹⁸ the observed difference being 2.0 ppm. The multiplet structure for the α -CH's in ZnSAL-MeDPT shows five components, with intensities 1:2:2:2:1. This is interpreted as arising from axial-equatorial coupling of 12.5 cps and coupling to the adjacent CH's of 5.5 cps. For ZnSAL-DPT, the peak at -4.4 resembles more a quartet, which could arise from equal coupling to the other α -CH and β -CH's. This would indicate that there might be some slight difference in structure, or in methylene chain configuration, between the ZnSAL-DPT and ZnSAL-MeDPT complexes (*vide infra*). However, since long-range coupling to the NH is also possible, no definite conclusions can be drawn. The assignment of the ring protons on the basis of multiplet structure and substitution is trivial. The peak locations, relative to TMS, are (in cps at 60 Mcps): 3-H, -404 ; 4-H, -430 ; 5-H, -387 ; 6-H, -422 ; 3-CH₃, -128 ; 4-CH₃, -130 ; 5-CH₃, -131 .

The pmr traces of three nickel chelates are illustrated in Figure 3 over the region where all the ring protons lie. What becomes immediately obvious is that there appears not a single peak per ring position, but two separate resonances. For some samples, as many as 21

peaks were observed with the complex containing a total of 23 protons. That two peaks arise per ring position was verified by the use of substituents, where peaks disappeared in pairs upon chloro substitution and shifted and tripled in intensity upon methyl substitution. The difference in resonance position for a pair of peaks is as large as 263 cps in chloroform solution. Also, the N-CH₃ peak in the MeDPT complexes illustrates that there should be two separate resonances per ring position by the fact that the intensity ratio for this methyl group to any single ring peak is only 3:1, instead of the expected 3:2. In a few cases, the 6-H peak was not split, and this resulted in the only peak attributable to this position having twice the intensity of any of the other "split" proton peaks.

Assignment was performed completely by substitution, as the line widths were too great (≥ 10 cps) to resolve any multiplet structure in all but a few cases. For 3-Cl-NiSAL-MeDPT, the two 4-H peaks each showed a doublet, as did the 6-H, while the 5-H exhibited a triplet, as is expected. This sample thus serves to confirm the 6-H assignment, as complexes with substituents at this position were not prepared. The peak positions are found to be quite independent of ring substituents, except that the 4-H resonated slightly further downfield upon substituting at the 3 position, as has been observed in other related chelates of nickel.¹³

The temperature dependences of the ring proton resonances of NiSAL-DPT and NiSAL-MeDPT in chloroform are plotted as a function of $1/T$ in Figure 4, and verify that the shifts generally follow a Curie law,¹⁴ eliminating any equilibrium such as was found for a number of nickel(II) systems.^{9, 11-13, 15, 16}

Assignment of the ring protons was facilitated by the fact that they exhibited line widths significantly

(18) J. S. Waugh and R. S. Fessenden, *J. Am. Chem. Soc.*, **79**, 846 (1957); D. J. Wilson, D. J. V. Boekelheide, and R. W. Griffin, *ibid.*, **82**, 6302 (1960).

r than for the remaining protons. Because of the solubility for most of the complexes and excessive dilutions, it was possible to locate all of the nonring protons in only a very few samples. Aside from the proton resonances for NiSAL-DPT in chloroform, the following peaks (cps) and their relative intensities have been observed: -13,300 (1), -10,500 (1), -4200 (2), -1960 (1), -850 (1), 80 (1), 529 (1), 780 (1), and -14,980 (1) and -16,700 (1). The four peaks between 80 and 780 cps can be entirely assigned to the four β -CH's, since only for position do spin polarization effects predict up- and downfield shifts. Both σ and π spin density result in upfield shifts for α -CH's and γ -CH's. This assignment is also consistent with the smaller line widths for these peaks, as they are one bond further removed from the nickel than the other two methylene positions. Two peaks at -14,980 and -16,700 cps can be assigned to the azomethine protons, again because of narrower lines due to a greater distance from the nickel.

A large downfield shift for this position has been observed in other nickel chelates with salicylaldimines.¹⁶ The two larger peaks at -6500 and -4700 cps can be assigned to the γ -CH's, since the β resonates at -4700 cps, and there would not be expected to be very much difference in the peak positions of the aminomethyl and aminomethylene groups. This leaves the four peaks at -13,300, -10,500, -1960, and -850 cps, which must arise from the α -CH's. This assignment is consistent in that the largest spread of α -CH's was also observed in the diamagnetic nickel chelates. The presence of unpaired spin in the paramagnetic system just greatly amplifies the effect. The assignments for the α -CH's and γ -CH's are speculative, however, and cannot be fully justified. It will be shown that these assignments are consistent with certain features of these complexes. This scheme of assignments holds true for all DPT complexes, as only minor differences in position occur. The N-H resonance was found presumably because it is too close to the

the NiSAL-MeDPT series, the nonring protons are found at: -13,200 (1), -11,400 (1), -6700 (4), -1630 (1), -1000 (1), -187 (1), 112 (1), 227 (1), and -11,930 (1) and -13,520 (1), cps. The four peaks between -187 and 227 cps are assigned to the β -CH's, and those at -11,930 and -13,520 cps to the azomethine protons, on the same basis as for NiSAL-DPT. The peak at -4700 cps from the aminomethyl group, due to its relative intensity and its absence in the DPT chelates. The peak of intensity 4 at -6700 cps is attributed to the γ -CH's, again because of its position being so similar to aminomethyl. The remaining peaks must belong to four α -CH's.

As can be seen from a comparison of the assignments for the DPT and MeDPT complexes, the resonance patterns are quite similar. Significant differences are in the spread of the β -methylene shifts, the extent of downfield shift for the azomethine protons, and the fact that the γ -methylene protons give rise to two peaks in DPT chelates, but only a single broad resonance (peak) for the MeDPT complexes.

Origin of the Double Peaks. The appearance of twice the number of peaks expected, even after

considering the nonequivalence of the methylene protons resulting from ring formation, can be considered to arise from two likely situations. One would be the presence of two distinct species in solution with differing shift patterns, the other possibility being that we have but one species, but the two salicylaldimine fragments are nonequivalent, such that their shift patterns differ.

The former case could result from two geometrical isomers or from optical isomers. There have been reported^{12,15} some cases of similar "doubling" of lines where the origin was traced to the presence of optical isomers. The doubled peaks did not appear with equal intensity, and both sets of peaks were indicative of identical spin distributions, with only a small scaling in magnitude between them.^{12,15} Also, the splittings^{12,15} represented only a very small fraction of the total shift. In the present study, it is found that the doubled peaks always appear with equal intensity, and this observation holds true over a wide temperature range and in a number of solvents. In view of these observations, plus the fact that the crystal structure² showed only one geometrical isomer, the doubling could only arise from optical isomers. However, the two sets of peaks for these five-coordinated complexes display significantly different shift patterns or spin distributions, since the splitting is not at all proportional to the shift magnitude. Often the smallest shift exhibits the largest splitting and *vice versa*. Moreover, the splitting here represents up to 100% of the shift in some cases. Therefore, though these complexes possess no center of symmetry and optical isomers have been observed,² their presence in solution cannot explain the observed pattern of peak splittings.

It can be shown, however, that the properties of the observed splittings are consistent with the presence of only one species in solution, with such coordination of the pentadentate ligand that the two salicylaldimine fragments are nonequivalent in some major respect. In NiSAL-MeDPT, for example, the only two positions for which no splittings are observed are the N-CH₃ and the γ -CH's. If two species produced the doubling, it might be expected that these positions should also display a splitting. However, for the case where we have only one species in solution with nonequivalent aromatic fragments, it is obvious that the N-CH₃ "belongs" to both fragments, such that no splitting can be expected. Furthermore, the γ -CH's are next nearest to this equivalence point, such that it would not be unexpected that they show small or negligible splittings. For NiSAL-DPT, the γ -CH's do split, but only into two peaks. Even in this complex, however, this splitting is the smallest for the methylene protons when expressed as fraction of the total shift. It should be pointed out here that a splitting of the γ -methylene peak into two resonances can arise from the effect of ring formation upon coordination to the nickel, even though this splitting was not observed in the diamagnetic zinc complex. The reason for this is that the effect of the unpaired spin can magnify an unobservably small chemical-shift difference in the diamagnetic chelate so that it is readily seen in a paramagnetic complex. However, the splitting of any methylene group into four peaks will only arise through the additional effect of nonequivalence of the two sides of the ligand.

The splitting of a methylene group into four peaks is most convincingly demonstrated in the pmr trace of 5-Cl-NiSAL-DPT, where the elimination of the 5-H peaks clearly reveals two sets of split peaks. The assignment for the β -CH's is quite definite, as no spin-transfer mechanism would result in upfield shifts for the α -CH's or γ -CH's.

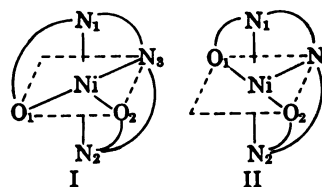
The observed shifts¹⁴ must arise from either a contact interaction or from the dipolar interaction, should the nickel possess an anisotropic g tensor. In view of the similarity of the presently observed shift patterns to that observed for the tetrahedral chelates,¹⁵ and the fact that methyl substitution always produces shifts of opposite sign to that of the proton,^{9,10,19} the shifts must arise primarily from unpaired spin in the ligand highest filled π orbital. However, since the splittings are not proportional to the shift, it is indicated that the spin distribution for the two rings must differ significantly. Isotropic shifts resulting, in part, from σ density^{20,21} for one of the rings could be a possibility, as would differing extents of interaction with higher ligand orbitals.²²⁻²⁴ Both effects have been reported.²⁰⁻²³ Because of the lack of any symmetry element for these complexes, the spin can probably be delocalized into any ligand orbital.

In order to be able to attribute the splittings to a different extent of dipolar interaction with the two rings, the two aromatic fragments must be oriented differently with respect to the major axes of the chelate; otherwise this interaction will affect both rings identically. For shift differences between the rings as large as 263 cps, the anisotropy will have to be very large, and the difference in ring orientations must represent a large deviation from equivalence. Nothing is known about the g -tensor anisotropy, due to the lack of esr data. Attempts to observe the esr signal for these complexes failed, perhaps due to large zero-field splittings. The magnetic moments for these complexes are inconsistent with sizable anisotropy, and the inverse cube of the distance dependence¹⁴ of the dipolar interaction makes it unlikely that it could cause such large splittings. However, both the contact and dipolar interaction are thus indicated as possible origins of the double set of peaks, as long as the two salicylaldehyde fragments are nonequivalent.

Such origins for the set of double peaks are quite consistent with the known structure of NiSAL-MeDPT, where the two aromatic fragments are seen to be slightly nonequivalent.²

The nonequivalence of the two SAL arises from the fact that the known structure lies somewhere between a trigonal bipyramid and a square pyramid. Steric effects of the methylene chains dictate that the two azomethine nitrogens tend to remain *trans* to each other, as verified in the X-ray analysis,² such that a trigonal bipyramidal structure would produce equivalent SAL rings. Coordination with pyridine shows that these ligands readily take up a square-pyramidal con-

formation,¹ as required in octahedral coordination. The two square-pyramidal structures consistent with *trans*-azomethine bonding are labeled I and II, for the SAL rings *cis* and *trans* to each other, respectively.



Of these two conformations, only I would produce non-equivalent SAL rings. It can be easily seen that for this case the two SAL rings would see radically differing ligand fields. Structure II, like the trigonal pyramidal form, would not produce splittings. It could thus be supposed that the extent of ring nonequivalence, as evidenced by the splittings, will increase with structure changes tending to approach I. The great similarity of the crystal and solution spectra indicates no major structure changes upon dissolution;¹ however, small changes in bond angles, perhaps a few degrees, cannot be precluded, as evidenced by the temperature and solvent effect on the splittings (*vide infra*).

The actual structure in any solvent is probably the result of a number of factors, such as repulsion between bonding ligand atoms, steric effects of the methylene chains and the amino nitrogen substituent, and relative crystal field stabilization energies, cfse. The atomic repulsions are likely to be insignificant, inasmuch as related salicylaldehyde ligands readily form octahedral complexes.^{12,13} The steric effect is definitely expected to exert a strong influence, probably favoring the trigonal bipyramidal structure, where the bands in the methylene chains are minimized. Crystal field calculations²⁵ have indicated that the cfse favors the square pyramid, though the high degree of covalent bonding²⁶ in salicylaldehyde could make such calculations inapplicable in the present case. The effect of coordinating and noncoordinating solvents upon the observed splittings will be seen to shed light on the pentadentate ligand conformation in the octahedral adducts and relate to the importance of steric effects in determining the solution structure.

Pmr Spectra in Deuteriopyridine. As shown previously,¹ these five-coordinated complexes all react with 1 mole of pyridine to form the adducts, NiSAL-RDPT·py. The observed isotropic shifts in this solvent are given in Table II. As is readily observable, the shifts for the pure five-coordinated complexes and their octahedral pyridine adducts differ significantly. The shifts are much smaller in the adduct for all but the 4-H position, and the alternation of signs for adjacent positions, very obvious in chloroform solution, almost disappears in pyridine. In addition, only one peak per ring proton is now observed in each case except that of the 4-H peak in 3-CH₃-NiSAL-DPT, where a splitting of about 16 cps remains. The peaks were generally too broad (25 to 75 cps) to resolve any smaller splittings. Assignment was carried out by substitution. However, the 5-H and 6-H peaks were found so close to each other that it was necessary to verify their

(19) A. Forman, J. N. Murrell, and L. E. Orgel, *J. Chem. Phys.*, **31**, 1129 (1959).

(20) J. A. Happe and R. L. Ward, *ibid.*, **39**, 1211 (1963).

(21) G. W. Everett, Jr., and R. H. Holm, *J. Am. Chem. Soc.*, **87**, 3534 (1965).

(22) D. R. Eaton, *ibid.*, **87**, 3097 (1965).

(23) D. R. Eaton and E. A. LaLancette, *J. Chem. Phys.*, **41**, 3534 (1964).

(24) G. N. La Mar, to be published.

(25) M. Ciampolini, *Inorg. Chem.*, **5**, 35 (1966).

(26) A. H. Maki and B. R. McGarvey, *J. Chem. Phys.*, **29**, 35 (1958).

ment by slowly adding pyridine to chloroform solutions of NiSAL-DPT and NiSAL-MeDPT. The ring resonance position as a function of excess pyridine is recorded in Figure 5.

The disappearance of the double peaks upon adduct formation is readily explained by the fact that, upon coordination of pyridine, the octahedral field produces more or less equivalent ligand fields for both SAL rings. That the ring nonequivalence has not totally disappeared is indicated by the 16-cps splitting of the 4-H peak in NiSAL-DPT. This splitting is larger than the expected spin-spin coupling. It might thus be concluded that the ring nonequivalence in pyridine has been reduced by adduct formation, such that the splittings are very small and are probably obscured by line broadening in all cases except the 3-CH₃-NiSAL-DPT.

In the pyridine adduct, the chelate must arrange itself in either conformation I or II. Of these two, only conformation I results in nonequivalent salicylaldehyde rings and splittings should be observed. The 16-cps splitting observed for the one complex adduct with relatively narrow line widths indicates that the more likely chelate arrangement is I. This conformation of the chelate in the adduct may be a bit surprising, since the "opening" or clearest approach to the five-membered complex is bisecting the O₁-Ni-O₂ angle. However, models show that the steric strain in the methylene chains resulting from structure II is quite large and that I is more favorable.

The pattern of the isotropic shifts for the pyridine adduct closely resembles that observed for other octahedrally coordinated nickel(II) complexes with related ligands.^{12,13} The shifts display some characteristics arising from spin in the π -ligand orbitals, since a hyperfine interaction does exist, and protons and methyl groups show shifts of opposite sign for any position.^{9,10,19} However, the distribution is inconsistent¹⁶ with that expected for delocalization into the top bonding ligand orbitals, and therefore other interaction may well be present. This problem will be treated elsewhere.²⁴

Effect of Noncoordinating Solvents. Although the isotropic shifts for both the NiSAL-MeDPT and NiSAL-DPT chelates exhibit quite similar patterns, a characteristic difference between the two series of shifts is readily observed. In Table I, in addition to the isotropic shifts, we list also for each ring position the difference, or splitting, between the two peaks, giving it δ . From a comparison of the analogous complexes, one with R = H, the other with R = CH₃, it is concluded that the splittings, δ , are always larger for the former than for the latter complex, sometimes by a factor of 2-3. This is true for every position save 6-H, where no splittings appeared for the DPT complexes at room temperature and only very small ones for the MeDPT series. The splittings for any given ring position do not vary significantly upon substitution at the other ring position. The methyl splittings for any complex are always smaller than for the proton.

The conclusion which appears most evident is that if the splittings can be interpreted as arising from nonequivalence of the two aromatic parts of the chelate, the extent of this nonequivalence is significantly greater for the NiSAL-DPT than for the NiSAL-MeDPT complexes in chloroform. The splitting for any given position should not be taken indiscriminately

as an index of this nonequivalence, since the electronic origin of the splittings in all probability does not affect all ring positions identically. However, if we sum over all the ring positions, we obtain the total splitting parameter, Δ_T , which should be a reasonable measure of the extent of nonequivalence. This splitting parameter, Δ_T , is also given for each complex in Table I. Comparing this parameter for any two complexes differing only in R, we find Δ_T for the NiSAL-DPT consistently larger by a factor 2.2-2.5 than for the NiSAL-MeDPT complex. This ratio of parameters is remarkably constant for all complexes where Δ_T can be summed over at least three ring positions.

Within the supposition that the solution structure does not deviate appreciably from that observed in the solid, and that the extent of ring nonequivalence increases as the structure deviates slightly in the direction of structure I, the difference in Δ_T between the DPT and MeDPT complexes in chloroform indicates that their structures differ slightly, with the former complexes displaying a structure slightly closer to I than the latter. This difference in proton splittings between the two series was also observed for the methylene protons. As indicated earlier, the β -CH's are spread over ≈ 420 cps and ≈ 700 cps for the MeDPT and DPT chelates, respectively. Similarly, the γ -CH's produced but a single peak in NiSAL-MeDPT, while NiSAL-DPT showed two peaks. These methylene proton splittings are consistent with the ring Δ_T parameters for the two series, and verify their apparent difference in ring nonequivalence, and thus structure. Unfortunately, nothing definite can be stated about the magnitude of the differences in structure between the two series, since it is not known how the splittings depend upon small variations of the bonding angles. However, changes of just a few degrees could be considered quite consistent with the observed changes in view of the high sensitivity of pmr measurements.

The difference in structures for these complexes depending on the R substituent seems to reflect steric effects.²⁷ As indicated above, these structures are probably determined by a compromise between the steric effect, probably favoring a trigonal bipyramid, and the crystal field, which favors a square pyramid.²⁶ Since the relatively more bulky methyl group will increase the steric effect in the NiSAL-MeDPT chelates more than the proton in the NiSAL-DPT series,²⁷ a structure for the former complexes tending more toward I should not be unexpected. That the steric effect of the methyl group influences the structure draws support from the equilibrium constant data for these complexes with pyridine.¹ As shown in Figure 5, for any given excess of pyridine in the two equally concentrated solutions of NiSAL-DPT and NiSAL-MeDPT, the extent of octahedral coordination, as determined by the pmr shift, is always greater for the former chelate. This indicates that the aminomethyl group must provide some steric inhibition¹ toward six coordination for NiSAL-MeDPT. This characteristic difference in equilibrium constants for the two series is observed also for all the ring-substituted isomers.

In order to determine if the solution structure for these complexes is dependent upon solvent, the isotropic shifts were measured in seven other solvents.

(27) F. G. Mann and R. H. Watson, *J. Chem. Soc.*, 2772 (1958).

In Tables III and IV we list the observed shifts, the splitting, δ , and the total splitting parameter, Δ_T , for 5-CH₃-NiSAL-MeDPT and 3-CH₃-NiSAL-DPT, respectively, in each of eight noncoordinating solvents.

Tables III and IV clearly indicate that the splittings are indeed sensitive to the solvent, particularly for 5-CH₃-NiSAL-MeDPT. Again, the δ 's should not be taken individually as indications of the extent of ring nonequivalence, but the sum over the four ring positions, Δ_T . It is readily observed that the four ring positions are affected differently by the various solvents in some cases. For the MeDPT chelate, Δ_T varies over the range 147–407 cps, while the DPT complex shows much less variation. The isotropic shift patterns are essentially identical in all the solvents. In none of the solvents listed in Tables III and IV does any additional coordination of the five-coordinated species occur. This was verified by studying the pmr lines of the solvent.

The dependence of Δ_T on the solvent indicates that the extent of ring nonequivalence, and hence the structure, are also a function of the solvent. Since there exists no direct bonding between these solvents and the five-coordinated chelates, the solvent sensitivity of the splittings and structure must reflect some sort of variable solvation effect. The observed splitting parameter, Δ_T , increases for these solvents in the order CCl₄ < CS₂ \approx C₆D₆ < CDCl₃ < CD₃COCD₃ < CD₃OD < CD₃NO₂ < CD₃CN, for the 5-CH₃-NiSAL-MeDPT complex. This apparent increase in ring nonequivalence, as indicated by Δ_T , correlates very well with the dielectric constants for these solvents, also included in Table III under ϵ . Since the ring nonequivalence increases as I is approached, the correlation between the parameter Δ_T and dielectric strength implies that increasing solvating power tends to stabilize the square-pyramidal structure (I) over the more trigonal bipyramidal one in solution for the MeDPT complex, or that the square-pyramidal structure is more highly solvated than the trigonal bipyramid. A very similar solvation effect has been observed¹⁶ for the nickel(II) chelates of aminotroponimine, where the sensitive solvent dependence of the square-planar, diamagnetic \leftrightarrow tetrahedral, paramagnetic forms was explained by the higher solvation of the square-planar form. Such solvation may be considered analogous to the microcrystalline ordering postulated^{28,29} to explain the line-width differences for the hyperfine components in the esr spectra of square-planar complexes. The extent of stabilization of the square pyramid over the trigonal bipyramid forms by this mechanism could be expected to increase with the solvent dielectric strength, though solvent shape and size probably also play an important part.

Another possible mechanism which would stabilize I and would be expected to produce the observed dependence on the dielectric strength is that of solvation of the complex as a whole, without any ordering of solvent molecules, which decreases the repulsion between the oxygens, thereby allowing them to take up a more *cis* position. Either mechanism would account for the increased stabilization of the square-pyramidal structure with solvent dielectric strength, but *only* if the con-

formation of the square-based structure approaches I. The observed changes in Δ_T with solvents are quite inconsistent with structure II as a limit.

For the 3-CH₃-NiSAL-DPT complex, the variation in Δ_T with solvent is much smaller than that for the DPT complex and does not seem to indicate any significant dependence on dielectric constant, except that the splittings are again largest in nitromethane and acetonitrile. The variations in Δ_T with solvent represent only a 10–20% deviation from the average, implying that the extent of nonequivalence of the two aromatic rings, and hence the solution structure, is more or less independent, or at least does not demonstrate the striking dependence noted for 5-CH₃-NiSAL-MeDPT.

Though the pmr spectra of the two other methyl-substituted chelates are available for only a very few solvents due to insolubility, as indicated at the bottom of Tables III and IV, it is observed that the available data are consistent with the above conclusions.

From Table I, we note for the DPT series, where it appears that the ring substituent does not significantly influence the splittings and thus the structure, that the 5-CH₃ derivative produces a $\Delta_T \approx 1.3$ times that for the 3-CH₃ isomer. This ratio of ≈ 1.3 for the two methyl-substituted isomers holds also for the MeDPT series. It can therefore be concluded that if the structures of 5-CH₃-NiSAL-MeDPT and 3-CH₃-NiSAL-DPT were identical in any given solvent, then their ratio of Δ_T 's should also be ≈ 1.3 . From a comparison of Δ_T 's for the same solvent in Tables III and IV, it is observed that this ratio is about 0.5 for the solvents of low dielectric strength and increases to 1.0 for solvents with high dielectric constant. This implies that the structures of the DPT and MeDPT complexes, or their extents of ring nonequivalence, differ, with the former chelate possessing a more nonequivalent pair of SAL fragments, but with the *difference* between the two series of complexes decreasing as the solvent dielectric strength increases. As a strong solvent effect was observed only for the MeDPT chelates, and since the difference in solution structure for the DPT and MeDPT complexes was attributed to the steric effect of the aminomethyl group, it appears that solvation tends to diminish the importance of this steric effect.

This difference between the two series of complexes is also evidenced in the temperature dependence of the ring proton shifts and serves to support the supposition that steric effects account for the difference in structure, as indexed by the splitting term, Δ_T . As illustrated in Figure 4, the isotropic shifts for NiSAL-DPT follow the Curie law exactly, and hence so do the splittings, δ , as expected. For the NiSAL-MeDPT chelate, however, though the shifts generally follow the Curie law, it is noticed, particularly for 3-H and 5-H, that the two peaks for each position diverge much more than predicted by a Curie behavior. This is demonstrated in the temperature dependence of the splittings, δ . It clearly shows that δ for 3-H decreases with temperature much more slowly than predicted while δ for 5-H actually *increases* with temperature, opposite to expectations. This effect can be interpreted such that if the smaller splittings for the MeDPT series arise because steric effects tend to stabilize a more trigonal-bipyramidal-like structure, where the extent of ring nonequivalence is less than in the DPT series, then in-

(28) H. M. McConnell, *J. Chem. Phys.*, **25**, 709 (1956).

(29) R. N. Rogers and G. E. Pake, *ibid.*, **33**, 1107 (1960).

g temperature would counter the steric effect h thermal motion, making the structures of the ries more nearly identical. This minute change cture is manifested in increasing δ , though the l shift still follows the Curie law. This char- ic difference in the temperature dependence plittings between the DPT and MeDPT chelates

observed for their two methyl-substituted iso- The temperature data are thus consistent with ative solvent sensitivities and splittings for the ies of complexes.

ll the foregoing discussions on differences in re, and the resemblance of the actual structure to , it was never possible to specify any exact struc- ut only relative tendencies. Perhaps when the nic origin of the nonequivalence and its effect isotropic shifts are better understood, it will be e to make the presently qualitative results more ative.

absorption spectra indicate no significant changes olvent,¹ but it is not known what the limits are ht changes in coordination geometry before they st themselves in the optical spectrum. It could the changes in the O_1-Ni-O_2 angle, for example, produce the differences in splittings between the nd MeDPT complexes, and in the various sol- are so small that absorption spectra could not be d to display observable differences. In view extreme sensitivity of pmr in detecting differ- in magnetic environment, this may well be the This further demonstrates the versatility and rity of pmr studies on paramagnetic complexes dicates that this technique could prove valu- a studying the conformation of multidentate i in complexes with unpaired spins.

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observed "doubling" of the pmr peaks in the rdinated complexes is attributed to the presence ingle species in solution which possesses non- lent salicylaldehyde fragments. The magnetic ivalence arises from the fact that the two aromatic nts see slightly different ligand fields, as indi- n the known X-ray structure. The pmr spectra line are consistent with octahedral coordination, e splitting of peaks disappears or is greatly re-

The appearance of a 16-cps splitting in one idicates that the conformation of the penta-

dentate ligand in the pyridine adduct has the salicyl- aldehyde fragments bonded *cis* to each other.

Changes in the observed splittings are related to slight changes in solution structure. Small deviations from the crystal structure in the direction of a square pyramid with the aromatic rings *cis* to each other increase the extent of nonequivalence of the aromatic rings, giving rise to larger splittings. The sum of the splittings for the four ring positions indicates that the extent of ring nonequivalence is greater for the DPT than the MeDPT complexes and is attributed to the steric effect of the aminomethyl group which tends to favor a more trig- onal-bipyramidal structure. The splittings for the methylene protons are consistent with these conclusions, as are the equilibrium constant data for the pyridine adduct formation and the temperature dependence of the ring splittings for the two series of complexes.

The magnitude of the splitting parameter and hence solution structure are shown to be very solvent sensitive for the MeDPT chelates and correlate well with solvent dielectric strength. The increase of splittings with sol- vent strength indicates that the structure tends to ap- proach a square-pyramidal structure with the SAL *cis* to each other. The solvent effect is interpreted as aris- ing from preferred solvation of the square-pyramidal over the trigonal-bipyramidal structure, apparently working to counter the steric effect of the aminomethyl group. The temperature dependence of the splittings confirms this assumption. For the DPT chelates, the splittings and solution structure are insignificantly af- fected by either solvent or temperature. The ability to observe these changes, in spite of the fact that absorption spectra are essentially independent of substituents or solvent, is related to the much greater sensitivity of the pmr method.

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The Off-Diagonal Matrix Element in Molecular Orbital Calculations for Metal Complexes

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Abstract: This work concerns an investigation of those considerations involved in the evaluation of the off-diagonal matrix elements which arise in molecular orbital calculations for metal complexes. The use of $FG_{ij}(H_{ii} + H_{jj})/2$ and related attempts to correlate H_{ij} with the group overlap integrals, G_{ij} , by a multiplicative factor, F , is examined from theoretical considerations and calculational results. It is shown that terms of considerable magnitude, which do not vary as functions of the overlap integrals, make substantial contributions to the off-diagonal elements. Hence, unpredictable fluctuations in the F factor occur, and the need for wide variations in the choices of F factors in previous calculations is understood. Evidence is also presented which indicates that sums of two-center electrostatic interaction integrals vary from complex to complex in a fashion analogous to the corresponding nuclear attraction integrals. Consequently, indications are that the former integrals may be evaluated from the latter in a systematic way.

Since the introduction of the Wolfsberg-Helmholz calculations² for the evaluation of the electronic energy levels in transition metal complexes, the matrix elements in the secular determinant, $|H_{ij} - EG_{ij}|$, have been approximated by a variety of techniques. In a previous paper³, we emphasized the importance of including the two-center Coulomb and exchange integrals as well as the free-ion orbital energies for the evaluation of the metal and ligand diagonal terms. Other authors⁴⁻⁶ have introduced similar adjustments to the diagonal terms using various means for approximating the integrals involved. However, most of these authors have continued to use an approximation for the off-diagonal matrix element which involves the overlap integral, S_{ij} , or the group overlap integral, G_{ij} . It is the purpose of this paper to examine the relation between the overlap integral and the off-diagonal matrix element.

It is interesting to note the various attempts to systematize the relationship between S_{ij} and the off-diagonal term. The original Wolfsberg-Helmholz calculation² set $H_{ij} = FG_{ij}(H_{ii} + H_{jj})/2$ with $F_s = 1.67$ and $F_r = 2.00$. Yamatera⁷ used the same expression for his calculations on $\text{Co}(\text{NH}_3)_6^{+3}$. The self-consistent charge and configuration (SCCC) method as originally applied by Ballhausen and Gray⁸ to the vanadyl ion employed $H_{ij} = FG_{ij}\sqrt{H_{ii}H_{jj}}$ with $F_s = F_r = 2.00$. Among others, this relation has been employed by Lohr and Lipscomb⁹, Fischer,¹⁰ Johansen and Ballhausen,¹¹ and in several applications by Gray and co-workers.¹²⁻¹⁴

However, Cotton and Haas¹⁵ have pointed out that in a series of ammine complexes, F_r had to be varied from 1.82 to 2.30 in order to obtain agreement with experimental values of $\Delta = 10Dq$. Similarly, the more recent applications of the SCCC method to halide and oxide complexes¹⁶ used $F_r = 2.10$ with F_s slowly varying from 1.53 to 1.81. In all of these calculations, the diagonal term consisted only of the free ion orbital energy and/or the ionization potential of the corresponding hydride.

Other variations for H_{ij} have been presented. Cusachs¹⁷ suggested $H_{ij} = (2 - |S_{ij}|)(H_{ii} + H_{jj})G_{ij}/2$, while Yeranov¹⁸ offered $H_{ij} = FG_{ij}[2(H_{ii}H_{jj})/(H_{ii} + H_{jj})]$, and Kettle¹⁹ employed the simplest relation, $H_{ij} = KS_{ij}$ with k as a variable.

A further complication arises with the introduction of the two-center Coulomb integrals in the evaluation of H_{ii} and H_{jj} . $H_{ii} = \epsilon_{ii} + \text{Coulomb repulsion terms}$. ϵ_{ii} is the orbital energy of the electron in the free ion which is frequently approximated by the negative of the valence-state ionization energy of the appropriate free ion. The two-center Coulomb repulsion integrals are positive. The effect of the latter terms is to raise the values of H_{ii} and H_{jj} appreciably above their original negative values, that is, to make them smaller in absolute value.

Indeed, it is possible and actually occurs²⁰ that in complexes of high negative charge, FeF_6^{-3} or CrCl_6^{-3} , for example, at self-consistent charge the Coulomb repulsion terms are larger in magnitude than the orbital energies for the metal 3d, 4s, and 4p orbitals so that H_{ii} for the metal is positive. Such a situation is possible because the calculations do not include the positive ions of the species, for example, the K^+ ions in K_3TiF_6 , which are presumed to add simply a constant potential

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system. At the same time, the ligand diagonal H_{jj} , is negative so that use of the root-mean-method results in imaginary values. To circumvent this dilemma, Ros²¹ returned to the original Werg-Helmholz average. But even this method led to difficulty in terms of the coefficients in the ligand orbitals. Consider solving the secular equation for the eigenvalues

$$[H(3d,3d) - E] + b[H(3d,3p) - EG(3d,3p)] = 0 \quad (1)$$

An expression can arise in the solution of a 2×2 matrix involving FeCl_6^{-3} , for example. The term a is the coefficient of the metal 3d wave function in the ligand orbital, while b is the coefficient for the symmetry-adapted ligand orbitals. $H(3d,3d)$ is the metal diagonal matrix element, $H(3d,3p)$ is the off-diagonal element between the 3d and 3p orbitals, and $G(3d,3p)$ is the positive overlap integral. Consider the case where $H(3d,3d)$ is positive and $H(3p,3p)$ is slightly negative in value.²² The energy of the bonding orbital, E_1 , will be more negative than either $H(3d,3d)$ or $H(3p,3p)$ so that $[H(3d,3d) - E]$ as well as $-EG(3d,3p)$ are positive.

For a positive value of a

$$b = -\frac{a[H(3d,3d) - E]}{H(3d,3p) - EG(3d,3p)} \quad (2)$$

b must have a positive value in keeping with the bonding character of the orbital, not only must $H(3d,3p)$ be positive but it must be larger in absolute value than $-EG(3d,3p)$. But if one uses

$$H(3d,3p) = FG[H(3d,3d) + H(3p,3p)]/2$$

the Coulomb terms included for the diagonal elements it can and does occur that $|H(3d,3p)| > |H(3d,3d)|$ so that $H(3d,3p)$ is positive and one is led to the erroneous conclusion that the bonding orbital is bonding in character. In any event, the off-diagonal term is substantially decreased in magnitude if evaluated from the H_{ii} terms in this way.

This situation cannot be rectified simply by the addition of the diagonal terms of some arbitrary negative value that will allow both terms to become negative. In principle, the addition of such a term, $-Z$, to the diagonal would not alter the calculated energy E , relative to each other or to the starting levels, H_{jj} . Without loss of generality, this can be rectified by recourse to a simplified 2×2 secular determinant in which $H_{ii} = H_{jj}$. Then

$$(H_{ii} - E)^2 - (H_{ij} - EG_{ij})^2 = 0 \quad (3)$$

$$E_1 = (H_{ii} - H_{ij})/(1 - G_{ij}) \quad (4)$$

$$E_1 - H_{ii} = [(H_{ii} - H_{ij})/(1 - G_{ij})] - H_{ii} \quad (5)$$

A constant potential for the diagonal terms yields $\langle \psi_i | = -Z$ so H_{ii}' becomes

$$H_{ii}' = H_{ii} - Z \quad (6)$$

For the off-diagonal term, one obtains $-Z\langle \psi_i | \psi_j \rangle = -H_{ij}'$ so H_{ij}' becomes

$$H_{ij}' = H_{ij} - ZG_{ij} \quad (7)$$

Ros and G. C. A. Schriut, *Theoret. Chim. Acta*, **4**, 1 (1966). This situation is not fictional but has occurred frequently in our work dealing with complexes with -3 charges.

Substitution of these terms into

$$(H_{ii}' - E')^2 - (H_{ij}' - E'G_{ij})^2 = 0 \quad (8)$$

yields

$$E_1' = [(H_{ii}' - H_{ij}')/(1 - G_{ij})] - Z \quad (9)$$

Then, $E_1' - H_{ii}' = E_1 - H_{ii}$, and constancy of the levels relative to one another is maintained. But this relation holds only if $H_{ij}' = H_{ij} - ZG_{ij}$. If one applies the Wolfsberg-Helmholz approximation for the off-diagonal term, then for $H_{ii} = H_{jj}$

$$H_{ij} = FG_{ij}H_{ii}$$

However, for H_{ij}' , one obtains

$$H_{ij}' = FG_{ij}(H_{ii} - Z) = H_{ij} - FG_{ij}Z \quad (10)$$

The requirement of unchanging relationships between the levels is maintained only if $F = 1.00$. Since this is never the case, introduction of a constant potential to the diagonal terms would be equivalent to the addition of another variable to the calculations, subtly altering the value of the off-diagonal term depending on the size of the chosen potential.

As an alternative to the foregoing undesirable state of affairs, Oleari, *et al.*,⁴ have chosen to set $H_{ij} = FG_{ij}(\epsilon_{ii} + \epsilon_{jj})/2$ where the ϵ 's are the orbital energies and $F = 1.00$ for all interactions with ligand p orbitals and $F = 0.30$ for metal-ligand interactions involving the ligand s orbitals. This removes the dilemma as to sign for the off-diagonal terms. However, as will be shown, it is our belief that the absolute magnitudes of the terms are too small.

Theoretical Considerations

Throughout the course of all the various attempts to approximate the off-diagonal terms, the considerations advanced by Richardson,²³ in an A.E.C. publication which unfortunately achieved only limited distribution, have been overlooked. Richardson shows that by application of the Mulliken²⁴ multicenter integral approximation to both Coulomb and exchange parts of the Fock operator in Roothaan's method for closed shells, the one-electron operator becomes

$$H = -1/2\Delta + V_M + \sum_j V_j$$

where $-1/2\Delta$ is the kinetic energy operator, V_M is the potential energy due to the nucleus and electrons of the metal, and V_j corresponds to the nucleus and electrons of the j th ligand. Additional information concerning the operator forms of the potentials can be found in our recent publication.⁸

Consider the matrix element $\langle \phi_i | \mathcal{H} | \chi_i \rangle$, where χ_i is a metal wave function and ϕ_i is a symmetry-adapted linear combination of ligand wave functions, ρ_{ij} , over the j ligands. Then $\langle \phi_i | \mathcal{H} | \chi_i \rangle = C(\rho_i | \mathcal{H} | \chi_i)$ where the constant, C , is the same coefficient which relates the diatomic overlap, $S(\rho_i, \chi_i)$ to the group overlap $G(\phi_i, \chi_i)$. Then the matrix element can be written as

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$$(\phi_i|\mathcal{H}|\chi_i) = C\left\{(\rho_n|-\frac{1}{2}\Delta + V_M|\chi_i) + \left(\rho_n\left|\sum_{j=2} V_j\right|\chi_i\right) + (\rho_n|V_1|\chi_i)\right\} \quad (11)$$

For computational reasons, the foregoing expression is a convenient form for the matrix element. However, since the Hamiltonian is Hermetian, it is also possible to write the off-diagonal term as

$$(\chi_i|\mathcal{H}|\phi_i) = C\left\{(\chi_i|-\frac{1}{2}\Delta + V_1|\rho_n) + \left(\chi_i\left|\sum_{j=2} V_j\right|\rho_n\right) + (\chi_i|V_M|\rho_n)\right\} \quad (12)$$

If one makes the reasonable approximation that χ_i is an eigenfunction of $-\frac{1}{2}\Delta + V_M$ and correspondingly ρ_n is an eigenfunction of $-\frac{1}{2}\Delta + V_1$, then the first term in $(\phi_i|\mathcal{H}|\chi_i)$ and $(\chi_i|\mathcal{H}|\phi_i)$ becomes $\epsilon_{\chi_i}S(\rho_n, \chi_i)$ and $\epsilon_{\rho_n}S(\rho_n, \chi_i)$ respectively. By considering the off-diagonal term as $H(\phi_i, \chi_i) = \frac{1}{2}[(\phi_i|\mathcal{H}|\chi_i) + (\chi_i|\mathcal{H}|\phi_i)]$, one can write

$$H(\phi_i, \chi_i) = C\left\{\frac{(\epsilon_{\chi_i} + \epsilon_{\rho_n})S(\rho_n, \chi_i)}{2} + \left(\rho_n\left|\sum_{j=2} V_j\right|\chi_i\right) + \frac{1}{2}[(\rho_n|V_M|\chi_i) + (\rho_n|V_1|\chi_i)]\right\} \quad (13)$$

Note that when the first term in the brackets is multiplied by C it becomes $(\epsilon_{\chi_i} + \epsilon_{\rho_n})G(\phi_i, \chi_i)/2$ which is identical with the Wolfsberg-Helmholz relationship for $F = 1.00$. This latter value, it will be recalled, was employed by Oleari, *et al.*⁴ Thus, their approximation assumes the additional Coulomb terms cancel one another. Correspondingly, as Richardson pointed out long ago,²² the use of F factors larger than 1.00 in the off-diagonal term attempts to correct by *multiplicative* factors for the *added* potential terms. What Richardson was not in a position to do at the time was to explore the reasonableness of an approximation involving the overlap integral, $S(\rho_n, \chi_i)$, for evaluation of the two- and three-center electrostatic interactions. As a by-product of our recently completed calculations on chloride complexes in octahedral and tetrahedral symmetry,²⁵ we have reached the conclusion that estimations of the electrostatic interaction and nuclear attraction integrals involved in $H(\phi_i, \chi_i)$ cannot be systematically made from the corresponding overlap integral. Consequently, it is not surprising that off-diagonal terms which are estimated from a product function involving overlap integrals should require substantial adjustments, by variable F factors and the other cited methods, when going from one compound to the next. Furthermore, it does not seem likely that product functions involving the overlap integral only can be systematized to reliably reproduce the value of the off-diagonal matrix elements. Computational evidence of these conclusions is given in the next section.

Calculations

Examination of eq 13 suggests that the Wolfsberg-Helmholz approximation for the off-diagonal matrix element would be adequate from one complex to another if one of two situations applied: (1) the additional terms, $(\rho_n|\sum V_j|\chi_i)$, etc., nearly cancel one another so that the dominant term in the expression for $H(\phi_i, \chi_i)$ is $CS(\rho_n, \chi_i)(\epsilon_{\chi_i} + \epsilon_{\rho_n})/2$; (2) the additional terms dis-

play the same variations from orbital to orbital and compound to compound as do the corresponding overlap integrals. Unfortunately, neither situation appears to hold.

The Magnitude of the Additional Terms. Consider the evaluation of the terms for $H(\phi_i, \chi_i)$ as given in eq 13. As we have previously indicated,³ the values of ϵ_{χ_i} , ϵ_{ρ_n} , and $S(\rho_n, \chi_i)$ present no computational problems once appropriate consideration is given to the charges and configurations of the metal and ligand species. Furthermore, it is quite reasonable to approximate the three-center interactions by

$$\left(\rho_n\left|\sum_{j=2} V_j\right|\chi_i\right) = -\sum_{j=2} q_j(1/r_j|\rho_n\chi_i) \quad (14)$$

where q_j is the calculated charge on the ligand j as obtained from a Mulliken electron population analysis²⁶ and $(1/r_j|\rho_n\chi_i)$ is a three-center nuclear attraction integral. The two remaining terms, $(\rho_n|V_M|\chi_i)$ and $(\rho_n|V_1|\chi_i)$, require special consideration. In terms of our previous techniques,³ the explicit forms of these terms are

$$(\rho_n|V_1|\chi_i) = \sum_k \bar{b}_{k1}\{2(\rho_{k1}\rho_{k1}|\rho_n\chi_i) - (\rho_{k1}\rho_n|\rho_{k1}\chi_i)\} - Z_1(1/r_1|\rho_n\chi_i) \quad (15)$$

$$(\rho_n|V_M|\chi_i) = \sum_k \bar{a}_{kM}\{2(\chi_k\chi_k|\rho_n\chi_i) - (\chi_k\rho_n|\chi_k\chi_i)\} - Z_M(1/r_M|\rho_n\chi_i) \quad (16)$$

where

$$(\psi_a\psi_b|\psi_c\psi_d) = \int \psi_a^*(1)\psi_b(1)1/r_{12}\psi_c^*(2)\psi_d(2) d\tau$$

$$(1/r_M|\psi_a\psi_b) = \int \psi_a^*(1)1/r_M\psi_b(1) d\tau$$

\bar{a}_{kM} and \bar{b}_{k1} are the fractions of the electron in the k th occupied orbital on the metal and ligand 1, respectively, as determined from the electron population analysis. For simplicity it is assumed that all inner-shell electrons, for example, those below the 3d in the metal and below the 3s on a chlorine ligand, can be incorporated into Z_M and Z_1 which then represent the core potentials rather than the nuclear charges. Even with this simplification the number of different two-center electrostatic interaction integrals associated with eq 16 becomes quite large when χ_k includes the 3d, 4s, 4p, and 4d metal wave functions with two or more Slater functions for each of the radial terms. The routine evaluation of all these integrals is computationally time consuming and expensive, particularly when one considers the many off-diagonal terms involved in $|\rho_n\chi_i\rangle$. It is for this reason that for routine calculations we have chosen to evaluate $H(\phi_i, \chi_i)$ by eq 11, since the evaluation of $(\rho_{k1}\rho_{k1}|\rho_n\chi_i)$ in $(\rho_n|V_1|\chi_i)$ need be summed only over $k = ns$ and np .

In the course of some recently completed computations,²⁵ we had an opportunity to investigate the off-diagonal term represented by eq 13 within the framework of our computational technique. If one makes the assumption²³ that the 3d orbitals are the only outer metal orbitals sufficiently contracted to result in a meaningful transfer of electron density to the metal and hence one can limit the electron population analysis to these orbitals, then $(\rho_n|V_M|\chi_i)$ becomes more computationally tractable. We have examined this and the other terms

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of the off-diagonal element for $H(3d\sigma, 3p\sigma_1)$ and $H(3d\pi, 3p\pi_1)$ in FeCl_6^{-3} at a self-consistent charge on the metal of +1.75. Within the framework of the Slater average of configuration approximations the calculated values for the various terms are summarized in Table I.

Table I. Terms in $(3p\sigma_1|\mathcal{H}|3d\sigma)$ and $(3p\pi_1|\mathcal{H}|3d\pi)$ of FeCl_6^{-3}

	$(3p\sigma_1, 3d\sigma)$	$(3p\pi_1, 3d\pi)$
$S(\rho_{il}, \chi_i)$	0.074	0.044
3d orbital energy, ev	-28.49	-28.49
3p orbital energy, ev	-6.86	-6.86
$(\rho_{il} \sum_{j=2}^5 V_j \chi_i)$, ev	+1.40	+0.89
$(\rho_{il} V_M \chi_i)$, ev	-3.07	-1.42
$(\rho_{il} V_1 \chi_i)$, ev	-1.30	-0.42
$H(\rho_{il}, \chi_i)$, eq 13, ev	-2.09	-0.81
$H(\rho_{il}, \chi_i)$, eq 11, ev	-2.01	-0.77
$S(\epsilon_{3d} + \epsilon_{3p})/2$	-1.31	-0.78
F	1.60 (1.54)*	1.04 (0.99)*

* The F value in parentheses is that required to obtain agreement between $FS(\epsilon_{3d} + \epsilon_{3p})/2$ and $H(\rho_{il}, \chi_i)$ obtained from eq 11. The F value not in parentheses is needed to duplicate $H(\rho_{il}, \chi_i)$ by eq 13.

First of all, one notes that there is very good agreement between the values of $H(\rho_{il}, \chi_i)$ determined by eq 11 and 13. When one considers the necessary approximations in each of these computations, such agreement is very satisfying. At the very least it indicates a substantial degree of internal consistency within the model framework. It might also be noted in passing that the addition of a constant potential to the Hamiltonian operator for the diagonal terms offers no dilemma for the off-diagonal elements as given by eq 11 or 13 since they would increase by the value $-ZG(\phi_{il}, \chi_i)$ as required to maintain the previously mentioned constancy of separation between the eigenvalues.

It is also apparent that the formula, $FS(\rho_{il}, \chi_i) \cdot (\epsilon_{3d} + \epsilon_{3p})/2$ with $F = 1$, does occasionally yield a value for the off-diagonal term which is approximately correct, as in the case of $(3p\pi_1|\mathcal{H}|3d\pi)$ for FeCl_6^{-3} . However, the relationship is not generally applicable as indicated by the values for $(3p\sigma_1|\mathcal{H}|3d\sigma)$. In general, the additional terms in eq 13 do not cancel one another, and they have an important influence on the value of the off-diagonal term.

If one assumes that the good agreement between results from eq 11 and 13 is maintained for other off-diagonal matrix elements, and that the values obtained by these equations are good estimates of the matrix elements, it is a simple task to examine the trends in F values necessary to obtain agreement between $FS \cdot (\epsilon_{3d} + \epsilon_{3p})/2$ and the values from eq 11. The F values for the two complexes, FeCl_6^{-3} and FeCl_4^{-} , are summarized in Table II. The wide variations in the values for F within and/or between the two complexes strikingly illustrates the futility of attempting to achieve identity between the sets of off-diagonal terms by means of one or two fixed values of F . It is obvious that the variations in the off-diagonal terms cannot be systematically related to the changes in overlap only.

Variations of the Terms from Complex to Complex. There is additional evidence that one cannot expect a simple correlation of overlap with the corresponding off-diagonal element. This is exemplified by examination of the trends in the term $(\rho_{il}|V_1|\chi_i)$, whose ex-

Table II. F Values for $FS(\epsilon_{3d} + \epsilon_{3p})/2 = (\rho_{il}|\mathcal{H}|\chi_i)$

	FeCl_6^{-3} (4.50 au)*	FeCl_4^{-} (4.14 au)*
$(3d\sigma, 3s)$	1.28	1.70
$(3d\sigma, 3p\sigma)$	1.53	2.18
$(3d\pi, 3p\pi)$	0.99	1.60
$(4s, 3s)$	1.32	1.73
$(4s, 3p\sigma)$	0.86	1.57
$(4p\sigma, 3s)$	1.36	1.81
$(4p\sigma, 3p\sigma)$	0.87	2.69
$(4p\pi, 3p\pi)$	0.62	1.41
$(4d\sigma, 3s)$	1.45	2.06
$(4d\sigma, 3p\sigma)$	2.75	4.49
$(4d\pi, 3p\pi)$	0.22	1.58

* Internuclear distance between the metal and chlorine atoms.

plicit form is given in eq 15. For simplicity of discussion, it is convenient to examine eq 15 in the ionic limit, that is, $b_{kl} = 1$ for $k = 3s$ and $3p$. In this case, the two-center electrostatic interaction integrals then become

$$\sum_{k=3s, 3p} 2(\rho_{kl}\rho_{kl}|\rho_{il}\chi_i) - (\rho_{kl}\rho_{il}|\rho_{kl}\chi_i)$$

In our previous paper³ we suggested that this summation might be approximated by the relationship, $7R \cdot (1/r_{il}|\rho_{il}\chi_i)$, where $(1/r_{il}|\rho_{il}\chi_i)$ is the two-center nuclear attraction integral, the value of 7 accounts for the summation over the s and p orbitals, and R is a constant which depends upon ρ_{il} and χ_i . We have now obtained some substantiation that the assumption implicit in our previous work has validity, namely, that the value of R for a given off-diagonal term is essentially invariant to changes in metal wave function, ligand wave function, and internuclear distance. To test this relationship, we carried out computations of the two-center interactions²⁷ for three chloride and two fluoride complexes involving octahedral and tetrahedral symmetry with internuclear distances ranging from 1.93 to 2.38 Å. The values of R for the metal 3d interactions with the ligand ns and np orbitals were then computed from the equation

$$7R(1/r_{il}|\rho_{il}\chi_i) = \sum_{k=ns, np} 2(\rho_{kl}\rho_{kl}|\rho_{il}\chi_i) - (\rho_{kl}\rho_{il}|\rho_{kl}\chi_i) \quad (17)$$

The R values corresponding to a given ρ_{il} and χ_i are given in the first part of Table III. Two conclusions

Table III. R and f Values as a Function of the Complex

	TiCl_4 (2.18 Å)	CrCl_6^{-3} (2.34 Å)	FeCl_6^{-3} (2.38 Å)	CrF_6^{-3} (1.93 Å)	NiF_6^{-3} (2.01 Å)
$R(3d\sigma, ns)$	0.78	0.76	0.77	0.76	0.79
$R(3d\sigma, np\sigma)$	0.84	0.83	0.84	0.83	0.86
$R(3d\pi, np\pi)$	0.88	0.88	0.90	0.88	0.90
$f(3d\sigma, ns)$	0.43	0.39	0.38	0.61	0.56
$f(3d\sigma, np\sigma)$	0.46	0.44	0.42	0.60	0.55
$f(3d\pi, np\pi)$	0.36	0.34	0.33	0.45	0.42

can be drawn: (1) each set (ρ_{il}, χ_i) has its appropriate value of R ; (2) the variations of R values with changing ligands, metals, symmetries, and distances are within

(27) The two-center electrostatic interaction program adapted to the Control Data Corp. computers was kindly supplied to us by Professor F. A. Matson, Molecular Physics Group, University of Texas, Austin, Tex.

4% of one another. This latter conclusion suggests that changes in electrostatic interactions of the type given by the right-hand side of eq 17 result in a similar change in the corresponding nuclear attraction integral. Having once determined the appropriate R values by exact calculation of the electrostatic interactions for one complex, one may use the same R values for related species with reasonable confidence. That this same relation does not hold true for the overlap integrals is indicated by the values of f in Table III calculated from the relationship

$$7fS(\rho_{i1}, \chi_i) = \sum_{k=3s, 3p} 2(\rho_{k1}\rho_{k1}|\rho_{i1}\chi_i) - (\rho_{k1}\rho_{i1}|\rho_{k1}\chi_i)$$

As indicated by the f values, the range of values within the chlorides is of the order of 10% and changing from chloride to fluoride complexes alters the f 's by about 30%. Thus, it is apparent that a single f factor times the overlap integral is incapable of properly approximating this important term in the off-diagonal matrix element.

By a similar study, it is possible to show that there is no consistent relation between the overlap integral, $S(\rho_{i1}, \chi_i)$, and the three-center term, $(\rho_{i1}|\sum_{j=2} V_j|\chi_i)$, in the off-diagonal element.

Summary

It seems fairly clear that the use of F factors which multiply the overlap integrals is incapable of consistent approximation of the off-diagonal matrix elements. On the contrary, there is good indication that the additional terms given by eq 11 or 13 are related to the corresponding nuclear attraction integrals. Since it has been shown that the relative positions and separations of the final energy levels are sensitive functions of the off-diagonal terms, it is not inconceivable that energy levels in systems of low symmetry, such as tetragonal or square-planar symmetry, might be incorrectly ordered in calculations in which the off-diagonal terms have been related to overlap integrals.

On the other hand, it appears that the relation given by eq 17 offers a convenient method to circumvent the time-consuming and expensive calculation of the two-center electrostatic interaction integrals.

Acknowledgment. The authors wish to thank the National Science Foundation (Grant GP-3413) and the Wisconsin Alumni Research Foundation for support of this work.

Organic and Biological Chemistry

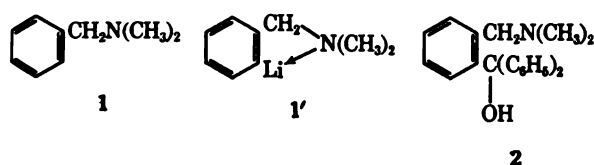
Lithiations of α - and β -Dimethylaminomethylnaphthalenes with *n*-Butyllithium and Condensations with Benzophenone. Some Related Results¹

Robert L. Gay and Charles R. Hauser

Contribution from the Department of Chemistry, Duke University, Durham, North Carolina 27706. Received November 18, 1966

Abstract: α -Dimethylaminomethylnaphthalene was lithiated with *n*-butyllithium in ether-hexane to form a mixture of the 8- and 2-lithioamines in which the former predominated in a ratio of about 91:9; this was shown by treatment of the mixture with benzophenone and nmr analysis of the resulting carbinolamines. The 8 derivative was isolated in 58% yield, suggesting a useful new route for the synthesis of *peri* compounds. β -Dimethylaminomethylnaphthalene was treated similarly to produce a mixture of the 3- and 1-lithioamines in a ratio of about 55:45; after treatment with benzophenone, the 2,3-disubstituted naphthalene compound was isolated in 25% yield. These lithioamine ratios were found not to change significantly over a wide range of lithiation times. Independent syntheses of three of the four carbinolamines indicated above were carried out and some further reactions of these compounds were effected.

Recently,² benzyldimethylamine (1) was lithiated with *n*-butyllithium in ether-hexane to form *o*-lithioamine 1', which was condensed with benzophenone to give carbinolamine 2. This product was converted to several derivatives.

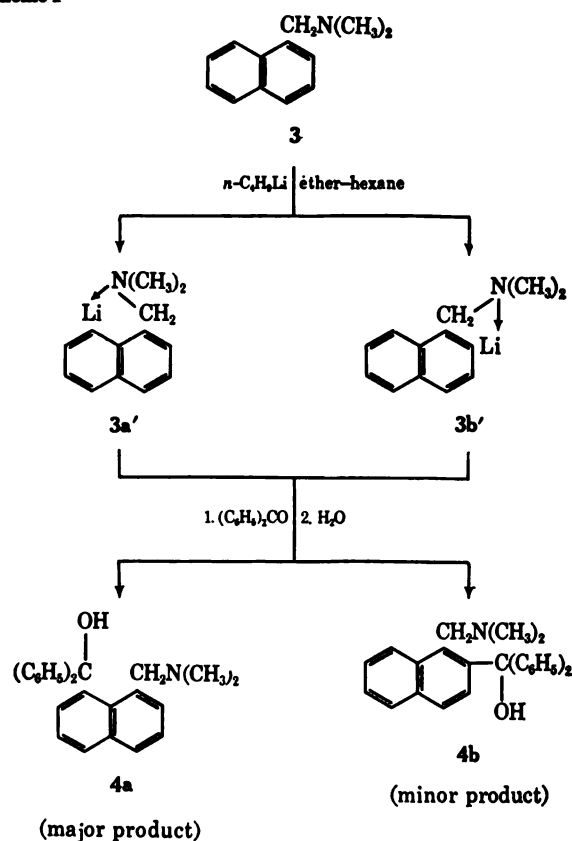


In the present investigation, a similar study was made of α - and β -dimethylaminomethylnaphthalenes which promised to be of special interest because of the possibility of lithiation at two nonequivalent positions in each case.

Results with α -Dimethylaminomethylnaphthalene (3). This amine might conceivably undergo lithiation at either the 8 position to form lithioamine 3a' or the 2 position to form lithioamine 3b'; condensations of 3a' and 3b' with benzophenone would afford carbinolamines 4a and b, respectively (Scheme I).

This lithiation-condensation reaction was found to afford largely carbinolamine 4a, which was readily isolated in 58% yield. The crude reaction product, obtained in about 79% yield, was shown by thin layer chromatography (tlc) to consist not only of 4a but also of another component, presumably the isomeric carbinolamine 4b; evidence for 4b as the minor product is presented below. Actually, predominant *ortho* lithiation of 3 leading to 4b had been expected, since such *ortho* lithiation of amine 1 occurs exclusively.^{2,3} The

Scheme I



product isolated was shown to be carbinolamine 4a or b by analysis and by infrared and nmr spectra (see Tables I and II). Its structure was established as 4a by independent synthesis from anhydride 5 through the known bromo acid 6 (Scheme II).

Bromo acid 6 agreed with its previously reported description.⁴ The structures of the intermediate bromo

(1) Supported by the Petroleum Research Fund administered by the American Chemical Society and by the Army Research Office (Durham).

(2) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963).

(3) For further demonstration of the strong tendency of the lithium atom to occupy an *ortho* position in lithioamine 1' see W. H. Puterbaugh and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 2467 (1963).

(4) H. G. Rule, W. Purcell, and R. R. H. Brown, *J. Chem. Soc.*, 170 (1934).

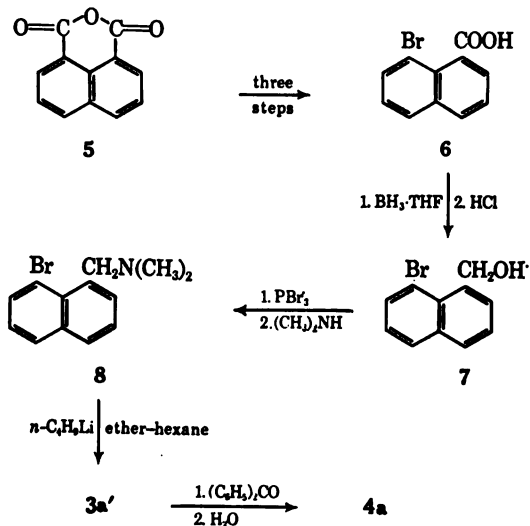
Table I. Infrared Data

Compd	Functional Group	group absorptions— Peak, cm ⁻¹	Aromatic absorptions, cm ⁻¹ ^a
3	CH ₂ N(CH ₂) ₂	840 ^b	765 ^c 790 ^d
4a	CH ₂ N(CH ₂) ₂	852 ^b	776, 703 ^f
7	OH (tertiary)	3425 (1171, 1379) ^e	763 ^d
8	OH (primary)	3401 (1058, 1304) ^e	759 ^d
11	CH ₂ N(CH ₂) ₂	847 ^b	765 ^d
16	C—O—C (cyclic)	1078, 1062 ^e	779, 699 ^f 768 ^d
17a	CH ₂ N(CH ₂) ₂	833 ^b	775 ^e 791 ^d
17b	OH (tertiary)	3436 (1175, 1346) ^e	759, 702 ^f 750 ^e 894 ^h
20	C=O (amide)	1633 ^f	744 ^e 888 ^h
21	CH ₂ N(CH ₂) ₂	837 ^b	743 ^e 881 ^h
24	CH ₂ N(CH ₂) ₂	847 ^b	754 ^e 812 ⁱ
25	CH ₂ N(CH ₂) ₂	845 ^b	754, 701 ^f 776 ^e 901 ^h
28	C—O—C (cyclic)	1032, 1025 ^e	759, 697 ^f 748 ^e 810 ⁱ

^a See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, pp 75–79. ^b See W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960). ^c Four adjacent aromatic hydrogens. ^d Three adjacent aromatic hydrogens. ^e See footnote a, p 96. ^f Five adjacent aromatic hydrogens. ^g See footnote a, p 119. ^h One aromatic hydrogen. ⁱ Two adjacent aromatic hydrogens. ^j See footnote a, p 205.

alcohol 7 and bromo amine 8 were supported by analysis and absorption spectra (see Tables I and II). The over-all yield of carbinolamine 4a from anhydride 5 was 23%, which is considerably lower than that (58%) obtained from amine 3 (see Scheme I).

Scheme II



Although carbinolamine 4b was not isolated from the product mixture obtained according to Scheme I, it was indicated to be present in relatively small amount by comparison of the nmr spectrum of this mixture

Table II. Nmr Data

Compd ^a	Type of hydrogen	Peak character	Peak center or over-all range, ppm ^b	No. of hydrogens ^c
3	Methyl	Singlet	2.13	5.9(6)
	Methylene	Singlet	3.63	2.0(2)
	Aromatic	Multiplet	7.10–8.30	7.2(7)
4a	Methyl	Singlet	1.95	5.9(6)
	Methylene	Singlet	3.24	2.0(2)
	Aromatic	Multiplet	6.90–7.99	16.8(17) ^d
4a + 4b (mixt) ^e	Methyl	Two singlets	1.95 2.17	5.46(6) 0.52
	Methylene	Two singlets	3.25 3.66	1.75(2) 0.17
	Aromatic	Multiplet	6.96–8.00	16.7(17) ^d
7	Hydroxyl	Singlet	3.05	1.1(1)
	Methylene	Singlet	5.38	1.9(2)
	Aromatic	Multiplet	6.90–7.92	5.9(6)
8	Methyl	Singlet	2.12	6.0(6)
	Methylene	Singlet	4.16	2.0(2)
	Aromatic	Multiplet	6.76–7.90	6.0(6)
11	Methylene	Singlet	4.88	2.0(2)
	Aromatic	Multiplet	6.70–7.85	16.3(16)
16	Methyl	Singlet	1.84	5.9(6)
	Methylene	Singlet	3.14	2.0(2)
	Aromatic	Multiplet	7.00–7.77	6.9(7)
17a	Methyl	Singlet	2.07	5.8(6)
	Methylene	Singlet	3.04	2.1(2)
	Aromatic	Multiplet	6.92–7.75	17.4(17) ^d
17b	Methyl	Singlet	2.06	6.1(6)
	Methylene	Singlet	3.60	1.9(2)
	Aromatic	Multiplet	6.58–7.79	17.5(17) ^d
17a + 17b (mixt) ^f	Methyl	Singlet	2.07	6.1(6)
	Methylene	Two singlets	3.06 3.63	1.12(2) 0.85
	Aromatic	Multiplet	6.67–7.86	17.0(17) ^d
20	Methyl	Two singlets	2.83 3.16	2.9(3) 3.1(3)
	Aromatic	Multiplet	7.26–8.24	6.1(6)
21 ^g	Methyl	Singlet	2.16	5.9(6)
	Methylene	Singlet	3.49	2.0(2)
	Aromatic	Multiplet	6.97–7.94	6.1(6)
24	Methyl	Singlet	1.79	6.0(6)
	Methylene	Singlet	3.27	2.0(2)
	Aromatic	Multiplet	6.65–8.16	6.0(6)
25	N-Methyl	Singlet	2.06	5.7(6)
	C-Methyl	Singlet	2.18	3.0(3)
	Hydroxyl	Singlet	3.14	1.0(1)
	Methylene	Singlet	3.67	1.9(2)
	Aromatic	Multiplet	6.93–8.20	15.6(15)
28	Methylene	Singlet	5.22	2.9(2)
	Aromatic	Multiplet	7.00–8.00	16.3(16)

^a The solvent used was deuteriochloroform unless otherwise stated. ^b Downfield from tetramethylsilane (TMS) = 0 (internal standard). ^c Obtained by integration of peak areas; usually the reported value is the average of three integrations. The value in parentheses is the theoretical number of hydrogens, based on the proposed structure. ^d See ref 5. ^e Data for a 1-hr lithiation of amine 3; see Table III, entry two, for calculations based on this data. ^f Data for a 24-hr lithiation of amine 16; see Table IV, entry three, for calculations based on this data. ^g Run as a neat liquid.

with that of authentic carbinolamine 4a (see Table II). Thus, the methylene and N-methyl peaks observed in the spectrum of 4a were found also in that of the mixture. In addition, the latter spectrum showed two similar, but much smaller, peaks that may be ascribed to the same groups in 4b (see Table II). In support of these conclusions, the areas (by integration) of the methyl and methylene peaks assigned to 4b afforded a ratio of 3.1:1 (theoretical ratio, 3:1). Also, the total values of the integrations for each type of hydrogen in

the spectrum of the mixture afforded a ratio of 6:1.9:16.7 for methyl:methylene:aromatic⁵ hydrogens (theoretical ratio, 6:2:17).

The relative amounts of isomeric carbinolamines **4a** and **b** in the mixture obtained according to Scheme I were estimated from the ratio of the integration values of their respective methyl (or methylene) peaks. Table III contains ratios of **4a** and **b** obtained in this manner from a series of experiments in which amine **3** was lithiated for various lengths of time followed by standardized periods for condensation with benzophenone and hydrolysis. These values show that the lithiation of amine **3** at the 8 position was favored over lithiation at the 2 position by about 91:9. The slight but steady increase in the amount of **4a** relative to lengths of reaction time may or may not be of significance. If a conversion of intermediate lithioamine **3b'** to lithioamine **3a'** occurs, it must do so very slowly, since the range of lithiation times employed was wide.

Table III. Reaction of Amine **3** According to Scheme I for Different Lithiation Times, Product Mixture Proportions by Nmr^a

Reaction time	Total yield 4a + 4b , %	Ratio ^b 4a : 4b	%—	
			4a ^c	4b ^d
5 min	27.7 ^e	9.8	90.7	9.3
1 hr ^f	66.4	10.4	91.2	8.8
24 hr ^g	79.4	11.3	91.8	8.2
48 hr	52.7 ^h	11.5	92.0	8.0

^a In all cases, three integrations were recorded and their average value was used for further calculations. ^b This ratio was obtained by dividing the average integration value for the methylene peak at 3.25 ppm by the average value for the methylene peak at 3.66 ppm. ^c This percentage was obtained by dividing the average integration value for the methylene peak at 3.25 ppm by the sum of the average values for both methylene peaks, and multiplying the resulting number by 100. ^d This percentage was obtained by subtracting the percentage obtained in *c* from 100. ^e In this experiment 53.8% of starting amine **3** was recovered by distillation. ^f See Table II, entry three, for additional data on this mixture. ^g In a similar experiment in which the *n*-butyllithium used was prepared in ether [see H. Gilman, J. Beel, C. Brannen, M. Bullock, G. Dunn, and L. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949)], the total yield (**4a** + **4b**) was 85%, the ratio (**4a**:**4b**) was 9.5, and the percentage of **4a** was 90.3. ^h In this experiment 30.2% of starting amine **3** was recovered by distillation.

Further evidence that lithiation of amine **3** involved mainly the 8-hydrogen (*peri* hydrogen) was obtained by treatment of a lithiation mixture of **3a'** and **3b'** (after 24 hr) with deuterium oxide. The nmr spectrum of the resulting deuterated amine showed that the 8-hydrogen, which appears downfield from the rest of the aromatic hydrogens because of deshielding,⁶ had been substituted by deuterium to the extent of 79%.

The highly preferential lithiation at the 8 position of amine **3** furnishes a new route to the synthesis of *peri* compounds, as illustrated by the condensation of the

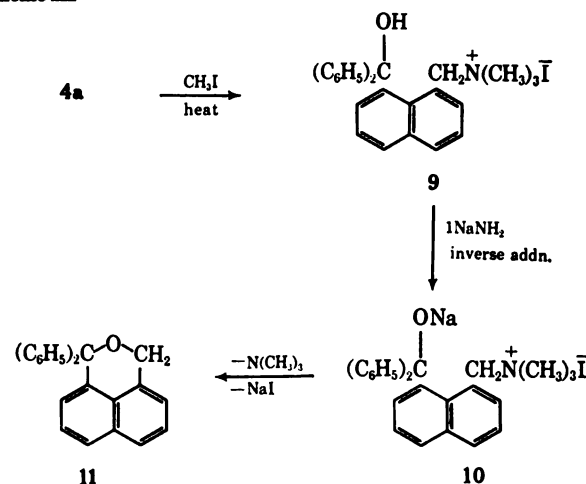
(5) It is assumed that the peak for the hydroxyl hydrogen, which could be found nowhere else in the spectra of either the pure carbinolamines or their mixtures, is hidden within the aromatic multiplet; when deuteriochloroform solutions of these compounds were treated with deuterium oxide prior to analysis, the area of the aromatic portion of their spectra was reduced.

(6) For a discussion (and other examples) of such deshielding of the *peri* hydrogen of other 1-substituted naphthalenes see G. O. Dudek, *Spectrochim. Acta*, **19**, 697 (1963). We are indebted to Dr. P. W. Jeffs for help in the interpretation of our nmr data.

resulting lithioamine **3a'** with benzophenone to form carbinolamine **4a**. Presumably intermediate **3a'** could be condensed with other electrophilic compounds to form the corresponding *peri* products.

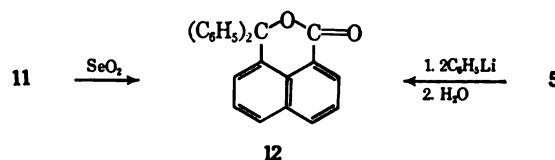
Moreover, such *peri* compounds may be converted to other 1,8 derivatives. For example, carbinolamine **4a** was converted to its methiodide **9**, which was cyclized by means of sodium amide to cyclic ether **11** in 89% yield (Scheme III).

Scheme III



The structure of **11** was supported by analysis and by infrared and nmr spectra (see Tables I and II). Also **11** was converted to lactone **12**, which was independently synthesized from anhydride **5** by a known method⁷ (Scheme IV).

Scheme IV



Although the selenium dioxide oxidation of ether **11** afforded lactone **12** in only 11% yield, no other product was isolated; probably the yield of **12** from **11** could be improved. Attempts to reduce lactone **12** back to ether **11** with lithium aluminum hydride in ethyl ether were unsuccessful; instead of **11**, an acetal was obtained on recrystallization from ethanol. A similar observation has previously been reported.⁸

Interestingly, the preferential lithiation at the 8 position of α -dimethylaminomethylnaphthalene **3** is to be contrasted with the previously observed^{9,10} preferential lithiation at the 2 position of α -methoxynaphthalene **13**.¹¹ Thus, lithiation of **13**, followed by carbonation, has afforded much more of acid **14** than acid **15**; the ratio of **14** to **15** was 83:17 with commercial *n*-butyllithium in hexane but 65:35 with the reagent prepared in ether.^{9a} Incidentally, we observed no appreciable

(7) G. Wittig, M. Leo, and W. Wiemer, *Ber.*, **64**, 2410 (1931).

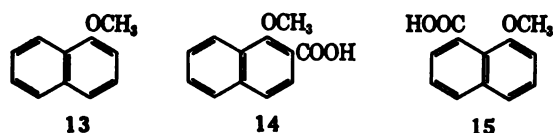
(8) R. L. Letsinger and P. T. Lansbury, *J. Am. Chem. Soc.*, **81**, 939 (1959).

(9) (a) B. M. Graybill and D. A. Shirley, *J. Org. Chem.*, **31**, 1221 (1966); (b) S. V. Sunthakar and H. Gilman, *ibid.*, **16**, 8 (1951).

(10) R. A. Barnes and L. J. Nehmsmann [*ibid.*, **27**, 1939 (1962)] proposed that, initially, 8-lithio-1-methoxynaphthalene was formed predominantly, followed by isomerization to 2-lithio-1-methoxynaphthalene; later work¹² presented evidence that such a change is negligible.

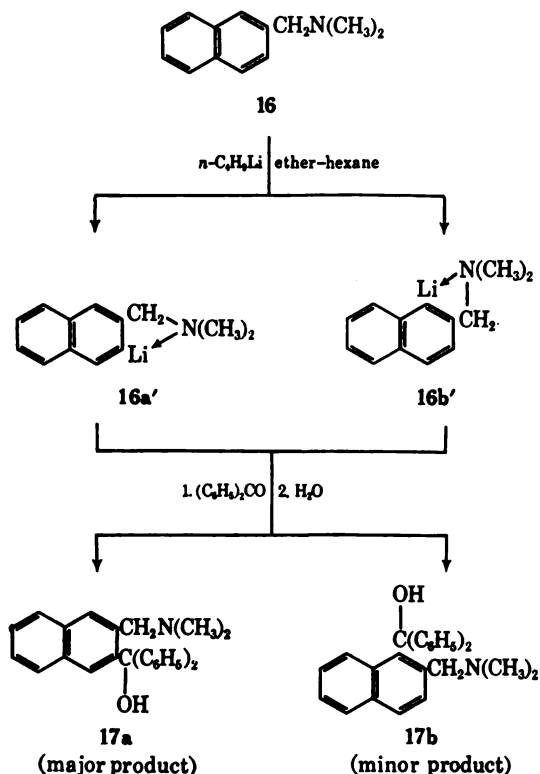
(11) The reason for this difference and the mechanism of the lithiation of these compounds are under investigation.

difference in lithiations of amine 3 under these two conditions (see Table III, footnote g).



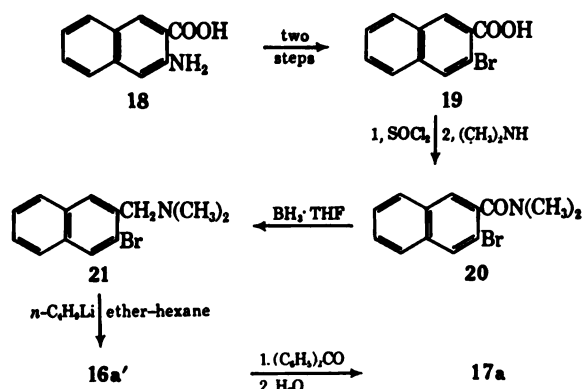
Results with β -Dimethylaminomethylnaphthalene (16). This amine might undergo lithiation at either the 3 position to form lithioamine 16a' or the 1 position to form lithioamine 16b'; condensations of 16a' and 16b' with benzophenone would afford carbinolamines 17a and b, respectively (Scheme V).

Scheme V



Actually, the crude condensation product, obtained in 79% yield, was shown by tlc to consist of two components, one of which was isolated in 25% yield by fractional crystallization. That the compound thus isolated was 17a was supported by analysis and by infrared and nmr spectra (see Tables I and II); its structure was confirmed by independent synthesis from amino acid 18 through the known bromo acid 19 (Scheme VI).

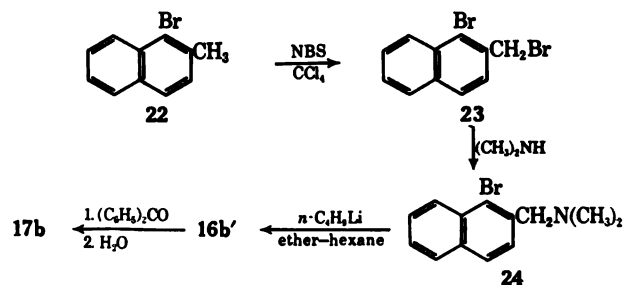
Scheme VI



Bromo acid 19 agreed with its previously reported description.¹² The structures of intermediate bromo amide 20 and bromo amine 21 were supported by analysis and absorption spectra (see Tables I and II). The over-all yield of carbinolamine 17a from amino acid 18 was 20%, which is lower than that (25%) obtained by the much easier method shown in Scheme V.

Although carbinolamine 17b was not isolated from the reaction mixture obtained according to Scheme V, it was shown to be present by comparison of the nmr spectrum of this mixture with those of independently synthesized samples of 17a (Scheme VI) and 17b; the latter was prepared from 22 through the known dibromide 23 (Scheme VII). Clearly the peaks exhibited by 17a and 17b accounted fully for those shown by the mixture (see Table II).

Scheme VII



Dibromide 23 agreed with its previously reported description.¹³ The structure of bromo amine 24 was supported by analysis and by infrared and nmr spectra (see Tables I and II). The over-all yield of carbinolamine 17b from bromide 22 was 46%.

The relative amounts of isomeric carbinolamines 17a and 17b in the mixture obtained according to Scheme V were estimated from the ratio of the integration values for their respective methylene peaks. Table IV contains ratios of 17a and b obtained in this manner for a series of experiments in which amine 16 was lithiated for various lengths of time followed by standardized periods for

Table IV. Reaction of Amine 16 According to Scheme V for Different Lithiation Times, Product Mixture Proportions by Nmr^a

Reaction time	Total yield 17a + 17b, %	Ratio ^b 17a:17b	Percentage ^c	
			17a ^e	17b ^d
5 min	7.4 ^f	1.11	52.7	47.3
1 hr	53.8 ^g	1.27	55.8	44.2
24 hr ^h	78.3	1.32	56.8	43.2
48 hr	79.4	1.37	57.8	42.2

^a In all cases, three integrations were recorded and their average value was used for further calculations. ^b This ratio was obtained by dividing the average integration value for the methylene peak at 3.06 ppm by the average value for the methylene peak at 3.63 ppm. ^c This percentage was obtained by dividing the average integration value for the methylene peak at 3.06 ppm by the sum of the average values for both methylene peaks, and multiplying the resulting number by 100. ^d This percentage was obtained by subtracting the percentage obtained in c from 100. ^e In this experiment 78.8% of the starting amine 16 was recovered by distillation. ^f In this experiment 21% of the starting amine 16 was recovered by distillation. ^g See Table II, entry ten, for additional data on this mixture.

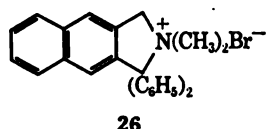
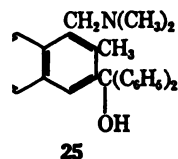
(12) J. Kenner, W. H. Ritchie, and R. L. Wain, *J. Chem. Soc.*, 1528 (1937).

(13) J. B. Shoosmith and H. Rubli, *ibid.*, 3102 (1927).

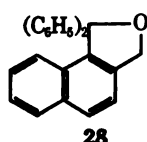
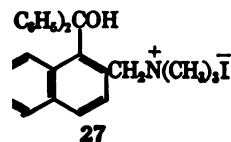
ation with benzophenone and hydrolysis. values show that the lithiation of amine 16 at position was favored over lithiation at the 1 position about 55:45. The slight but steady increase in amount of 17a relative to lengths of reaction time may not be of significance.

preferential lithiation of amine 16 at the 3 position furnishes an easy route to the synthesis of 2,3-substituted naphthalene compounds, as illustrated by the condensation of lithioamine 16a' with benzophenone to form 17a. Presumably intermediate 16a' could be condensed with other electrophilic compounds to afford other 2,3-substituted naphthalenes.

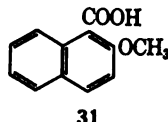
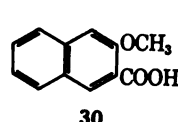
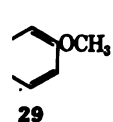
Moreover, such 2,3-substituted naphthalenes may be used to other 2,3 derivatives. Thus, carbinol-17a was converted to its methiodide which was reduced by means of excess potassium amide to amine 25 in 70% yield.¹⁴ The structure of 25 is supported by analysis and by infrared and nmr (see Tables I and II). Also, 17a was treated with hydrobromic acid to form apparently quaternary 195% yield.



In connection with this work, carbinolamine 17b (Scheme VII) was converted to its methiodide 27, which was thermally cyclized to naphthofuran 28 by a previously developed in this laboratory.¹⁵ The structure of cyclic ether 28 was supported by analysis and by infrared and nmr spectra (see Tables I and



preferential lithiation at the 3 position of amine comparable to that at the 3 position of β -methoxy-1-ene 29 observed previously.^{9b} The latter was evidenced by carbonation to form methoxy 30 in 50% yield; none of the isomeric acid 31 was observed.^{9b}



have observed that lithiation of methoxy compound 9 with *n*-butyllithium in ether-hexane appears to give a mixture of lithio intermediates, since treatment with benzophenone afforded two products (by

Experimental Section

Melting points, taken on a Thomas-Hoover capillary melting point apparatus, are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord. Solids were prepared as potassium bromide pellets and liquids were run neat between sodium chloride plates. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer using deuteriochloroform solutions and tetramethylsilane as an internal standard. These spectra were integrated three times and the average value used to calculate the relative number of hydrogens associated with each peak. Thin layer chromatographic (tlc) analyses were performed on microscope slides covered with a thin layer of Silica Gel G (Merck). Chloroform solutions of the material to be tested were spotted onto the plates, which were eluted with benzene and subsequently developed by standing in a jar containing crushed iodine crystals. Elemental analyses were performed by Paul Demoen, Janssen Pharmaceutical Research Laboratories, Beerse, Belgium.

α -Dimethylaminomethylnaphthalene (3). A solution of 500 g (2.83 moles) of 1-chloromethylnaphthalene and 550 g (12.2 moles) of anhydrous dimethylamine in 4 l. of absolute ethanol was stirred magnetically in a tightly stoppered flask at room temperature for 1 week. The solvent was removed, and the residue was stirred with excess 6 *M* sodium hydroxide and ether. The layers were separated. The alkaline aqueous layer was extracted with ether and the ethereal extracts were combined with the original ether layer. This ether solution was extracted with 3 *M* hydrochloric acid, and the acidic extracts were then made strongly alkaline. The resulting mixture was shaken with ether, and the layers were separated. The ether layer was dried over anhydrous magnesium sulfate, and the solvent was removed. The residual oil was distilled to give 475 g (91%) of α -dimethylaminomethylnaphthalene (3), bp 98–103° (0.5 mm) [lit.¹⁶ bp 148–152° (16 mm)]. The picrate, after several recrystallizations from 95% ethanol, melted at 144–146° (lit.¹⁶ mp 145°).

Lithiation of Amine 3 and Condensation with Benzophenone. In Table III are summarized the total yields and the estimated ratios of carbinolamines 4a and b obtained after various lithiation times. A typical experiment is described below.

To a stirred solution of 4.63 g (0.025 mole) of α -dimethylaminomethylnaphthalene (3) in 200 ml of dry ether was added 17.7 ml (0.0275 mole) of 1.55 *M* *n*-butyllithium in hexane¹⁷ to form lithioamines 3a' and 3b' (see Scheme I). The mixture was stirred magnetically in a tightly stoppered flask for 24 hr. The resulting dark red solution was added cautiously to a solution of benzophenone in 50–75 ml of dry ether, which had been brought to reflux on a steam bath. The resulting blue solution was refluxed on the steam bath for about 5 min, the volume being reduced to about 100 ml. The flask was then tightly stoppered and the solution was stirred magnetically for 12 hr to produce a precipitate. The reaction mixture was hydrolyzed with 100 ml of water, stirred for 12 hr, and filtered. The solid was washed with water and a little cold ether and dried to give 6.58 g of a mixture of carbinolamines 4a and b, mp 190–197°. The layers of the filtrate were separated. The ethereal layer was combined with three ethereal extracts of the aqueous layer. This ether solution was extracted three times with 1 *M* hydrochloric acid, and the combined acidic extracts were made strongly alkaline with 6 *M* sodium hydroxide. The resulting mixture was extracted three times with ether and the combined ethereal extract was dried over anhydrous magnesium sulfate. The solvent was removed and the residue was recrystallized from hexane to give 0.72 g of a mixture of carbinolamines 4a and b, mp 150–190°; total yield, 7.30 g (79.4%).

This product mixture was crushed and mixed well in a mortar. A sample was dissolved in deuteriochloroform for nmr analysis. The data for a similar case are listed in Table II, entry three, and the calculations based on these data are listed in Table III, entry two.

From a similar reaction (larger scale), in which the lithiation time was 48 hr, 13.55 g (73.7%) of a mixture of 4a and b was obtained. One recrystallization from acetonitrile afforded 10.72 g (58.3%) of pure 1-dimethylaminomethyl-8-diphenylhydroxymethylnaphthalene (4a), mp 198–201°, and 200–201° after further recrystallization from this solvent.

Anal. Calcd for $C_{26}H_{25}NO$: C, 85.00; H, 6.85; N, 3.82. Found: C, 85.32; H, 6.69; N, 4.05.

(16) J. V. Braun and K. Moldaehke, *Ber.*, 56B, 2169 (1923).

(17) Used as obtained from Foote Mineral Co., New Johnsonville, Tenn.

previous work on the *ortho*-substitution rearrangement of carbinolamines see R. L. Vaulx, G. C. Jones, and C. R. Hauser, *J. Org. Chem.*, 27, 4385 (1962).
R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, 29, 505 (1964).

Independent Synthesis of Carbinolamine 4a. 1,8-Naphthalic anhydride (5) was converted in 55% yield to 8-bromo-1-naphthoic (6), mp 177–179° (lit.⁴ mp 177–178°), as described previously.⁴

A solution of 25.15 g (0.10 mole) of bromo acid 6 in 60 ml of dry diglyme¹⁸ was added slowly to a stirred suspension of 3.5 g (0.093 mole) of sodium borohydride in 40 ml of dry diglyme¹⁸ under a positive nitrogen pressure, followed by a solution of 24.5 g (0.12 mole) of freshly distilled boron trifluoride etherate in 25 ml of dry diglyme¹⁸, essentially as described previously for a similar reduction.¹⁹ After stirring for 8 hr, the thick white suspension was poured onto ice (1500 ml) and 3 M hydrochloric acid (100 ml). After the ice had melted, the cold suspension was filtered, and the solid obtained was treated with sodium bicarbonate solution to remove 2.18 g (3.7%) of bromo acid 6, mp 176–178.5°. The bicarbonate-insoluble material was boiled with 100 ml of hexane, and the mixture was filtered; this treatment was repeated several times, and the combined filtrates were concentrated to afford 16.0 g (67%) of 8-bromo-1-naphthylmethanol (7), mp 86–88°, and 87–88.5° after several more recrystallizations from hexane.

Anal. Calcd for $C_{11}H_9BrO$: C, 55.72; H, 3.82; Br, 33.71. Found: C, 55.78; H, 3.79; Br, 33.92.

The phenylurethane, recrystallized from benzene, melted at 140–141°.

Anal. Calcd for $C_{19}H_{14}BrNO_2$: N, 3.93; Br, 22.43. Found: N, 4.04; Br, 22.32.

To a solution of 14.5 g (0.06 mole) of bromocarbonyl 7 in 500 ml of dry ether at –80° was added 10.8 g (0.04 mole) of phosphorus tribromide; the mixture was stirred at room temperature for 7 hr. Work-up afforded the crude dibromide (white solid), which was dissolved in 700 ml of absolute ethanol and treated with 25 ml of anhydrous dimethylamine. After stirring in a tightly stoppered flask for 24 hr, the mixture was processed as described above for the preparation of 3. Distillation of a portion of the yellow oil obtained seemed to cause decomposition, so the remaining portion was chromatographed on alumina, eluting with dry ether. The colorless oil obtained by this process was magnetically stirred *in vacuo* (1 mm) for 30 min to afford 12.23 g (75%) of 8-bromo-1-dimethylaminomethylnaphthalene (8). This colorless oil was used for spectral samples and for the further reactions described below. The picrate of 8, recrystallized three times for 95% ethanol, melted at 187–188°.

Anal. Calcd for $C_{19}H_{17}BrN_2O_7$: C, 46.27; H, 3.47; N, 11.36; Br, 16.21. Found: C, 46.22; H, 3.60; N, 11.66; Br, 16.48.

A stirred solution of 4.5 g (0.017 mole) of bromo amine 8 in 100 of dry ether was treated with 16.5 ml (0.026 mole) of 1.55 M *n*-butyllithium in hexane.¹⁷ The clear orange-red solution was stirred for 60 min in a stoppered flask and then poured cautiously into a refluxing solution of 4.97 g (0.027 mole) of benzophenone in 100 ml of dry ether. After refluxing for 1 min, the flask was stoppered, and the solution was stirred for 6 hr. The resulting suspension was hydrolyzed with 100 ml of water and processed as described above for the lithiation of amine 3 to give 4.76 g (76.3%) of carbinolamine 4a, mp 198–200°, undepressed on admixture with a sample of 4a prepared from 3. The infrared spectra of the two samples of 4a were identical.

Preparation of Methiodide 9. A solution of 9.19 g (0.025 mole) of carbinolamine 4a in 25 ml of methyl iodide was refluxed for 3 hr. Evaporation of the excess methyl iodide afforded 12.56 g (98.4%) of 1-(8-diphenylhydroxymethyl)naphthylmethyltrimethylammonium iodide (9), mp 213.5–215°, and 212–213° after precipitation from an acetonitrile solution with ether.

Anal. Calcd for $C_{27}H_{31}I_2NO$: C, 63.65; H, 5.54; N, 2.75. Found: C, 63.34; H, 5.50; N, 2.80.

Cyclization of Methiodide 9 to Ether 11. To a stirred suspension of 26 g (0.051 mole) of methiodide 9 in 600 ml of commercial anhydrous liquid ammonia was added, during 5 min, a solution of 0.054 mole of sodium amide in 150 ml of liquid ammonia.²⁰ After 1 hr, the ammonia was replaced with 500 ml of dry ether (steam bath), and the resulting suspension was shaken with 150 ml of water. Filtration afforded 8.35 g of 1,1-diphenyl-3H-naphtho[1,8-*cd*]pyran (11), mp 158–160°. The ether layer of the filtrate was separated and washed with dilute hydrochloric acid, followed by dilute sodium hydroxide. After drying over anhydrous magnesium sulfate, the solvent was removed to afford 6.40 g more of 11, mp 158–160°;

total yield 14.74 g (89%). Several recrystallizations from ethanol failed to raise the melting point.

Anal. Calcd for $C_{24}H_{16}O$: C, 89.41; H, 5.63. Found: C, 89.12; H, 5.76.

Oxidation of cyclic ether 11 was effected by heating a 1.0-g (0.0031 mole) sample with 0.5 g (0.0045 mole) of selenium dioxide at 180° for 30 min, then at 150–160° for 2.5 hr (Woods metal bath). After cooling the solid was crushed under dry ether, and the mixture was filtered. The ethereal filtrate was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed to afford 0.30 g of a solid, mp 170–190°. Two recrystallizations from absolute ethanol gave 0.11 g (11%) of 1,1-diphenyl-3-oxonaphtho[1,8-*cd*]pyran (12), mp 200–202.5°. Two more recrystallizations raised the melting point to 203–205° (lit.⁷ mp 203–205°), undepressed on admixture with authentic lactone 12 (mp 204–205.5°) prepared from anhydride 5 and phenyllithium.⁷ The infrared spectra of the two samples of 12 were identical.

Attempted reduction of lactone 12 (prepared from 5 by Wittig's method)⁷ with lithium aluminum hydride in dry ether employing a Soxhlet extractor²¹ afforded, after treatment with absolute ethanol, apparently 1,1-diphenyl-3-ethoxynaphtho[1,8-*cd*]pyran, mp 196–198°, and 198.5–201° after several more recrystallizations from absolute ethanol (lit.⁸ mp 197.5–198.5°). The yield was 76%.

β -Dimethylaminomethylnaphthalene (16). 2-Chloromethylnaphthalene, bp 102–108° (0.8 mm) [lit.²² bp 125–132° (2 mm)], was prepared in 64% yield from 2-naphthoic acid as described previously.²²

A solution of 32.6 g (0.185 mole) of this chloride and 100 ml (1.51 moles) of anhydrous dimethylamine in 300 ml of absolute ethanol was allowed to stand in a tightly stoppered flask in an ice-salt bath (dewar) for several days. The reaction mixture was then processed as described above for the preparation of amine 3 to give 23.1 g (67.4%) of β -dimethylaminomethylnaphthalene (16), bp 89–91° (0.45 mm) [lit.¹⁶ bp 130–132° (14 mm)]. The picrate of 16, recrystallized from 95% ethanol, melted at 151–152° (lit.¹⁶ mp 152°).

Lithiation of Amine 16 and Condensation with Benzophenone. In Table IV are summarized the total yields and the estimated ratios of carbinolamines 17a and 17b obtained after various lithiation times. A typical experiment is described below.

To a stirred solution of 4.63 g (0.025 mole) of β -dimethylaminomethylnaphthalene (16) in 200 ml of dry ether was added 17.7 ml (0.0275 mole) of 1.55 M *n*-butyllithium in hexane¹⁷ to form lithioamines 16a' and 16b' (Scheme V). The mixture was stirred magnetically in a tightly stoppered flask to produce a dark red suspension containing an orange precipitate. This suspension was added to benzophenone and processed as described above for the lithiation of amine 3 to give 7.19 g (78.3%) of a mixture of 17a and b, mp 142–178°. A sample was prepared for nmr analysis as there described; the resulting data for this experiment are listed in Table II, entry three, while calculations based on these data may be found in Table IV, entry three.

From a similar reaction (larger scale), in which the lithiation time was 45 hr, 19.04 g (76.4%) of a mixture of 17a and b was obtained. This product was refluxed with 500 ml of acetonitrile; after filtering, the solution was allowed to stand undisturbed overnight. The precipitated crystals were filtered and the process was repeated. Filtration afforded 6.3 g (25.3%) of pure 2-dimethylaminomethyl-3-diphenylhydroxymethylnaphthalene (17a), mp 194–197°. The analytical sample of 17a, isolated similarly, but recrystallized twice from acetonitrile and once each from ligroin and hexane, melted at 193–194.5°.

Anal. Calcd for $C_{24}H_{21}NO$: C, 85.00; H, 6.85; N, 3.82. Found: C, 84.87; H, 6.96; N, 3.72.

Independent Synthesis of Carbinolamine 17a. Amino acid²³ 18 was converted in 65% yield to 3-bromo-2-naphthoic acid (19), mp 216–218.5° (lit.¹³ mp 219–220°), as described previously.¹³

A solution of 15.86 g (0.063 mole) of bromo acid 19 and 50 ml of thionyl chloride in 50 ml of dry benzene was refluxed for 30 min. After removing the excess thionyl chloride and benzene, the residue was cooled and dissolved in 100 ml of methylene chloride. This solution was added to a cold suspension of 50 ml of dimethylamine and 250 ml of 1 M sodium hydroxide. After stirring for 3 hr, the

(18) Freshly distilled from lithium aluminum hydride.

(19) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 686 (1960).

(20) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(21) See R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1198 (1947).

(22) C. R. Hauser, D. N. van Eenam, and P. L. Bayless, *J. Org. Chem.*, **23**, 354 (1958).

(23) The preparation of amino acid 18 by Dr. D. L. Heywood and C. E. Moyer, Jr., of Union Carbide Corp., Olefins Division, South Charleston, W. Va., is gratefully acknowledged.

re was heated until the temperature of the escaping vapors reached 80°, then cooled and extracted with ether. The ethereal extract was washed with dilute acid and alkali and dried. The extract was removed to give a red liquid, which solidified *in vacuo*. The residue was boiled with 1 l. of water and the mixture filtered; the filtrate was cooled to deposit N,N-dimethyl-3-bromo-2-naphthylamine (20). This treatment was repeated several times with the solid material to give a total of 12.0 g (68.2%) of 20, mp 112–115°, 14–115° after another recrystallization from boiling water.

Anal. Calcd for $C_{13}H_{13}BrNO$: C, 56.21; H, 4.35; N, 5.03. Found: C, 55.94; H, 4.34; N, 5.10.

Solution of 6.2 g (0.022 mole) of bromo amide 20 in 50 ml of tetrahydrofuran (THF) was reduced with 66 ml (0.066 mole) of a 1 M solution of diborane in THF¹⁴ essentially as described previously for similar amides.²⁴ After stirring for 1 hr at room temperature and for another hour at reflux, the reaction mixture was cooled and hydrolyzed, first with water dropwise (caution, exothermic) and then with 50 ml of 6 M hydrochloric acid. The solution was distilled until the temperature of the vapor reached 90°, the residual mixture was cooled and extracted with ether. The ether extract was removed from the dried ethereal solution and the residual oil was distilled to afford 3.69 g (63%) of 3-bromo-2-dimethylaminomethylnaphthalene (21), bp 82–83° (0.03 mm).

Anal. Calcd for $C_{13}H_{14}BrN$: C, 59.10; H, 5.36; N, 5.32. Found: C, 58.88; H, 5.41; N, 5.21.

The picrate, recrystallized several times from 95% ethanol, melted at 172–173.5°.

Anal. Calcd for $C_{13}H_{14}BrN_4O_7$: N, 11.37. Found: N, 11.71. A stirred solution of 2.0 g (0.0076 mole) of bromo amine 21 in 10 ml of dry ether was treated with 7.3 ml of *n*-butyllithium in ether¹⁷ to produce an amber-colored suspension. After stirring magnetically for 75 min, this suspension was added to a refluxing solution of 2.21 g (0.012 mole) of benzophenone in dry ether and processed as described above for the similar reaction of bromo amine 8 to give 2.05 g (73.7%) of carbinolamine 17a, mp 192–196°, recrystallized on admixture with a sample of 17a prepared as described above. The infrared spectra of the two samples of 17a were identical.

10-Substitution Rearrangement of Methiodide of Carbinolamine 17a. A solution of 7.65 g (0.021 mole) of carbinolamine 17a in 10 ml of methyl iodide was refluxed for 36 hr. The resulting solid was collected to give 8.13 g (77%) of, presumably, 2-(3-nylhydroxymethyl)naphthylmethyltrimethylammonium iodide, mp 195–196° (temperature raised from 100°). Evaporation of the filtrate afforded some (20%) of the starting carbinolamine.

A sample of unrecrystallized methiodide of 17a (6.0 g, 0.0118 mole) was added to a stirred solution of 0.05 mole of potassium amide in 500 ml of commercial anhydrous liquid ammonia. After 4 hr, the mixture was neutralized with ammonium chloride and processed as described previously¹⁴ for the reaction of the methiodide of the related carbinolamine 2. There was obtained, on recrystallization of the product from hexane, 3.13 g (70%) of 1-dimethylaminomethyl-2-methyl-3-diphenylhydroxymethylnaphthalene, mp 126–129°, and 126–128° after several more recrystallizations from this solvent.

Anal. Calcd for $C_{27}H_{27}NO$: C, 85.01; H, 7.13; N, 3.67. Found: C, 85.02; H, 7.05; N, 3.73.

Obtained from Metal Hydrides, Inc., Beverly, Mass.
H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3567 (1964).

Cyclization of Carbinolamine 17a. This compound (0.75 g, 0.002 mole) was refluxed with 25 ml of hydrobromic acid for 6 hr. The resulting solid was collected and washed with small portions of water and dry ether to give 0.81 g (92%) of apparently 2,2-dimethyl-3,3-diphenylbenz[*f*]isoindolinium bromide (26), mp 288–290°, and 299–300° after recrystallization from acetonitrile.

Anal. Calcd for $C_{26}H_{26}BrN$: C, 72.60; H, 5.62; N, 3.25. Found: C, 72.64; H, 5.73; N, 3.38.

Independent Synthesis of Carbinolamine 17b. A mixture of 53.4 g (0.242 mole) of 1-bromo-2-methylnaphthalene (22) and 49.1 g (0.273 mole) of *N*-bromosuccinimide (NBS) in 300 ml of dry carbon tetrachloride was stirred and refluxed (no catalyst was used) for 14 hr, essentially as described previously.¹³ The product was recrystallized from ligroin to afford 48.80 g (67%) of 1-bromo-2-bromomethylnaphthalene (23), mp 105.5–107.5° (lit.¹³ mp 107°).

A cold stirred solution of 88 g (0.293 mole) of dibromide 23 in 600 ml of absolute ethanol was treated with 53 g (1.18 moles) of anhydrous dimethylamine. After stirring and heating at 110° in a tightly stoppered flask for 20 hr, the reaction mixture was processed as described above for amine 3 to give 69.7 g (90%) of 1-bromo-2-dimethylaminomethylnaphthalene (24), bp 98° (0.14 mm).

Anal. Calcd for $C_{13}H_{14}BrN$: C, 59.10; H, 5.36; N, 5.32. Found: C, 59.29; H, 5.42; N, 5.65.

The picrate, recrystallized from 95% ethanol, melted at 142–143.5°.

Anal. Calcd for $C_{13}H_{14}BrN_4O_7$: C, 46.23; H, 3.47; N, 11.36. Found: C, 45.88; H, 3.57; N, 11.15.

To a stirred solution of 13.31 g (0.05 mole) of bromo amine 24 in 200 ml of dry ether was rapidly added 38 ml (0.059 mole) of 1.55 M *n*-butyllithium in hexane.¹⁷ After stirring magnetically in the tightly stoppered flask for 70 min, the solution was added to a refluxing solution of 12.4 g (0.068 mole) of benzophenone in dry ether and processed as described above, for the similar reaction of bromo amine 8, to give 14.05 g (76.5%) of 1-diphenylhydroxymethyl-2-dimethylaminomethylnaphthalene (17b), mp 160–162°. Several more recrystallizations from hexane failed to raise the melting point.

Anal. Calcd for $C_{23}H_{23}NO$: C, 85.00; H, 6.85; N, 3.80. Found: C, 84.94; H, 6.69; N, 3.93.

Thermal Cyclization of Methiodide 27 to Cyclic Ether 28. A solution of 3.67 g (0.01 mole) of carbinolamine 17b in 25 ml of methyl iodide was refluxed for 7 hr, and the excess methyl iodide was evaporated. The solid residue was dissolved in refluxing acetonitrile and the solution allowed to cool while 500 ml of dry ether was added dropwise. The cold suspension was filtered to afford 4.21 g (82.6%) of 2-(1-diphenylhydroxymethyl)naphthylmethyltrimethylammonium iodide (27), mp 204–206°. This melting point was not raised by several more such treatments.

Anal. Calcd for $C_{27}H_{27}INO$: C, 63.65; H, 5.54; N, 2.75. Found: C, 63.36; H, 5.50; N, 3.00.

A 3.69-g (0.0073 mole) sample of methiodide 27 was heated at 210–220° (Woods metal bath) for 15 min under dry nitrogen. After cooling, the solid was processed as described previously¹⁴ for the related cyclization of the methiodide of 2. Recrystallization of the product afforded 1.87 g (80%) of 1,1-diphenyl-1,3-dihydronaphtho[1,2-*c*]furan (28), mp 156–158°, and 157–158.5° after several recrystallizations from hexane.

Anal. Calcd for $C_{23}H_{19}O$: C, 89.41; H, 5.63. Found: C, 89.04; H, 5.63.

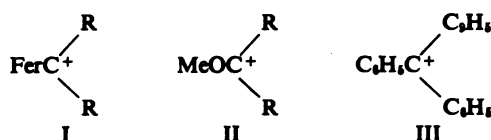
The Chemistry of Metallocenes. I. Carbonium Ion Stabilization by the Ferrocenyl Group^{1,2}

T. G. Traylor and J. C. Ware

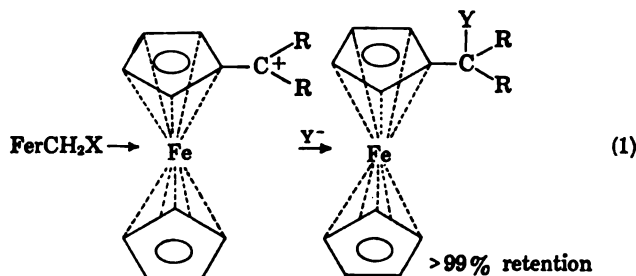
Contribution from the Department of Chemistry, Revelle College, University of California at San Diego, La Jolla, California. Received July 8, 1966

Abstract: The rapid solvolyses of α -ferrocenylcarbonyl derivatives, FerCR_2X , have been accurately correlated with carbonyl stretching frequencies of FerCOCH_3 , ArCOCH_3 , FerArCOCH_3 , and with σ^+ values. These correlations are interpreted as evidence that the main contribution of the iron atom to the FerC^+R_2 stability is hyperconjugation ($\sigma-\pi$ conjugation). The σ^+ values for the ferrocenyl (Fer) group have been determined: $\sigma^+_{\alpha\text{-Fer}} = -1.35$, $\sigma^+_{\beta\text{-Fer}} = -0.71$, and $\sigma^+_{\text{m-Fer}} = 0$. Reactivities of metallocenes are discussed in terms of breaking and making the metal-carbon bond in a step analogous to $\text{S}_\text{E}2$ reactions. The presence of filled d orbitals in the metal is suggested to influence reactivities by their influence on cyclopentadienide-metal bonding rather than by direct interaction with electrophilic reagents. The terminology applied to the effects of β substituents on solvolysis reactions and mechanisms of such effects is reviewed.

The α -ferrocenylcarbonium ions I generated by solvolyses^{3,4} or protonation of vinylferrocenes⁵



have about the same stability as α -methoxymethyl II³ or triphenylmethyl III³ cations and react with high stereospecificity with nucleophiles.^{3b,4a}



A molecular orbital description of I incorporating both direct backside participation of iron orbitals and delocalization into the ring has been formulated by Hill and Richards^{3b} to explain the observed reactivity and stereospecificity of reaction 1.

A comparison of this reaction with reactions of other β -metalloalkyl derivatives⁶ and a consideration of the ease of oxidation of ferrocene^{7a} suggest that iron

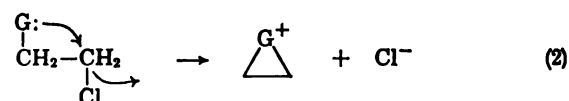
hyperconjugation ($\sigma-\pi$ conjugation) might be exceptionally facile.

This phenomenon may also explain the observed rate acceleration and stereochemistry but can be differentiated from neighboring nucleophilic participation in several ways. In this paper we describe and document methods for differentiating these two effects and then use these methods to indicate the nature of the stabilization provided by the ferrocenyl group.

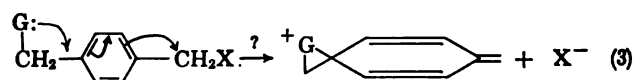
Results

We have employed four experimental methods to test whether a substituent accelerates $\text{S}_\text{N}1$ reactions by neighboring nucleophilic attack or by σ delocalization (including hyperconjugative or $\sigma-\pi$ delocalization). Two of these tests are well documented in the published literature and will be discussed below. We offer the following evidence for the other two.

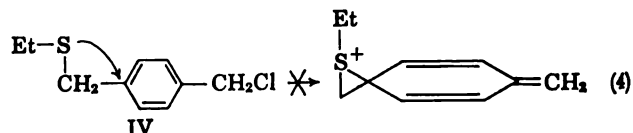
Internal Nucleophilic Attack at the *para* Position in Benzyl Chlorides. It seems reasonable that a group which accelerates $\text{S}_\text{N}1$ solvolysis by neighboring nucleophilic attack



will not show this accelerating effect in the *para* position of a benzyl derivative because the aromaticity would then be lost.



In order to determine whether such *para*-nucleophilic attack occurs to a significant extent we have studied the effect of one of the best neighboring groups (EtS-) on benzyl chloride solvolysis as shown below.



Rosenblum, J. O. Santer, and W. Glenn Howells, *J. Am. Chem. Soc.*, **85**, 1450 (1963); (c) M. Rosenblum, *ibid.*, **81**, 4530 (1959).

(1) Supported by Air Force Office of Scientific Research Grant AF-AFOSR-514-64.

(2) Partially reported in a previous communication: *Tetrahedron Letters*, 1295 (1965).

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(4) D. S. Trifan and R. Bacskai: (a) *Tetrahedron Letters*, No. 13, 1 (1960); (b) *J. Am. Chem. Soc.*, **82**, 5010 (1960).

(5) G. R. Buell, W. E. McEwen and, J. Kleinberg, *Tetrahedron Letters*, No. 5, 16 (1959).

(6) (a) G. E. Coates, "Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1960; (b) E. G. Rochow, D. T. Hurd, and R. N. Lewis, "The Chemistry of Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957; (c) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965.

(7) (a) M. Rosenblum, "Chemistry of the Iron Group Metallocenes," Part 1, John Wiley and Sons, Inc., New York, N. Y., 1965, p 63; (b) M.

Table I. Carbonyl Stretching Frequency of RCOCH_3 in Dilute Carbon Tetrachloride Solution

R	ν , cm^{-1}		
	Present work	Jones, <i>et al.</i> ^a	Fuson, <i>et al.</i> ^b
3-Indolyl	1662.8		
2-Thienyl	1672.2		
<i>p</i> - $\text{H}_2\text{NC}_6\text{H}_4$	1676.2	1677	1677
Fer	1676.4		
9-Phenanthryl	1681.3		
1-Naphthyl	1681.6		
3,4- $\text{CH}_2\text{O}_2\text{C}_6\text{H}_4$	1681.9		
<i>p</i> - $\text{CH}_2\text{OC}_6\text{H}_4$	1682.9		1684
<i>p</i> - FerC_6H_4	1684.3		
<i>p</i> - $\text{CH}_2\text{COHNC}_6\text{H}_4$	1684.4 ^c		1686
<i>p</i> - $\text{CH}_2\text{C}_6\text{H}_4$	1687.5	1687	
2-Furyl	1687.5		
<i>m</i> - $\text{H}_2\text{NC}_6\text{H}_4$	1688.3	1689	
<i>p</i> - $\text{C}_6\text{H}_4\text{C}_6\text{H}_4$	1688.5		
<i>m</i> - $\text{CH}_2\text{OC}_6\text{H}_4$	1689.3		
<i>m</i> - $\text{CH}_2\text{C}_6\text{H}_4$	1689.7		
<i>m</i> - FerC_6H_4	1690.0		
<i>o</i> - FerC_6H_4	1690.2		
<i>p</i> - $\text{CH}_2\text{CO}_2\text{C}_6\text{H}_4$	1690.8		
C_6H_5	1691.0	1691	1692
<i>p</i> - FC_6H_4		1692	
<i>p</i> - ClC_6H_4	1692.2	1692	1692
<i>p</i> - BrC_6H_4	1692.8	1693	1693
<i>m</i> - ClC_6H_4	1695.6	1696	
<i>p</i> - $\text{O}_2\text{NC}_6\text{H}_4$	1700.2	1700	1703
<i>m</i> - $\text{O}_2\text{NC}_6\text{H}_4$	1700.7	1701	1701
9-Anthryl	1700.8		
CH_3	1717.7		
CH_3O	1751.0		

^a Reference 12. ^b Reference 13. ^c Limited solubility required use of expanded per cent transmission scale; position of maximum absorption is recorded.

p-Ethylthiomethylbenzyl chloride (IV) was synthesized by the reaction of the sodium salt of ethanethiol with a fourfold excess of *p*-xylylene dichloride. The rates of solvolysis of benzyl chloride and the substituted chloride IV in 50% aqueous dioxane were determined conductometrically. The rate constants at 80.0° were $5.90 \times 10^{-5} \text{ sec}^{-1}$ for benzyl chloride and $8.70 \times 10^{-5} \text{ sec}^{-1}$ for IV. This indicates no appreciable acceleration in benzyl chloride solvolysis by nucleophilic participation in the *para* position.⁸

Carbonyl Stretching Frequencies. The rates of solvolyses of alkyl tosylates R_3CHOTos have been quantitatively correlated with carbonyl stretching frequencies in $\text{R}_3\text{C=O}$.⁹ Similarly the solvolyses of aralkyl chlorides¹⁰ ArCHClCH_3 may be correlated with ArCOCH_3 stretching frequencies¹¹⁻¹³ because both correlate with σ^+ . It has been shown that, although neighboring groups may accelerate $\text{S}_\text{N}1$ solvolysis, such groups do not make a corresponding change in carbonyl stretching frequencies of the ketones.⁹ In order to have a consistent set of carbonyl stretching frequen-

(8) We also showed that *p*-hydroxymethylbenzyl chloride reacts with ethoxide ion at the same rate as does benzyl chloride, but this finding is not conclusive to the point due to the ease of $\text{S}_\text{N}2$ displacement on benzyl chloride.

(9) (a) C. S. Foote, *J. Am. Chem. Soc.*, **86**, 1853 (1964); (b) P. R. Schleyer, *ibid.*, **86**, 1856 (1964).

(10) C. Mechelynck-David and P. J. C. Flerens, *Tetrahedron*, **6**, 232 (1959).

(11) C. N. R. Rao and G. B. Silverman, *Current Sci. (India)*, **26**, 375 (1957).

(12) R. N. Jones, W. F. Forbes, and W. A. Mueller, *Can. J. Chem.*, **35**, 504 (1957).

(13) N. Fuson, M.-L. Josien, and E. M. Shelton, *J. Am. Chem. Soc.*, **76**, 2526 (1954).

cies of acetophenones with which to compare the ferrocenyl derivatives we have remeasured a large number of such frequencies. The data, along with those for the ferrocenyl-substituted ketones, are shown in Table I. A plot of $\nu_{\text{C=O}}$ vs. known σ^+ values appears in Figure 1 where previously unknown σ^+ values are assigned from the measured $\nu_{\text{C=O}}$. The carbonyl stretching frequencies reported here are in good agreement with those of Jones, Forbes, and Mueller.¹² The correlation for *para* derivatives is excellent, while that for *meta* derivatives is less satisfactory. It may be that the latter should be correlated by a line of greater slope. The σ^+ values can be calculated from the equation

$$\sigma^+ = 0.0877(\nu_{\text{C=O}} - 1691.1) \quad (5)$$

Because these frequencies can now be measured to an accuracy of $\pm 0.5 \text{ cm}^{-1}$, the maximum error in σ^+ will be ± 0.044 . This equation should make possible the determination of σ^+_a for a variety of other aromatic systems (σ^+_a is defined as the σ^+ constant for the group at the position of reaction. Thus $\sigma^+_{a-\text{Ph}} \equiv 0 \equiv \sigma^+_{p-\text{H}}$. Therefore σ^+_a includes Brown's σ^+ constants¹⁴ and is equivalent to the σ_r and " σ " constants referred to by Streitwieser.¹⁵

The correlation of solvolysis rates (see below) with corresponding ketone carbonyl frequencies for α -phenethyl chlorides is shown in Figure 2. The equation of the line may be written $\log k = 0.64(\nu_{\text{C=O}} - 1691)$, as contrasted with $\log k = 0.132(\nu_{\text{C=O}} - 1720)$ found by Foote^{9a} for aliphatic systems. Obviously a single line will not correlate both aralkyl and alkyl derivatives. In addition the correlation of $\nu_{\text{C=O}}$ for RCOCH_3 with σ^+ of the very electronegative R groups F, Cl, Br, NH_2 , CH_3O , $\text{C}_6\text{H}_5\text{O}$ (attached directly to the carbonyl) is very poor and has a slope which reflects a very strong inductive effect on $\nu_{\text{C=O}}$. Therefore, we have omitted such groups^{16,17} (as well as $\text{R} = \text{alkyl}$) from our plots of $\nu_{\text{C=O}}$ vs. σ^+ . Each of these correlations appears to be limited to a narrow range of inductive effects. The inclusion of ferrocenyl with the aromatic series in our treatment seems justified, since it is aromatic and has an inductive effect^{7a} within the range covered by the α substituents treated in Figures 1 and 2.

Syntheses. The phenylferrocenes employed in this study were synthesized by treating acetylbenzene-diazonium salts with ferrocene,^{7b} reducing the ketones, and treating the resulting alcohols with concentrated hydrochloric acid or dry hydrogen chloride.

The analyses and nmr spectra of the intermediate products and the final chlorides are definitive for structure

(14) H. C. Brown in "Steric Effects in Conjugated Systems," C. W. Gray, Ed., Academic Press Inc., New York, N. Y., 1958, p 109.

(15) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962: (a) p 35; (b) p 103; (c) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 326.

(16) A referee has suggested that the omission of the MeO group from Figure 1 invalidates the treatment for the ferrocenyl group. The omission of alkyl and electronegative substituents from Figure 3 or the omission of aromatic or electronegative groups in the treatment of Foote^{9a} do not, in our opinion, invalidate the correlations (see ref 17).

(17) Although inductive effects appear to dominate in the carbonyl stretching frequencies of RCOCH_3 for MeO , Cl , etc., inductive destabilization of carbonium ions by MeO is seen to be negligibly small by the following comparison. Whereas we would calculate from eq 14 (using τ 2) that $\sigma^+_{p\text{-alkyl}}$, $\sigma^+_{p\text{-MeO}}$, and $\sigma^+_{a\text{-MeO}}$ should be in the ratio -0.35 , -0.70 , and -1.4 , the observed values are -0.35 , -0.78 , and -1.4 , in good agreement: T. Inukai, *Bull. Chem. Soc. Japan*, **35**, 400 (1962).

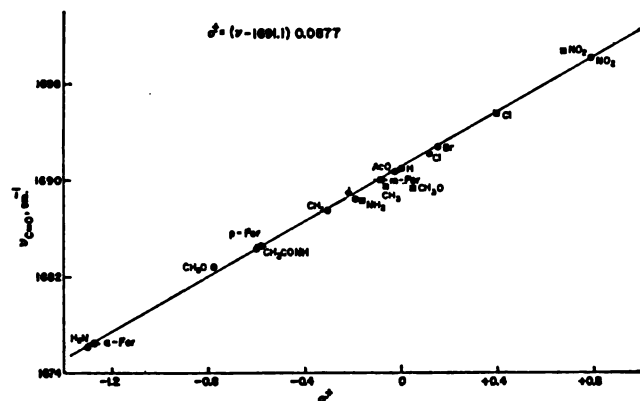
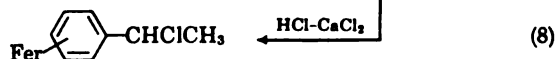
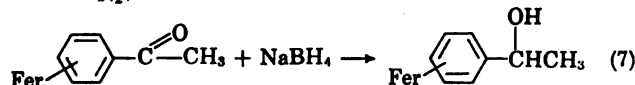
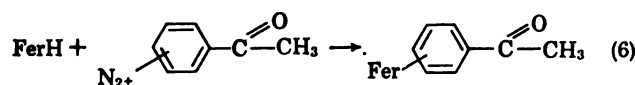


Figure 1. Plot of carbonyl stretching frequencies of substituted acetophenones against σ^+ : \blacksquare , *meta* derivatives; \bullet , *para* derivatives; $-\bullet-$, $-\blacksquare-$, σ^+ values assigned by this plot.

proof. Other chlorides were synthesized by standard methods and similarly identified.



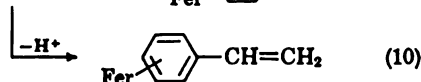
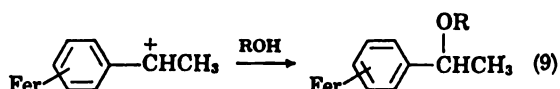
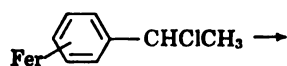
Solvolysis Products. The products of solvolyses of various α -phenethyl chlorides in ethanol-water or acetone-water are known to consist of the ether or alcohol and traces of the corresponding styrenes.¹⁰ We have, therefore, determined only the products of the ferrocenylphenethyl chlorides under our solvolysis conditions. The products, shown in Table II, are con-

Table II. Products of Solvolysis of $\text{RC}_6\text{H}_4\text{CHClCH}_3$ in 95% Aqueous Ethyl Alcohol

R	Temp, °C	%			
		R'OEt ^a	R'OH ^b	R-Styrene	Other
<i>o</i> -Fer	40	92	3	3	...
<i>m</i> -Fer	70	68	3	6	...
<i>p</i> -Fer	0	69	4	2	Hydrocarbon, ^a ketone, etc.

* A small amount of unidentified high molecular weight ferrocene was obtained from the *para* derivative only. R' = $\text{RC}_6\text{H}_4\text{CHCH}_3$.

sistent with the $\text{S}_{\text{N}}1$ mechanism previously proposed and documented for α -phenethyl chloride solvolysis.^{10,18}



(18) (a) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948); (b) A. H. Fainberg and S. Winstein, *ibid.*, **79**, 1597 (1957); (c) S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948).

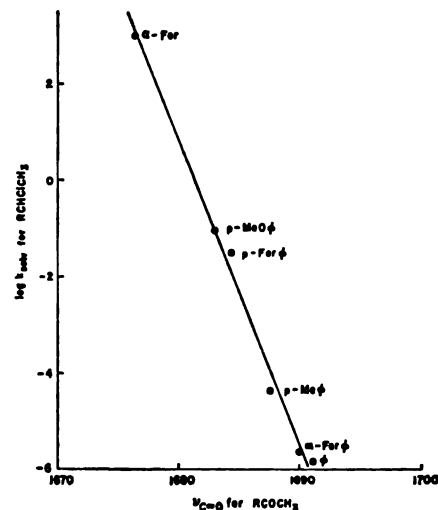


Figure 2. Plot of carbonyl stretching frequencies of acetophenones and ferrocenyl methyl ketone against $\log k$ for chloride (RCHClCH_3) solvolysis.

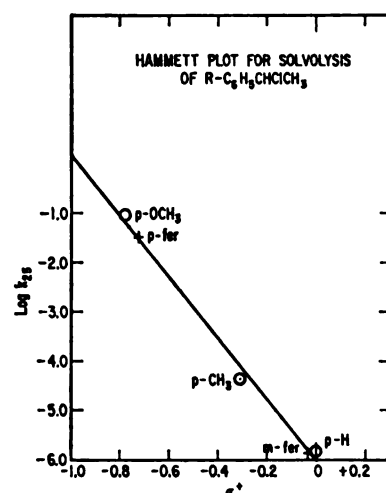


Figure 3. Plot of $\log k$ vs. σ^+ values for solvolyses of substituted α -phenethyl chlorides in 95% aqueous ethanol at 25°.

Kinetics. Solvolysis rates were determined by conductivity, by titration of aliquots for acid, or by pH-Stat titration. When two methods were used the agreement was good. Although limited solubilities of the ferrocenes required that we use less aqueous solvents than those reported for α -phenethyl chloride solvolyses, our data agreed with literature values after correction for solvent polarity by the method of Grunwald and Winstein.^{18a} The kinetic data for solvolyses are listed together with activation parameters in Table III.


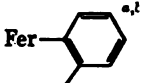
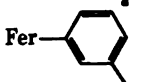
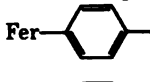
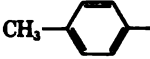
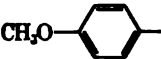
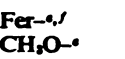
A plot of $\log k_{25}$ vs. σ^+ shown in Figure 3 yields a slope $\rho = -6.1$ and indicates that $\sigma^+_{p\text{-Fer}} = -0.7$, $\sigma^+_{m\text{-Fer}} = +0.1$, and $\sigma^+_{\alpha\text{-Fer}} = -1.4$ (off the plot).

Dimerization of the 1-(*p*-Ferrocenylphenyl)ethyl Carbonium Ion. *p*-Ferrocenyl- α -phenethyl chloride was treated with concentrated sulfuric acid in chloroform, and the resulting ferricinium products were extracted into water and reduced. A 17% yield of product whose properties agreed with the structure V was obtained. We interpret this reaction as shown below by analogy to the α -ferrocenyl carbonium ion behavior.^{19,20}

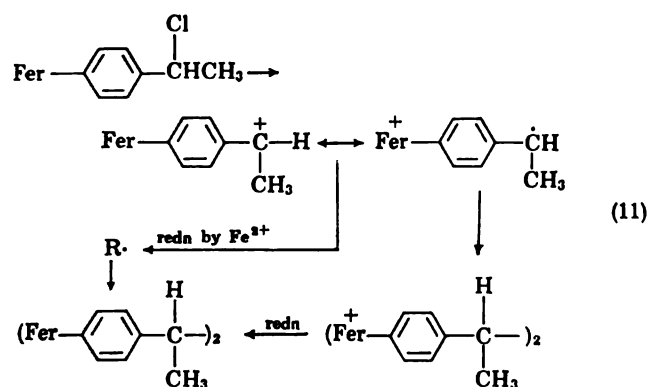
(19) K. L. Rinehart, C. J. Michejda, and P. A. Kittle, *Angew. Chem.*, **72**, 38 (1960).

(20) M. Cais and E. Eisenstadt, *J. Org. Chem.*, **30**, 1148 (1965).

Table III. Solvolyses of RCHClCH₃ in 95% Aqueous Ethyl Alcohol

R	Temp, °C	10 ⁴ k, sec ⁻¹	ΔH‡, kcal/mole	ΔS‡, eu	k ₂₅ , sec ⁻¹	log k ₂₅	k _R /k _{Ph₃}
	60.0 70.0 78.0	0.526 1.16 2.37	19.1	-21.2	1.54 × 10 ⁻⁴	-5.811	(1)
	40.0 50.0 60.0	6.20 17.2 40.0	18.7	-13.6	1.33 × 10 ⁻⁴	-3.876	86
	55.0 60.0 70.0 80.0	0.575 0.918 2.80 7.32	23.3	-7.1	1.38 × 10 ⁻⁴	-5.859	0.90
	-9.04 -0.02 10.0	5.37 16.6 59.3	18.3	-4.0	3.16 × 10 ⁻³	-1.500	20,000
	35.0 45.0 55.0 65.0	1.30 3.66 ^a 8.64(8.81) ^d 23.5	19.1	-14.4	4.40 × 10 ⁻⁵	-4.357	29
	-19.61 -9.90 -0.02 +0.10	5.34 17.5 61.8 (63.2)	16.8	-7.0	8.97 × 10 ⁻⁵	-1.047	58,000
	-66.2 -69.6	5.4 ± 5 4.1 ± 4				2.8 ^e	4 × 10 ⁸ 4 × 10 ⁸

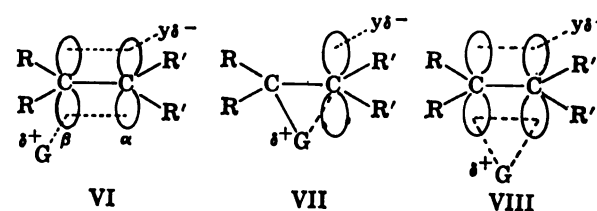
* Containing 0.5% diethyl ether. ^b Fer = ferrocenyl. ^c Rate, $3.64 \times 10^{-5} \text{ sec}^{-1}$ when the solvent contained 0.5% diethyl ether. ^d Values in parentheses were obtained titrimetrically. ^e Solvent 60:40 ether-ethanol. ^f Reference 4c. ^g Calculated using mY relationship of ref 18 assuming $m = 1$ and Y for 60% ether-ethanol = -4.3 estimated from data of P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Prestt, *J. Chem. Soc.*, 3641 (1955).



Discussion

Effects of β Substituents on Solvolysis Reactions. Before discussing in detail the effects of β -metal substitution on solvolysis reactions, we wish to reconsider the various phenomena attributed to the effects of β substituents upon the stabilities of developing carbonium ions.

The terms "hyperconjugation,"²¹ "elimination,"²² "fragmentation,"²³ and " σ - π conjugation,"²⁴ have been applied to processes in which a carbonium ion is stabilized by π conjugation with an orbital previously bonding to another atom²⁵ (see VI). The names "neighboring group participation,"^{26b} "anchimeric assistance,"²⁸



or "synartetic acceleration"²⁷ are used to designate stabilization of a carbonium ion by direct bonding to a neighboring atom as in VII or VIII. In most calculations of anchimeric assistance (or bridged ion stabilities)^{26c,28} some π bonding of the type VI is included, and the structure generally written is VIII. There is thus some ambiguity in these terms and we believe that this ambiguity has contributed to the controversy concerning the nature and extent of occurrence of such processes.²⁹

In this discussion we will consider one extreme, VI, in which the groups G can form stable cations ($G = R_2NCH_2$, C_7H_7 , Li, MgX , etc.), and another extreme, VII, in which the G is a poor cation but a rather good nucleophile ($G = RS$, R_2N , O^- , C_2H_5 , etc.). We will call VI σ - π conjugation (as a general term for hyperconjugation) and VII internal nucleophilic displacement. (The latter term has been considered synonymous with neighboring group participation.^{12b}) The term "anchimeric assistance" might be applied to both extremes and to all intermediate cases (VIII). Neighbor-

(21) M. S. Dewar, "Hyperconjugation," The Ronald Press Co., New York, N. Y., 1962; numerous references are given there.

(22) J. F. Bunnett, *Angew. Chem. Intern. Ed. Engl.*, 1, 225 (1962).

(23) C. A. Grob, "Theoretical Organic Chemistry," The Kekule Symposium, Butterworth and Co., Ltd., London, 1959, p 114.

(24) (a) A. N. Nesmeyanov, K. A. Perchakaya, A. N. Akramovich, and L. M. Minakova, *Dokl. Akad. Nauk SSSR*, 121, 660 (1958); (b) A. N. Nesmeyanov and I. I. Kritskaya, *ibid.*, 121, 447 (1958).

(25) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 208.

(26) (a) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, 61, 1576 (1939); (b) S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingraham, *ibid.*, 75, 147 (1953).

(27) F. Brown, E. D. Hughes, C. K. Ingold, and J. F. Smith, *Nature*, 168, 65 (1951).

(28) Reference 15, p 380.

(29) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965.

ing aliphatic carbon is considered to use a bonding orbital to form VIII.

The σ - π conjugation by the G-C β bond is seen by C α as a simple π -resonance effect (see ref 15c), and will be expected to correlate quantitatively with other π -delocalization effects. In contrast, in the extreme VII, the α -carbon sees the participation of G as an SN2 process, and this process should not correlate with π delocalization. Furthermore, internal nucleophilic substitution will be expected to compete with rather than accelerate external nucleophilic attack.

Based on these considerations we have used four experimental methods which might differentiate between cases where the driving force is almost exclusively VI and those where it is VII: (1) substitution of resonance-stabilizing groups such as MeO-, HO-, ArO-, for R' in VI-VIII; such substitution has been shown essentially to destroy^{30a} neighboring group participation²⁹ but should only reduce somewhat any resonance stabilization afforded by R₂C(G) (this follows from the fact that SN1 reactions are accelerated much more by resonance stabilization than are SN2 reactions and the consideration that neighboring groups perform an internal SN2 reaction); (2) insertion of an aromatic group between the α and β carbons; whereas conjugation effects are transmitted through a *p*-phenylene group, neighboring nucleophilic participation is apparently not so transmitted (eq 4); (3) correlation of solvolysis rates with carbonyl stretching frequencies; this effective correlation for aryl substituents (Figure 1) fails when neighboring group participation is involved in the solvolysis;^{30a,b} (4) substitution of very good π -donating substituents at the α -carbon; this accelerates both SN1 and SN2 processes, and such accelerations of SN1 reactions correlate with those of SN2 reactions^{15c} whereas, by contrast, neighboring groups such as EtS, Cl, Br, and AcNH do not accelerate SN2 reactions.^{15a}

Application of These Criteria to the Effect of the Ferrocenyl Group. In relating the behavior of the iron electrons in ferrocene (bonding and nonbonding) to the behavior of the electrons on the common neighboring groups EtS, R₂C, AcNH, Br, I, etc., it must be remembered that the iron electrons which are involved are probably those in the 3d orbitals whereas in most neighboring groups 2s, 2p or 3s, 3p electrons are used. This could account for some of the differences we observe.³¹ However, neighboring iodine behaves like RS⁻¹⁵ with respect to the criteria mentioned, and yet iodine uses much more diffuse orbitals. In the absence of evidence to the contrary we prefer to consider nucleophilic participation by d electrons to be similar to that by s and p electrons.

σ^+ Correlations. We propose that σ - π conjugating systems will show the same kind of response to π -electron demand as do other resonance-stabilizing groups. Therefore exclusive σ - π conjugation requires that any quantitative correlation which holds for conjugating aromatic groups (anisyl, thienyl, etc.) will include the ferrocenyl group. The σ^+ parameter is commonly used in such correlations, and a test of the purely resonance character of the substituent is the accuracy with which a variety of reactions correlates with the σ^+ value.

(30) (a) T. G. Traylor and C. L. Perrin, *J. Am. Chem. Soc.*, **88**, 4934 (1966); (b) T. T. Tidwell and T. G. Traylor, *ibid.*, **88**, 3442 (1966).

(31) Suggested by a referee.

We have used the carbonyl stretching frequency eq 5 to calculate $\sigma^+_{\alpha\text{-Fer}}$, $\sigma^+_{m\text{-Fer}}$, and $\sigma^+_{p\text{-Fer}}$ and compared them with those determined by other methods in Table IV.³²

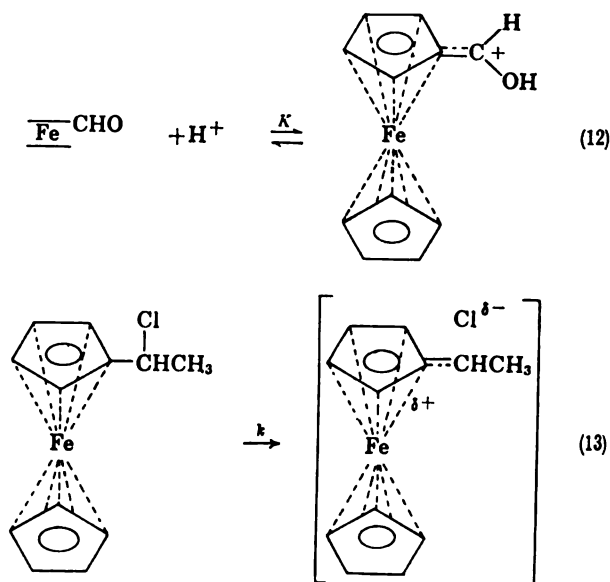
Table IV. σ^+ Values

σ^+			Method
$\alpha\text{-Fer}$	$m\text{-Fer}$	$p\text{-Fer}$	
-1.3	-0.09	-0.6	Carbonyl frequency vs. ArCOCH ₃
-1.4 ^a	-0	-0.7	Solvolysis of RCHClCH ₃ vs. ArCHClCH ₃
-1.3 ^b	Basicity of RCOCH ₃ vs. ArCOCH ₃

^a From Figure 1. ^b Reference 33.

Whereas neighboring nucleophilic participation in solvolysis might account for the extreme reactivity of FerCHClCH₃, which leads to our value for $\sigma^+_{\alpha\text{-Fer}} = -1.4$, no such phenomenon has been observed to affect carbonyl basicities or stretching frequencies. Since these three values of $\sigma^+_{\alpha\text{-Fer}}$ are so close, it is attractive to attribute all three phenomena (including solvolysis) to σ - π conjugation. This correlation is demonstrated in the plot of log *k* (solvolysis) vs. carbonyl stretching frequency shown in Figure 2.

Effect of Resonance-Stabilizing α Groups on α -Ferrocenyl Group Acceleration. The correlation of basicities of aromatic aldehydes with ferrocenecarboxaldehyde (eq 12) yields $\sigma^+_{\alpha\text{-Fer}} = 1.30$.³² In solvolysis of RCHClCH₃ (R = aryl, ferrocenyl), we have shown $\sigma^+_{\alpha\text{-Fer}}$ to be -1.4, in remarkably close agreement (see Table IV).



Since substitution of a methoxy group on a carboxonium ion completely removes the participation by neighboring carbon,^{30a} clearly, if there is participation by iron, it is not like that by neighboring carbon.

(32) A. N. Nesmeyanov, E. G. Perevalova, S. P. Gubin, K. I. Grandberg, and A. G. Kozlovsky, *Tetrahedron Letters*, 2381 (1966), have calculated $\sigma^+_{\alpha\text{-Fer}} = -1.09$ from rates of protonolysis of R₂Hg. Because this reaction does not follow σ^+ we feel that the number is less reliable than our value of -1.35. We find the ratio $\sigma^+_{\alpha\text{-Fer}}/\sigma^+_{\alpha\text{-MeO}}$ to be 2.1 for either MeO or Fer, while they use the value 1.55 determined from σ_{α}/σ_p , rather than from $\sigma^+_{\alpha}/\sigma^+_p$.

(33) E. M. Arnett and R. D. Bushick, *J. Org. Chem.*, **27**, 111 (1962).

mission of Resonance Effects through a Phenyl-group. The basis of the $\rho\sigma^+$ treatment is the transmission of resonance effects through a phenylene group.¹⁴ Furthermore, a phenylene transmission coefficient, τ , independent of substituent, may be defined.¹⁴

$$\log k/k_0 = \tau(\rho\sigma^+) \quad (14)$$

implies that the free-energy difference introduced in the transition state by α substitution should be proportional to that caused by *para* substitution of the substituent if steric effects are small.

$$\Delta\Delta F^\ddagger_{(\alpha-\text{MeO})} = \tau\Delta\Delta F^\ddagger_{(p-\text{MeO})} \quad (15)$$

ferrocenyl (or any other) group stabilizes only by conjugation the same relationship should hold.

$$\Delta\Delta F^\ddagger_{(\alpha-\text{Fer})} = \tau\Delta\Delta F^\ddagger_{(p-\text{Fer})}$$

$$\log k_{\alpha-\text{Fer}}/k_{\alpha-\text{MeO}} = \tau \log k_{p-\text{Fer}}/k_{p-\text{MeO}}$$

If $k_{\alpha-\text{Fer}} = k_{\alpha-\text{MeO}}$ then $k_{p-\text{Fer}} = k_{p-\text{MeO}}$. This is the case if we chose to compare the ferrocenyl group with the ethoxymethyl group.¹⁵

On the other hand, transmission of a neighboring group effect through a phenylene group destroys the relationship.



as we have shown, does not occur. If the ferrocenyl group is acting as a neighboring nucleophile, it should be without effect in the *para* position. If it is not, in both ways, then it should lose (relative to *p*-ethoxymethyl) a fraction, $1/\tau$, of the free energy contributed by neighboring group participation when insulated by a methyl group. Because we are discussing $\Delta\Delta F_a^\ddagger$ of about 18 kcal and $\tau \cong 2$, this test is a sensitive one.

The relevant rate data are shown in Table V. This table shows first that the EtSCH_2 group, which is an excellent neighboring group, has little effect in the *para* position. Secondly, although the data for the α - and α -Fer are rather inaccurate, it is clear that in a factor of two)

$$\frac{k_{\alpha-\text{FerCHClCH}_3}}{k_{\alpha-\text{MeOCHClCH}_3}} = \frac{k_{p-\text{FerC}_6\text{H}_4\text{CHClCH}_3}}{k_{p-\text{MeOC}_6\text{H}_4\text{CHClCH}_3}}$$

In addition to these solvolysis data, the carbonyl stretching frequencies for α - and *p*-ferrocenyl ketones are almost identical transmission coefficients for a phenylene.

$$\left(\frac{\sigma^+_{\alpha-\text{Fer}}}{\sigma^+_{p-\text{Fer}}}\right)_{\text{CO stretch}} = \frac{1.3}{0.6} = 2.1$$

$$\left(\frac{\sigma^+_{\alpha-\text{Fer}}}{\sigma^+_{p-\text{Fer}}}\right)_{\text{solvolysis}} = \frac{1.4}{0.7} = 2.0$$

Therefore, this criterion also indicates that neighboring group participation makes a negligible contribution.

J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963. A better choice would have been the *p*-aminophenyl group except for synthetic and analytic difficulties (see ref 16).

Table V. Relative Solvolysis Rates of Alkyl Chlorides at 25°

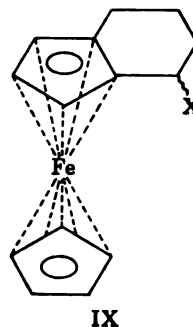
Compd	Rel rate	Compd	Rel rate
EtCl	(1)		(1)
	10^{14}		5×10^4
	10^{14}		2×10^4
$\text{EtSCH}_2\text{CH}_2\text{Cl}$	10^7		1.6^d
$\text{OCH}_2\text{CH}_2\text{Cl}$	10^{10}		1.0
			0.5

* This work. ^b Reference 3c. ^c Reference 15c. ^d Relative to benzyl chloride. ^e From $\sigma^+_{m-\text{MeO}} = +0.05$, $\rho = -6.1$.

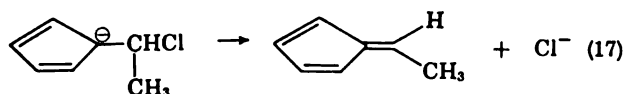
tion to the stabilization of α -ferrocenyl carbonium ions. The neighboring iron has little in common with other neighboring groups.

Correlation of SN1 with SN2 Reactions on Ferrocenylmethyl Chloride. We have recently reported^{30b} that ferrocenylmethyl chloride is about eight times more reactive than methoxymethyl chloride toward either SN1 ethanolysis or bimolecular reaction with ethoxide ion. Since ferrocenylmethyl chloride competes with methoxymethyl chloride as well in SN2 as in SN1 reactions and neighboring group participation does not accelerate SN2 reactions, we concluded that no such acceleration was indicated in the SN1 reaction of ferrocenylmethyl chloride.

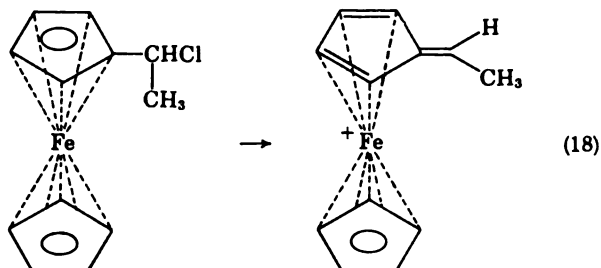
Mechanism of Solvolysis. Having presented experimental evidence against neighboring nucleophilic participation, we must account for rate acceleration, *exo:endo* rate ratios in IX, and retention of configuration in some other way.



We conceive the metallocene structure to be a rather basic aromatic system, which might be expected of a somewhat complexed cyclopentadienide anion. Thus, although reaction 17 would certainly be too fast to measure reducing the negative charge by bonding to

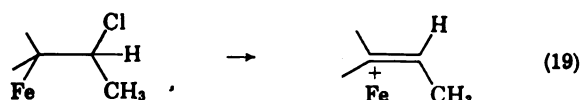


Fe^{2+} (eq 18) would make the reaction sufficiently slow

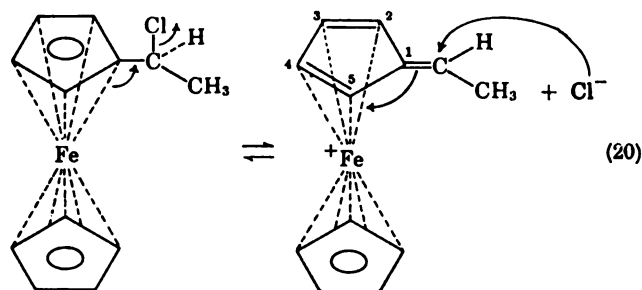


to be observable. (Cr^0 may be donating in $(\text{C}_6\text{H}_5)_2\text{Cr}$.) The rate acceleration (relative to phenyl) is therefore easily explained.

The only thing which would differentiate this system (reaction 19) from other aromatic systems is the Fe-C bonding, which we conceive to be greatly weakened in the transition state by σ - π conjugation.^{36a,b} This will



determine the stereochemistry because such conjugation is much more facile when the two groups are in a *trans* configuration.³⁷



By microscopic reversibility, the lowest energy reaction path for the reverse process takes the same *trans* geometry and gives retention of configuration.^{38a} Therefore this process (which might be compared to an E2 elimination if the second cyclopentadienide ring is considered as the base) gives the same stereochemistry as would nucleophilic participation by unshared electrons on iron. For the same reasons, the *exo:endo* rate ratios in the solvolyses of IX are clearly consistent with the σ - π conjugation mechanism.

Either neighboring nucleophilic attack as we describe it or "direct back-side participation of iron elec-

(36) (a) Rosenblum has formulated this stabilization similarly: ref 7a, p 133; (b) the weakening of the iron carbon bonds on formation of an α -ferrocenylcarbonium ion has been suggested and documented by Nesmeyanov, *et al.* For example, the diphenylferrocenyl carbonium ions readily dissociate to 6,6-diphenylfulvenes; (c) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, 154, 1393 (1964); (d) A. V. Nesmeyanov, V. A. Sazonova, V. N. Drozd, N. A. Rodionova, and G. I. Zudkova, *Izv. Akad. Nauk SSSR*, 2061 (1965).

(37) V. J. Shiner, Jr., *J. Am. Chem. Soc.*, 82, 2655 (1960).

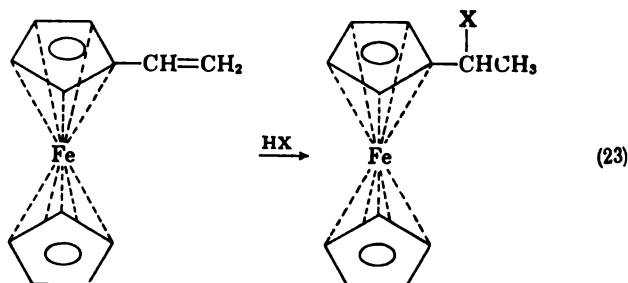
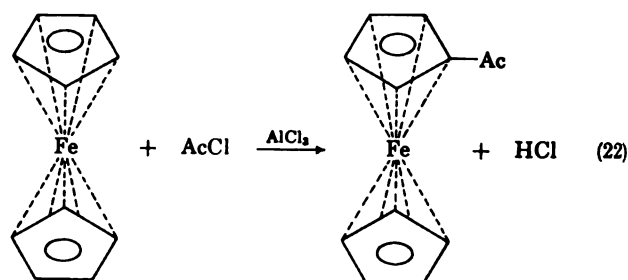
(38) (a) In the process shown in eq 20 all the upper Fe-C bonds are conceived to be weakened in going to the ion but the Fe-C₁ bond should probably weaken much more than the others. We have called this process "elimination" or " σ - π conjugation." The latter term is probably preferable since the iron atom is not removed from the molecule. (b) We do not mean to imply that the carbonium ion has no positive character at the α -carbon. Rather the resonance hybrid XV \leftrightarrow XVI looks more like XVI than like XV (see nmr section for structures).

trons"^{38b} as formulated by Hill and Richards suggests that the Fe-C₁ distance decreases during ionization to the cation I whereas the σ - π conjugation mechanism predicts no appreciable decrease.^{38b} A comparison of the crystal structure of the cation salt with that of the alcohol should be very informative.

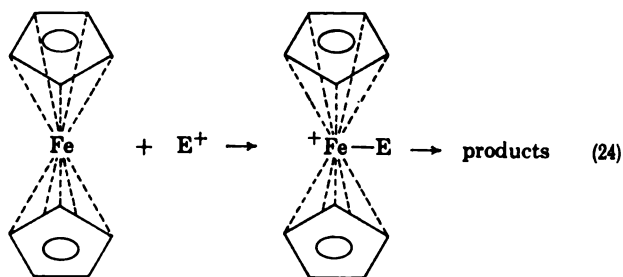
Comparison of Ferrocene Reactions with Those of Alkylmetal Compounds. Cyclopentadienylmetal compounds other than those of transition metals react rapidly with electrophiles and show other chemical behavior typical of alkylmetal compounds.^{39a,b}



Ferrocene and other metallocenes are much less reactive toward electrophiles than are other cyclopentadienylmetal compounds.^{6,40-42} They are also much more stable toward homolysis than are alkyl transition metal compounds. On the other hand, rates of substitution on the ring in ferrocene are much faster than those on benzene. Typical reactions which are much faster on ferrocene than on benzene are depicted in eq 1, 22, and 23.



A popular mechanism which has been considered general for these processes is^{6,39c,d}



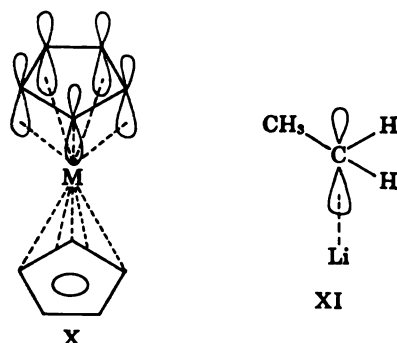
(39) (a) P. L. Pauson, *Quart. Rev. (London)*, 9, 391 (1955); W. F. Little, "Survey of Progress in Chemistry," Vol. 1, A. F. Scott, Ed., Academic Press Inc., New York, N. Y., 1963; (b) p 188; (c) p 153; (d) however, see M. Rosenblum and F. W. Abbate, *J. Am. Chem. Soc.*, 88, 4178 (1966), where additional results suggest that attack on iron is not a necessary part of the mechanism of electrophilic substitution on ferrocenes.

(40) T. J. Kealy and P. L. Pauson, *Nature*, 168, 1039 (1951).

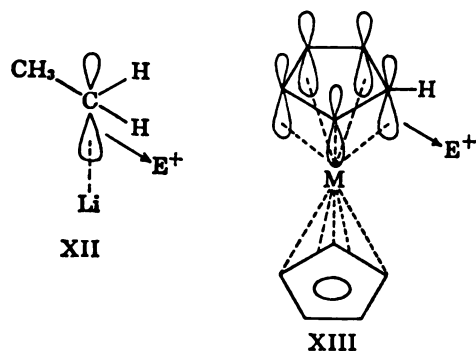
(41) S. A. Miller, J. A. Tebbboth, and J. F. Treamine, *J. Chem. Soc.*, 632 (1952).

(42) R. B. Woodward, M. Rosenblum, and M. C. Whiting, *J. Am. Chem. Soc.*, 74, 3458 (1952).

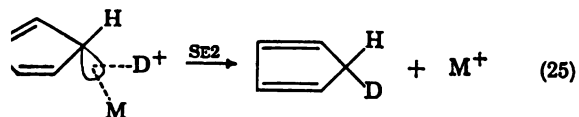
E^+ can be the external electrophiles Ac^+ , H^+ , Ac^+ , RN_2^+ , or the internal electrophiles C^+R_2 , CH^+ .⁴³ We offer an alternative view which proposes an individual cyclopentadienylmetal bond in a metallocene retains some of the characteristics which are usually associated with carbon-metal bonds.⁶ Thus regard to a single Fe-C bond we might consider it to be a more covalent counterpart of cyclopentadienyllithium. According to this interpretation the cyclopentadienide moiety has higher electron density on the metal side than on the opposite side of the ring just as ethyllithium has greater electron density on the lithium side of the carbon than on the opposite (C1).



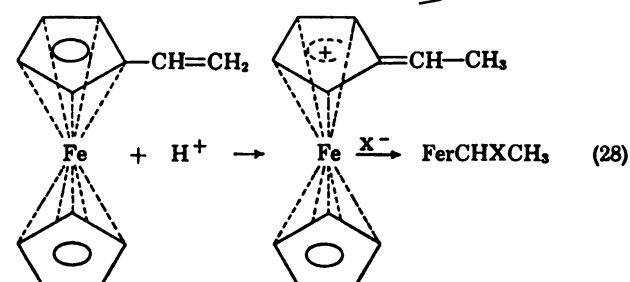
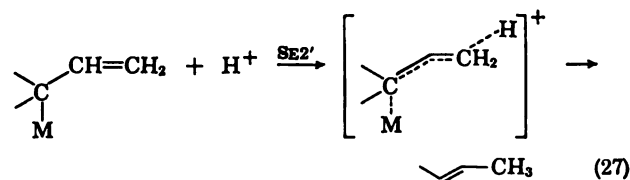
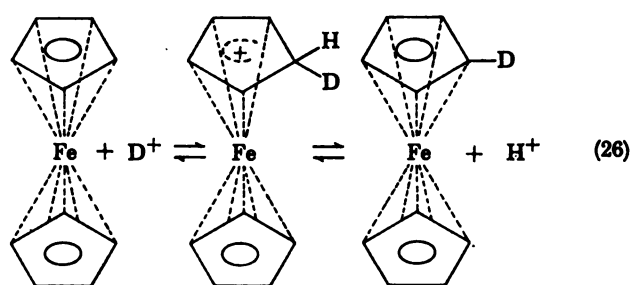
Now consider reactions 1, 22, and 23 with reference to structures X and XI and the known stereochemical behavior of organometallic compounds.⁴⁴ Electro-attack on XI is facile and occurs with retention of configuration^{6,44a,b} by attack on the electron-rich side shown in XII. Similarly (under conditions which



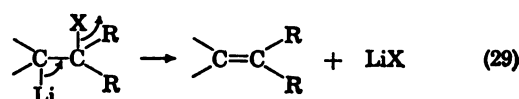
in SE_1 reactions), attack should occur preferentially on the metal side of the cyclopentadienide moiety XIII or the compound is the σ -bonded lithium derivative, or the covalent sandwich, ferrocene.



Thus the addition of HX to vinylferrocene, as in reactions of other allylmetal compounds,⁴⁵ should be

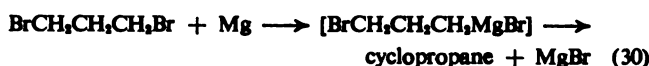


The well-known elimination of organometallic compounds,⁶ e.g.

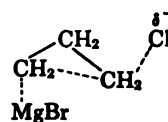


might also be expected to occur rather readily with metallocene compounds as discussed above and shown in eq 20.

Participation in β -Ferrocenylethyl Tosylate Solvolysis. The formation of cyclopropanes from γ -metalloalkyl halides is well known.⁴⁶



If we write these reactions with the usual retention of configuration observed for carbon-metal bond cleav-



age,⁴⁴ it becomes clear that cyclopentadienyl compounds of this type should show the same stereochemical preference whether they are σ bonded or sandwich compounds (eq 32 and 33).

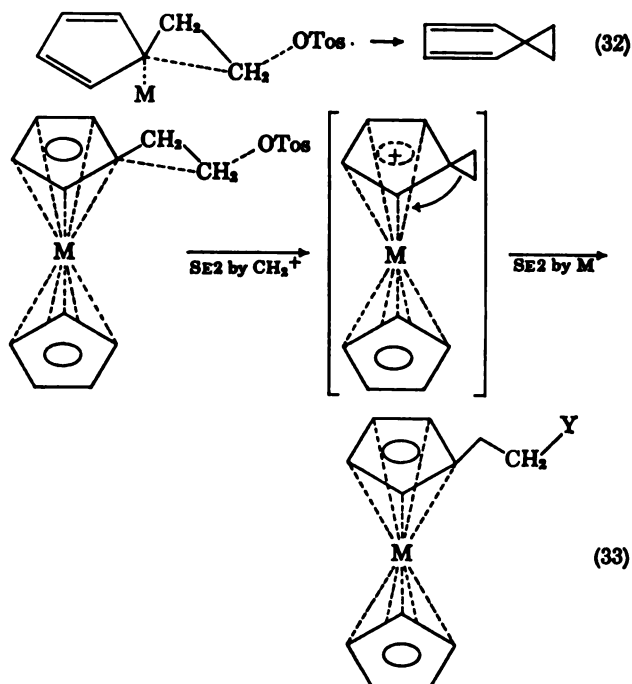
The intermediate formed from solvolysis of β -ferrocenylethyl tosylate is pictured as a structure like the phenonium ion, but it is formed by a simple SE_2 attack on the cyclopentadienyl carbon. The rapid rate of solvolysis of this tosylate (500 times that of phenethyl tosylate) observed by Trifan and Bacskai^{4a} is entirely

(46) (a) L. H. Sommer, R. E. van Strien, and F. C. Whitmore, *J. Am. Chem. Soc.*, **71**, 3056 (1949); (b) M. F. Hawthorne, *ibid.*, **82**, 1886 (1960); (c) P. Binger and R. Köster, *Tetrahedron Letters*, 156 (1961).

See ref 7a for a review of these studies.

(a) R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 4842 (1950); (b) S. N. T. G. Traylor, and C. S. Garner, *ibid.*, **77**, 3741 (1955). See 6c, p 116, for a review.

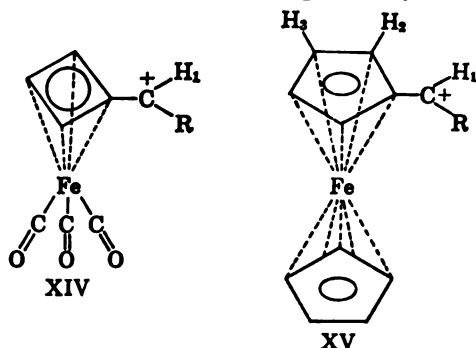
(a) H. G. Kuivila and J. A. Verdone, *Tetrahedron Letters*, **2**, 64; (b) P. D. Sleezer, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, **85**, 1890 (1963); (c) B. M. Mikhailov and A. Ya. Bezmenov, *Usp. Nauk SSSR*, 904 (1965).



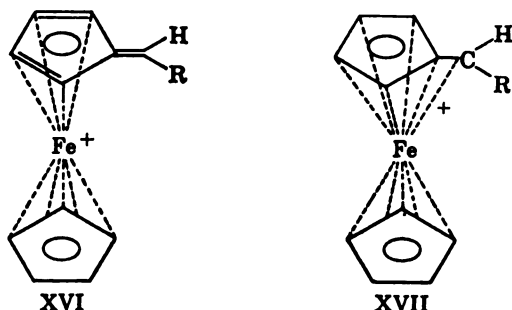
consistent with the mechanisms we propose. Indeed, we would suggest that this reaction would be much more facile if iron were replaced by, *e.g.*, magnesium, which has no d electrons because C-Mg is more ionic than C-Fe.

In all these proposed reaction mechanisms, the difference between "ionic" or σ -bonded RM compounds and covalent sandwich compounds is considered to be that in the latter the metal is retained by bonding to the remaining diene group whereas in the σ -bonded compounds the metal does not bind with dienes and is lost.³⁸

Nmr Spectra of Metallocenylmethyl Cations. The chemical shifts of ring (H_2 , H_3) and α hydrogens (H_1) in XIV⁴⁷ and XV³⁸ have been interpreted by Fitzpatrick,



Watts, and Pettit⁴⁷ in terms of structures such as XVI and by Cais, *et al.*,³⁸ in terms of structure XVII. While



(47) J. D. Fitzpatrick, L. Watts, and R. Pettit, *Tetrahedron Letters*, 1299 (1966).

Table VI. Nmr Spectra of Cations and Olefins

R	$\Delta\nu^{a,d}$	$\delta_{H_1}^{a,b}$	$\delta_{H_2}^{a,c}$	$\delta_{H_1}^{c,b}$
H	118	5.75	5.3	
CH ₃	94	7.03	5.70	
Isopropyl	93	6.98	...	
Cyclohexyl	5.64	
<i>t</i> -Butyl	90	7.07	5.65	
C ₆ H ₅	66	7.92	6.16	9.80
<i>p</i> -MeC ₆ H ₄	71	7.94	6.21	
<i>p</i> -MeOC ₆ H ₄	79	7.96	6.26	9.06

^a Chemical shift in parts per million from TMS. ^b Reference 3e. ^c Reference 48a. The data were given in cps downfield from water. We have used $\delta_{H_2O} = 5.00$ to compute the chemical shifts in ppm. ^d $\Delta\nu = (\delta_{H_1} - \delta_{H_2})60$.

we agree that the data of Cais, *et al.*,³⁸ may be explained by structure XVII, they do not appear to exclude XVI. In Table VI are listed the data for the α protons in ions XV, and in similarly substituted olefins and carbonium ions.

Table VI shows a striking similarity between the α -substituent effects on the chemical shifts of H_1 in ferrocenylmethyl cations and those in olefins.^{48a,c} It is especially striking that anisyl substitution ($R = \text{anisyl}$) has no greater effect than phenyl substitution ($R = \text{phenyl}$) in olefins and in the cations XV. This differs from the effects of anisyl *vs.* phenyl substitution in other carbonium ions.³⁹

Similarly, the changes in $\Delta\nu$ shown in Table VI and attributed by Cais, *et al.*, to changes in extent of iron participation are also explicable by formulation XV. Such $\Delta\nu$ values have been observed for metal π complexes of butadiene and cyclopentadiene.^{48d-f} Furthermore, the $\Delta\nu$'s within the aryl series are inconsistent with the notion of decreased iron participation with increased electron supply from R.




Therefore, we believe that either the proposal of Pettit, *et al.*, or that of Cais, *et al.*, is consistent with the nmr data now available. Neither the chemical shifts of the α protons nor those of the ring protons differentiate between these proposals.

Conclusion

The results of this study appear to be inconsistent with a mechanism of solvolysis of FeCR_2X involving the same kind of neighboring group participation usually displayed by carbon or by RS groups. While we cannot exclude some novel involvement of filled d orbitals which might be consistent with our findings, we consider a mechanism of σ - π conjugation simpler and preferable at this time.

(48) (a) W. Brügel, T. Ankel, and F. Krückeberg, *Z. Elektrochem.*, 64, 1121 (1960); (b) G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.*, 83, 2045 (1961); (c) C. Pascual, J. Keier, and W. Simon, *Helv. Chim. Acta*, 49, 164 (1966); (d) M. L. H. Green, L. Pratt, and G. Wilkinson, *J. Chem. Soc.*, 3759 (1959); (e) R. Pettit and G. F. Emerson, *Advan. Organometal. Chem.*, 1, 12 (1964); (f) M. L. Maddox, S. L. Stafford, and H. D. Kaez, *ibid.*, 3, 96 (1965).

II. Nmr Absorptions in Units of τ

τ	CH ₃			Ar		OH
FerC₅H₄COCH₃						
7.92		5.92	5.62 (quartet)	2.9-2.1 (complex)		
7.39		5.98	5.50 (sextet)	2.9-1.9 (complex)		
7.43		5.98	5.45 (sextet)	2.30 (quartet)		
FerC₅H₄CH(OH)CH₃						
8.58 (doublet)		5.92	5.8-5.5 ^a	2.9-2.1 (complex)	^a	8.36 (complex)
8.49 (doublet)		5.98	5.53 (sextet)	2.9-2.5 (complex)	5.17 (triplet)	8.07 (broad)
8.50 (doublet)		5.98	5.54 (sextet)	2.8-2.5 (complex)	5.14 ^b	8.14 (broad)

esolved from CH. ^b Not fully resolved.

interpretation is similar to that proposed earlier¹ and Richards^{2b} (delocalization into the ring) as to the major stabilization of α -ferrocenyl-ium ions (*i.e.*, about 80% of the stabilization). Our interpretations differ mainly with respect to stereospecific solvolyses, the *exo:endo* rate ratios and the position of the iron atom in the carbonium ion and C_a in the carbonium ion whereas ds, *et al.*, and Trifan, *et al.*, postulate that such σ is sufficient to govern stereochemistry and *exo:endo* rate ratios.^{4a}

Experimental Section^{4b}

Procedures followed for all preparations of substituted ferrocenes and α -phenethyl alcohols are the same as those used for ferrocenyl derivatives.

Ferrocenylacetophenone. *p*-Aminoacetophenone (11.0 g, 0.05 mole) was dissolved in 100 ml of 25% fluoroboric acid and cooled to 0° in an ice-salt bath. An ice-cold solution of 6.3 g of sodium nitrite in water was added dropwise, keeping the temperature at 5°, until a positive test was obtained with starch-iodide. The white precipitate was collected on a suction filter and washed with small amounts of water, ethanol, and ether. It was dried in 50 ml of cold acetic acid-water (1:1) and added to a cooled, stirred suspension of 15 g (0.805 mole) of sodium acetate in 600 ml of acetic acid. After addition was complete, the mixture was stirred overnight at room temperature. Then 2 l. of water was added, and the mixture was filtered. The solid was washed with water and sodium carbonate solution, dissolved in ether, and dried. It yielded 10.4 g of a brick red solid on evaporation. The solid was chromatographed on neutral activity II using petroleum ether-benzene mixtures. First, 5.9 g of *p*-acetophenone odor) was eluted with petroleum ether (0°). Then 5.4 g of *p*-ferrocenylacetophenone was eluted with petroleum ether-benzene, mp 173-174°, after recrystallization from cyclohexane (lit.^{7b} mp 176-178°). No attempt was made to separate other products in any of the arylation reactions. *Anal.* Calcd for C₁₈H₁₄FeO: C, 71.07; H, 5.30. Found: C, 71.07;

aqueous layer was reduced with stannous chloride to yield a brown solid. This was chromatographed in a similar manner and yielded 2.35 g of ferrocene. There were several other peaks in the column but only a trace of the desired ketone. Yield of *p*-ferrocenylacetophenone based on unrecovered ferrocene was 10%.

Ferrocenylacetophenone. *m*-Aminoacetophenone (11.0 g, 0.05 mole) was diazotized and the salt added to 30 g (0.161 mole) of sodium acetate in 1 l. of acetic acid. The ether-soluble portion of the

product on chromatography yielded 13.8 g of ferrocene. The desired ketone (6.0 g, 31% yield) was eluted next with 1:1 benzene-petroleum ether. It formed orange-brown prisms, mp 73.5-74°, after two recrystallizations from ethanol. *Anal.* Calcd for C₁₈H₁₄FeO: C, 71.07; H, 5.30. Found: C, 71.39; H, 5.27.

From the blue aqueous layer there was isolated 5.4 g of a brown solid, much of it evidently ferric oxide, which on chromatography afforded 3.4 g of ferrocene and 0.4 g of *m*-ferrocenylacetophenone.

***o*-Ferrocenylacetophenone.** *o*-Aminoacetophenone (5.0 g, 0.037 mole) was diazotized and added to 10.0 g (0.0538 mole) of ferrocene in 300 ml of acetic acid. Following work-up as usual, the ether-soluble product was chromatographed. Ferrocene (3.6 g) was eluted first, followed by the ketone (2.9 g, 35% yield), which was eluted with 1:1 benzene-petroleum ether. It was recrystallized from ethanol to form brown-red prisms, mp 87-87.5°. *Anal.* Calcd for C₁₈H₁₄FeO: C, 71.07; H, 5.30. Found: C, 70.83; H, 5.23.

Ferrocene (1.4 g, mp 171-173°) precipitated from the aqueous layer on reduction with stannous chloride. The infrared spectrum showed no detectable impurities.

α -(*p*-Ferrocenylphenyl)ethyl Alcohol. A solution of 3.0 g (0.0097 mole) of *p*-ferrocenylacetophenone in 50 ml of isopropyl alcohol was refluxed for 4 hr with 6 g of sodium borohydride. Excess sodium borohydride was then destroyed with acetone, and a few drops of water were added. The solvent was removed by evaporation and the residual yellow solid recrystallized from cyclohexane, mp 113-114°, yield 96%. *Anal.* Calcd for C₁₈H₁₆FeO: C, 70.61; H, 5.92. Found: C, 70.30; H, 5.96.

α -(*m*-Ferrocenylphenyl)ethyl Alcohol. The carbinol, prepared in 85% yield, was recrystallized from ether-petroleum ether, mp 86.5-87°. *Anal.* Calcd for C₁₈H₁₆FeO: C, 70.61; H, 5.92. Found: C, 70.62; H, 6.05.

α -(*o*-Ferrocenylphenyl)ethyl Alcohol. The carbinol was obtained as yellow needles, mp 113.5-114.5°, following recrystallization from cyclohexane; yield of purified material 80%. *Anal.* Calcd for C₁₈H₁₆FeO: C, 70.61; H, 5.92. Found: C, 70.41; H, 5.95.

α -(*p*-Tolyl)ethyl Alcohol. The crude reduction product was distilled at reduced pressure. The alcohol [bp 113° (13 mm)] was obtained in 80% yield; n_D^{20} 1.5205 (lit.¹⁰ n_D^{20} 1.5232).

α -(*p*-Anisyl)ethyl Alcohol. The yield of purified alcohol [bp 128° (15 mm), lit.¹⁰ bp 109-110° (2.5 mm)] was 71%; n_D^{20} 1.5335 (see Table VII for nmr readings).

α -(*p*-Ferrocenylphenyl)ethyl Chloride. Procedure A.¹⁰ A solution of 0.2 g of α -(*p*-ferrocenylphenyl)ethyl alcohol in 50 ml of ether was cooled to 0°. Several pieces of calcium chloride were added. The solution was purged with nitrogen, and then hydrogen chloride was passed into it for 1 hr.

Procedure B.¹¹ To the cooled ethereal solution of the carbinol was added 10 ml of concentrated hydrochloric acid. The mixture was shaken and kept at 0° for 1 hr. About 50 ml of petroleum ether was added, and the layers were separated.

The ethereal solution was dried with calcium chloride for 1 hr and filtered and the solvent removed at reduced pressure. Two portions of dry petroleum ether were added and evaporated. The residual

NOTE ADDED IN PROOF. After this paper was submitted M. S. Newman, *Rev.*, 1, 435 (1966) criticized our initial² proposal of delocalization. The suggestions of Cais should be compared with those presented here.

Boiling points are uncorrected. Analyses were performed by Dr. Pascher, Bonn, Germany.

(50) R. Fuchs and C. A. Vander Werf, *J. Am. Chem. Soc.*, **76**, 1631 (1954).

(51) Procedure of J. F. Norris, M. Watt, and R. Thomas, *ibid.*, **38**, 1071 (1916).

yellow solid, mp 83–84°, was highly reactive and was used without further purification. Analysis indicated that it contained 8% of starting material. *Anal.* Calcd for $C_{18}H_{17}ClFe$: C, 66.59; H, 5.28; Cl, 10.92. Found: C, 67.23; H, 5.78; Cl, 10.03.

α -(*m*-Ferrocenylphenyl)ethyl Chloride. Procedure B was used and the crude product, mp 86.5–88.5°, was chromatographed on activity II basic alumina, using petroleum ether. It was eluted rapidly, mp 90–90.5°, after recrystallization from petroleum ether. *Anal.* Calcd for $C_{18}H_{17}FeCl$: C, 66.59; H, 5.28; Cl, 10.92. Found: C, 66.04; H, 5.29; Cl, 10.94.

α -(*p*-Methylphenyl)ethyl Chloride.⁵² α -(*p*-Methylphenyl)ethyl alcohol (2 ml) was dissolved in dry benzene and cooled in an ice bath. Then 0.9 ml of phosphorus trichloride was added cautiously. A second phase appeared within 1 min. The mixture was kept at 0° for 1.5 hr. Then solid lithium carbonate was added and the solvent almost entirely removed at reduced pressure. The residual mass was suspended in petroleum ether and chromatographed on activity II basic alumina. The chloride was eluted before the carbinol. Portions of eluate were evaporated, and the infrared spectra of the chloride thus obtained were checked for absence of hydroxyl. The rest of the chloride-containing eluate was stored as the petroleum ether solution in the freezer in order to discourage polymerization; n_D^{25} 1.5242 (lit.¹⁰ n_D^{20} 1.5232).

α -(*p*-Methoxyphenyl)ethyl Chloride. Procedure B was used. The infrared spectrum of the product, n_D^{25} 1.5370, showed no hydroxyl absorption. When a weighed portion of the chloride was added to water it liberated 99.6% of the theoretical amount of hydrochloric acid, as determined by titration with sodium hydroxide.

The nuclear magnetic resonance spectrum, taken in carbon tetrachloride solution, had a three-proton doublet centered at τ 8.26 (side-chain methyl), a three-proton sharp peak at 6.32 (methoxy), a one-proton quartet centered at 5.01 (tertiary hydrogen), and a four-proton quartet centered at 2.99 (aromatic hydrogen).

***p*-Ferrocenylstyrene.** A petroleum ether solution of α -(*p*-ferrocenylphenyl)ethyl chloride was passed over a column of basic activity II alumina. Immediately a green-brown band appeared on the column. Rapid elution yielded an orange-yellow solid, mp 128–128.5°, after recrystallization from petroleum ether, in about 50% yield. (Other products were not examined.) The presence of peaks at 1623, 991, and 910 cm^{-1} in the infrared spectrum of the material (carbon tetrachloride solution) was indicative of a styrene derivative. *Anal.* Calcd for $C_{18}H_{14}Fe$: C, 75.02; H, 5.39. Found: C, 75.19; H, 5.33.

α -Chloroethyl methyl ether was prepared by the method of Henze and Murchison.⁵³

Products of Solvolysis of α -Ferrocenylphenylethyl Chlorides.

A. α -(*o*-Ferrocenylphenyl)ethyl Chloride. A solution of 0.0105 g (3.23×10^{-4} mole) of α -(*o*-ferrocenylphenyl)ethyl chloride in 95% ethyl alcohol was purged with nitrogen for 15 min. After the solution had been immersed in a 40° bath for 3.5 hr, the solvent was removed with a rotary evaporator. The residue was chromatographed on basic activity II alumina. Petroleum ether first eluted 0.003 g of a material (3%) whose infrared spectrum was characteristic of a styrene. This was followed by 0.099 g of a yellow solid, mp 71–72°, after recrystallization from ether–petroleum ether. It showed strong absorption in the infrared at 1090 cm^{-1} , and analysis confirmed its identity as ethyl α -(*o*-ferrocenylphenyl)ethyl ether (92% yield). *Anal.* Calcd for $C_{18}H_{18}FeO$: C, 71.87; H, 6.64. Found: C, 71.96; H, 6.80. Increasing proportions of benzene then eluted 0.003 g (3%) of a yellow solid, shown by its infrared spectrum to be α -(*o*-ferrocenylphenyl)ethyl alcohol.

B. α -(*m*-Ferrocenylphenyl)ethyl Chloride. A solution of 0.100 g (3.08×10^{-4} mole) of α -(*m*-ferrocenylphenyl)ethyl chloride in 95% ethyl alcohol was purged with nitrogen and then held at 70° for 7 hr. The solvent was removed with a rotary evaporator and the residue, a dark orange oil, chromatographed on neutral activity II alumina. About 0.009 g of the residue, dark brown in color, was insoluble. Petroleum ether first eluted 0.005 g of a yellow solid (6%) judged to be a styrene from its infrared spectrum. The styrene was followed by 0.070 g (68%) of an orange-yellow solid, mp 59.5–60.5° after two recrystallizations from petroleum ether. On the basis of infrared spectrum and elementary analysis it was identified as ethyl α -(*m*-ferrocenylphenyl)ethyl ether. *Anal.* Calcd for $C_{18}H_{18}FeO$: C, 71.87; H, 6.64. Found: C, 72.03; H, 6.75.

Benzene–ether solutions eluted about 0.003 g (3%) of α -(*m*-ferrocenylphenyl)ethyl alcohol, which was incompletely separated from a carbonyl-containing material (ca. 0.003 g), judging from infrared spectra. Some remaining darkly colored bands were very reluctantly eluted with ethanol and acetic acid and could not be characterized further.

C. α -(*p*-Ferrocenylphenyl)ethyl Chloride. A solution of 0.416 g of α -(*p*-ferrocenylphenyl)ethyl chloride (1.18×10^{-3} mole, allowing for 8% carbinol contamination) was dissolved in 100 ml of 95% ethyl alcohol that had been cooled to 0° and purged with nitrogen. After 3 hr at 0°, the solvent was removed by rotary evaporator. The dark orange oil was dissolved in petroleum ether and chromatographed on basic activity II alumina. Petroleum ether rapidly eluted 0.006 g (2%) of a yellow solid, shown by comparison of infrared spectra to be *p*-ferrocenylstyrene. The styrene was followed by 0.273 g (69%) of an orange oil which crystallized after vacuum drying, mp 47.5–48.5° after recrystallization from ethyl alcohol. On the basis of infrared and nmr spectra and elementary analysis it was identified as ethyl α -(*p*-ferrocenylphenyl)ethyl ether. *Anal.* Calcd for $C_{20}H_{20}FeO$: C, 71.87; H, 6.64. Found: C, 72.00; H, 6.61.

The nmr spectrum in deuteriochloroform had a triplet centered at τ 8.85 and a quartet centered at 6.69 (ethoxy), a doublet centered at 8.63 (methyl β to aromatic ring), a singlet at 6.03 (unsubstituted ferrocene ring), a sextet centered at 4.65 (substituted ferrocene ring), and a quartet centered at 2.76 (aromatic ring). The tertiary hydrogen was not resolved from the sextet at 5.65.

The ether was followed by 0.029 g (8% by weight) of a yellow solid which was eluted very slowly by petroleum ether and had mp 190–210°. It was poorly soluble in ordinary solvents, and a portion which was recrystallized from cyclohexane melted from 195 to 210°. Nearly the same melting range (195–205°) was shown by a portion which was recrystallized from ethanol. The infrared spectrum showed no bands that could not arise from a ferrocene nucleus with a hydrocarbon side chain. Lack of material and insolubility prevented obtaining a good nmr spectrum, the only clear peak being that at ca. τ 6, characteristic of unsubstituted ferrocene rings. *Anal.* (relative to those for 2,3-di-*p*-ferrocenylphenylbutane): Calcd for $C_{28}H_{24}Fe_2$: C, 74.76; H, 5.93; mol wt, 576. Found: C, 75.62; H, 8.02; mol wt, 611 (melting point depression).

Small percentages of benzene in the eluate brought off 0.017 g of an orange-red oil, the infrared spectrum of which had a carbonyl peak at ca. 1690 cm^{-1} . Its infrared spectrum consisted of the peaks characteristic of *p*-ferrocenylacetophenone, but there were others as well, in particular, one at 1090 cm^{-1} (strong), possibly an ether. Attempts to rechromatograph this fraction were unsuccessful because decomposition occurred after prolonged contact with the adsorbent.

Benzene–petroleum ether (1:3) eluted 0.049 g (4.5% allowing for that initially present) of α -(*p*-ferrocenylphenyl)ethyl alcohol, characterized by melting point and infrared spectrum. The small amount of material remaining on the column, eluted with mixtures ranging to 100% ether, could not be identified. The infrared spectra were complex, and prominent in all was a strong peak at ca. 1680 cm^{-1} . The “9–10 bands” characteristic of unsubstituted ferrocene rings were also evident.

Kinetic Measurements. The solvents were made up by volume at room temperature, using redistilled water, USP absolute alcohol, ethanol which had been refluxed and distilled over calcium hydride (for ethanol–ether mixtures), and sodium-dried reagent ethyl ether. These were saturated with nitrogen both before and after dilution. Temperature control in the range –20 to +80° was $\pm 0.02^\circ$ or less; the very low temperatures are estimated to be accurate within $\pm 0.3^\circ$. Thermometers in the normal range were calibrated against an NBS thermometer, and the low temperatures were measured with a vapor pressure thermometer.

The reactions were run in conductance cells unless titration procedures were to be used. Generally, the thermally equilibrated solvent was added to the substrate in the cell. The ferrocene derivatives had to be dissolved in a small amount of ether in order to effect immediate solution. It was necessary to use quite dilute solutions (ca. 0.001 *M*) in order to avoid a falloff in rate which became pronounced after one half-life.⁵⁴ Insolubility of the fer-

(52) K. Schlögel, *Monatsh.*, **88**, 601 (1957).

(53) H. R. Henze and J. T. Murchison, *J. Am. Chem. Soc.*, **53**, 4077 (1931).

(54) It is unlikely that this rate change is due to internal return. We tested for ether cleavage by allowing α -(*p*-tolyl) ethylethyl ether and 0.004 *M* HCl to stand in the solvolysis solvent for several half-lives of solvolysis and found no change in conductance. We conclude that the rate decrease results from readdition to the product styrene.

derivatives also necessitated dilute solutions. Infinity κ were taken after at least ten half-lives. Under optimum conditions, good first-order rate plots for up to three half-lives were obtained. Conductance was shown to be proportional to hydrochloric acid concentration under the conditions employed. Two or more runs were made at each temperature, and a typical measurement follows in Table VIII.

TABLE VIII. Run 118, Solvolysis of α -(*m*-Ferrocenylphenyl)ethyl chloride, 0.00161 *M*, at 55.00°

Time, sec	10 ⁴ κ , ohm ⁻¹	Time, sec	10 ⁴ κ , ohm ⁻¹	Time, sec	10 ⁴ κ , ohm ⁻¹
293	2.1	4066	31.3	9,560	52.8
386	2.7	4692	35.7	10,074	55.0
501	3.7	5838	38.8	10,797	58.8
593	4.7	6459	41.0	15,550	70.2
890	7.2	6786	41.8	16,483	76.0
930	12.7	7200	43.0	17,247	78.3
909	15.7	7622	44.7	17,641	79.6
471	20.0	8464	47.3	17,988	80.4
275	26.2	8770	49.1	79,200	121.5
798	28.8	9303	51.3	165,600	123.6

$$k_1 = 5.68 \times 10^{-4} \text{ sec}^{-1}$$

solvolysis rate of α -(*p*-methylphenyl)ethyl chloride at 55° was determined by titration of liberated hydrochloric acid with sodium hydroxide. It was necessary to add an excess of 2,6-dimethylphenol to the reaction mixture, which was more than ten times as much as the conductance solutions, in order to avoid a drop in first-order reaction rate with time.

Solvolyses of α -(*p*-methoxyphenyl)ethyl chloride at 0° and of α -methyl methyl ether at -70° were followed by an *in situ* titration procedure. Sodium ethoxide in the ether-ethanol kinetics was dropped in as needed in order to keep the reaction at the green end point of brom thymol blue. The titrant, added in a bulb, was forced out by mercury from a 5-mm buret. Reaction rate was controlled manually, using the valve from a meter titrator TTT1. The height of the mercury in the buret was read by a transducer, and this mercury pressure was recorded as a function of time. Thus, a continuous record of volume of ethoxide added (and of hydrochloric acid formed) could be obtained. Good linear first-order plots were obtained from these measurements, and rates compared well with those determined kinetically.

Rate parameters were calculated by the method of least squares and these values were used to calculate rates at 25°.

Measurement of Carbonyl Frequencies. The ketone carbonyl frequencies were measured as 0.002–0.004 *M* solutions in carbon tetrachloride, using the double beam mode of a Cary-White Model 14 spectrophotometer. The slit width was 1.4 cm⁻¹ and thickness 1 mm. The instrument was calibrated against water vapor peaks in the 1700-cm⁻¹ region. The mid point of the peak maximum intensity was taken as the absorption maximum. Uncertainty in the absolute values is estimated to be about 1%. Uncertainties in relative values are smaller.

The ketones were carefully purified. The more volatile were purified by vpc, using a silicone column in an Aerograph A-700 "Autoprep" gas chromatograph. Acetophenone *n*- and *p*-chloro, methyl, and methoxy derivatives were purified this way. Amino, nitro, and phenyl derivatives were reduced to constant melting point. *p*-Acetoxyacetophenone was prepared from *p*-hydroxyacetophenone by the pyridine method. *p*-Acetamidoacetophenone was obtained by acetylation of the corresponding amino derivative, mp 173–174°, after crystallization from ethyl alcohol (lit.⁵¹ mp 167°).

Anthracene, Chemicals Procurement Laboratories materials was chromatographed on neutral activity II alumina with methyl ether. Anthracene was eluted first, followed immediately

by 9-acetylanthracene, which was recrystallized from methanol to yield yellow prisms, mp 75–77° (lit.⁵² mp 75–76°).

9-Acetylphenanthrene, obtained from Aldrich, was treated with Norit and recrystallized twice from methyl alcohol to yield colorless needles, mp 73–74° (lit.⁵³ mp 73–74°).

3-Acetylinole was treated with Norit and recrystallized from benzene. Colorless needles, mp 194.5°, were obtained (lit.⁵⁴ mp 191°).

2-Acetylfuran was treated with Norit and recrystallized from ether at 0°. It was stored in the refrigerator, since the melting point is 29°.⁵⁵

1-Acetonaphthone, Eastman Kodak Technical, was separated with difficulty from 2-acetonaphthone by vapor phase chromatography, using a 5% Apiezon L on Chromosorb column (1/8 in. × 10 ft) at 180°. The collected material showed only a single peak when rechromatographed.

3,4-Methylenedioxyacetophenone, obtained from Aldrich, was treated with Norit and recrystallized from ether to yield colorless prisms, mp 86–87° (lit.⁵¹ mp 88°).

2-Acetylthiophene was obtained from Matheson Coleman and Bell and its purity was checked by vapor phase chromatography on a DEGS column (0.25 in. × 10 ft) at 120°. A single peak was observed.

Preparation and Solvolysis of *p*-Hydroxymethylbenzyl Chloride. *p*-Xylylenediol (10 g, 0.0724 mole) was added to a mixture of 150 ml of carbon tetrachloride and 50 ml of 6 *N* HCl at 0°. The glycol dissolved, and the aqueous layer turned yellow. The mixture was stored in the freezer for 2 days and then warmed to room temperature. A carbon tetrachloride extract at that time yielded nothing, but after 1 hr much yellow oil had appeared between the two layers. The oil was removed and extracted with ether to yield white crystals, mp 55–58°, melting point unchanged after recrystallization from carbon tetrachloride. The aqueous layer had developed by then a white precipitate, which was extracted into ether; mp 53–55°.

All the crystals were combined, dissolved in chloroform, and crystallized by adding petroleum ether to the solution. In this way there was obtained 1.35 g of crystals, mp 55.5–57.5°.

A second crop, 0.49 g, was obtained in the same way, mp 56–57.5°. The second crop was sublimed at 65° (1 mm), and white crystals, mp 55–60°, were obtained. Resublimation afforded 0.224 g of material of mp 59–60°. This sample was used for analysis and kinetics. (The compound was found to be quite irritating to the skin.) Anal. Calcd for C₈H₉ClO: C, 61.35; H, 5.97; mol wt, 157. Found: C, 60.99; H, 5.63; mol wt, 174.

The chlorohydrin yielded 99% of the anticipated amount of hydrochloric acid when hydrolyzed by 50% aqueous acetone (0.1 *M* in NaOH) at 35° for 3 days.

Kinetics. The substrate (0.04–0.09 *M*) was dissolved in ethyl alcohol containing 0.1 *M* NaOEt at 55°. Aliquots were quenched with hydrochloric acid and back-titrated with sodium ethoxide. In both instances the reaction followed second-order kinetics. For *p*-xylene dichloride, k_2 was 6.20×10^{-4} , and for the chlorohydrin, $k_2 = 6.21 \times 10^{-4}$ mole⁻¹ sec⁻¹.

Dimerization of *p*-Ferrocenylphenethyl Carbonium Ions. A solution of 0.406 g (0.00125 mole) of α -(*p*-ferrocenylphenyl)ethyl chloride in 7 ml of chloroform was added to 10 ml of 1:1 sulfuric acid-chloroform at 0°. After 1 hr the mixture was warmed to room temperature. It stood for 3 days, after which 35 ml of water was added. The dark green aqueous layer was separated from a pale yellow organic layer. The latter yielded only a few milligrams of yellowish oil on evaporation and was not examined further. The green solution was reduced with stannous chloride and extracted with benzene to yield 0.280 g of a yellow-brown solid.

The solid was chromatographed on neutral activity II alumina with benzene-petroleum ether mixtures. An orange solid (0.065 g), mp 220–225° and only slightly soluble, was eluted with 0.5% benzene. The infrared spectrum was consistent with that of a ferrocenyl hydrocarbon although it was very weak. A petroleum

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(58) H. F. Miller and G. B. Bachman, *J. Am. Chem. Soc.*, **57**, 766 (1935).

(59) B. Oddo and L. Sessa, *Gazz. Chim. Ital.*, **41**, I, 234 (1911).

(60) H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.*, **69**, 1012 (1947).

(61) E. Mameli, *Gazz. Chim. Ital.*, **39**, II, 165 (1909).

(62) Conditions used were those of A. Berger, W. E. McEwen, and J. Kleinberg, *J. Am. Chem. Soc.*, **83**, 2274 (1961).

an adaptation of the apparatus used for continuous pressure; see T. G. Traylor and C. A. Russell, *J. Am. Chem. Soc.*, **87**, 55.

L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 5th ed, John Wiley and Sons, New York, N. Y., 1964: (a) p 247; (b) p 259.

ether extract of the material yielded 0.005 g, mp 188–210°. The insoluble material then melted at 225–228°. Limited solubility of the latter forced use of such a high spectral amplitude that only a qualitative nmr could be obtained (benzene). Neither chloroform, DMSO, nitromethane, nor DMF would dissolve enough of the material for a spectrum. There appeared to be the following absorptions: a doublet at τ 8.96 and 8.87; sharp peak at 6.30 (unsubstituted ferrocene ring); and two poorly resolved triplets at 6.13 and 5.73 (substituted ferrocene ring). Aromatic proton absorption could not be distinguished from that of the solvent. *Anal.* Calcd for $C_{18}H_{14}Fe_2$: C, 74.76; H, 5.93; Fe, 19.31; mol wt, 576. Found: C, 74.47; H, 5.89; Fe, 19.73; mol wt, 549. This represents a 17% yield of dimer, based upon amount of starting chloride.

Elution mixtures containing 5–10% benzene eluted 0.010 g of solid of mp 258–261°. *Anal.* Found: C, 69.58; H, 6.52; mol wt, 3092.

Increasing amounts of benzene eluted additional amounts of solids, which had very wide melting ranges and variable but limited solubility. These could not be recrystallized, and infrared spectra indicated little because of insolubility. Mulls were also unsatisfactory. It was assumed that these fractions were polymers of a polystyrene type.

Preparation and Solvolysis of *p*-Chloromethylbenzyl Ethyl Sulfide (IV). A solution of 13 ml (0.17 mole) of ethanethiol in 100 ml of absolute alcohol containing 0.40 g (0.16 g-atom) of sodium as sodium ethoxide was added to 61 g (0.34 mole) of α, α' -*p*-xylylene dichloride in 700 ml of *t*-butyl alcohol (precipitate). The mixture was maintained at 70–75° during the addition which required about 15 min. After an additional hour stirring at this temperature the mixture was cooled to 0° for a few hours to precipitate the excess dichloride and filtered and the solvent evaporated. The product was distilled through a short Vigreux column at reduced pressure. Four fractions were obtained at 0.4 mm. The first two cuts, bp 103–104.5°, solidified and were shown by their infrared spectra to contain starting dichloride. The third cut, 3 g, bp 104.5–106.4°, $n_D^{21.5}$ 1.5686, showed none of the dichloride absorption at 14.4 μ in the infrared. The fourth cut, bp 106.5–115°, $n_D^{21.5}$ 1.5691, also showed no dichloride. Thin layer chromatography of cuts 3 and 4 using silica gel and cyclohexane–benzene also demonstrated the

absence of dichloride, but cut 4 contained appreciable amounts and cut 3 a small amount of a second, slower moving component, presumably the disulfide. Fraction 3, which was used in kinetic runs, gave the following. *Anal.* Calcd for $C_{10}H_{10}SCl$: C, 59.98; H, 6.54; Cl, 17.70; S, 15.90. Found: C, 60.00; H, 6.73; Cl, 15.58; S, 18.10.

Nmr. Whereas α, α' -dichloro-*p*-xylene showed singlets at τ 5.56 and 2.77, fractions 3 and 4 had the spectra shown in Table IX. Solvolyses of benzyl chloride, α, α' -dichloro-*p*-xylene, and IV in 50 vol. % aqueous dioxane, followed as described above, gave the first-order rate constants shown in Table X.

Table IX

Position, τ	Areas under nmr peaks				
	CH_2-CH_2	$-S-CH_2$	$-C_6H_4-$	$-CH_2-$	$-Cl$
Areas, fraction 3	2.9	1.9	1.8	3.9	2.2
Areas, fraction 4	3.6	2.2	2.0	3.6	1.7

Table X

	Rate constants, $k \times 10^4$, sec $^{-1}$		
	60°	80°	90°
Benzyl chloride		5.73, 6.10	
α, α' -Dichloro- <i>p</i> -xylene		5.08, 5.27	
IV	1.57, 1.45	8.53, 8.81, 8.74	21.6, 21.0

$$\Delta H^\ddagger_{IV} = 20.4 \text{ kcal}, \Delta S^\ddagger = -19 \text{ eu}$$

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Substituent Effects in the Chronopotentiometric Oxidation of Ferrocene Derivatives. Internal Solvation of Certain Substituted Ferricenium Ions¹

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Contribution from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology,³ Pasadena, California, and the Marathon Oil Company, Denver Research Center, Littleton, Colorado. Received August 12, 1966

Abstract: Chronopotentiometric quarter-wave potentials of a number of substituted ferrocenes were measured in acetonitrile solution. These new data, together with previously published data, indicate that substituent effects in this reaction are best correlated by a blending of Hammett σ_m and σ_p constants, rather than by the Hammett σ_p constants alone as was previously suggested. The quarter-wave potentials of acetamido- and urethano-substituted ferrocenes are anomalously low compared with those of the other compounds studied. This unusual behavior is explained in terms of direct interaction of the acetamido and urethano substituents with the positive iron atom in the oxidized species.

The degree of correlation of chronopotentiometric quarter-wave potentials of substituted ferrocenes with substituent constants such as Taft's polar con-

stants,⁴ Brown's σ^+ constants,⁵ and Hammett's σ_m

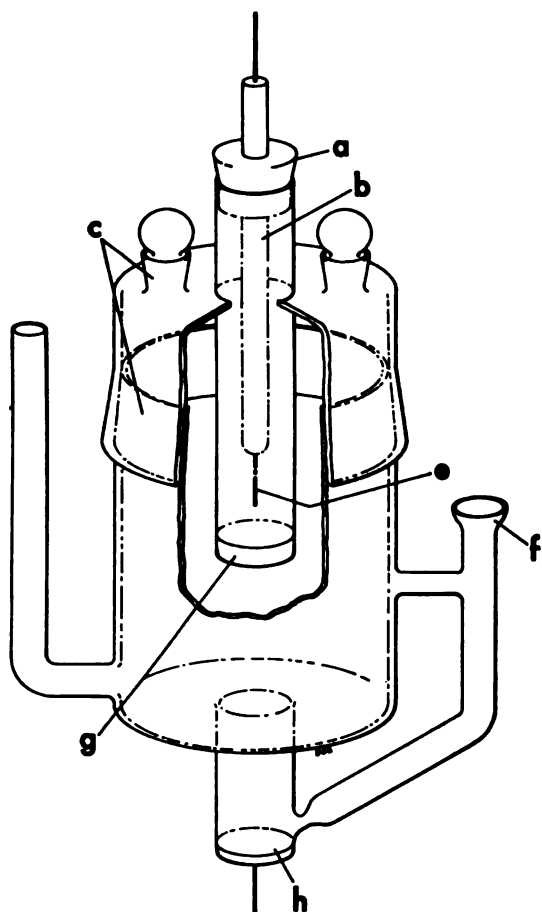
(1) (a) Presented in part at the 34th Annual Meeting of the Colorado-Wyoming Academy of Science, Colorado State University, Fort Collins, Colo., May 1963. The experimental portion of this paper is taken from: (b) the Ph.D. Thesis of D. W. Hall, California Institute of Technology, Pasadena, Calif., 1963; (c) the Ph.D. Thesis of C. D. Russell, California Institute of Technology, Pasadena, Calif., 1963.

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(3) Contribution No. 3462.

(4) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

(5) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).



1. Electrolysis cell: a, cork; b, glass tube; c, ground glass joint; d, N_2 inlet for deaeration; e, platinum wire auxiliary electrode; f, ball joint socket; g, fine porosity fritted glass; and h, disk working electrode.

, constants⁶ has been the subject of several investigations to date.⁷⁻⁹

It was concluded that these quarter-wave potentials are correlated with the Hammett σ_p constants, and the resulting Hammett plot can then be used to determine secondary σ_p constants¹⁰ for substituents for which such data are not tabulated. It was further concluded that the same regression line can be used to determine the monosubstituted ferrocenes and disubstituted ferrocenes.⁹

In addition to the chronopotentiometric measurements in acetonitrile solution, the reduction potentials of ferrocene derivatives have been measured in ethanol solutions¹¹ and in acetic acid solution.^{12,13}

It is the purpose of the present paper to point out the accepted view of substituent effects in the oxidation of ferrocene derivatives and, indeed, in several reactions of ferrocene compounds warrants re-evaluation.

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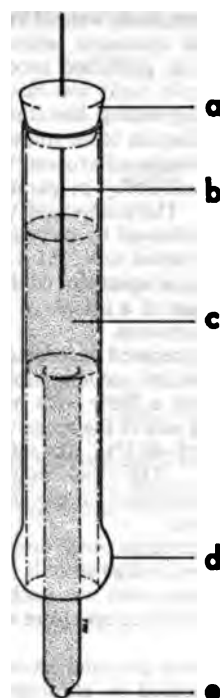


Figure 2. Silver-silver perchlorate reference electrode: a, cork; b, silver wire; c, 0.01 *M* silver nitrate, 0.2 *M* tetraethylammonium perchlorate, and acetonitrile; d, ball joint; e, soft glass bead in Pyrex stem.

Experimental Section

Measurements. Solutions of approximately 2 mM concentration in the ferrocene compound and 0.20 *M* in reagent grade, anhydrous $NaClO_4$ (G. F. Smith Chemical Co.) were prepared using spectral grade acetonitrile (Matheson Coleman and Bell Co.). The electrolysis cell is illustrated in Figure 1 and the reference electrode in Figure 2. The current source was a Wenking potentiostat (Elektronische Werkstätten, Göttingen, Germany) which controlled the voltage across a standard resistor in series with the cell and hence the current through the cell. Chronopotentiograms were recorded on a Moseley X-Y time recorder connected to the anode and to the reference electrode through two follower amplifiers of the DeFord type¹⁴ constructed with George A. Philbrick Co. plug-in amplifiers. The ohmic drop between anode and reference electrode was measured using a method described by Anson¹⁵ and found to be only a few millivolts; due correction was made to the measured potentials. All measurements were performed at 25.0°. The chronopotentiometric quarter-wave potentials determined in the present work are reproducible to within at least 10 mv.

The chronopotentiometric quarter-wave potential was interpreted as the formal oxidation potential for the given solution composition, after verifying reversibility of the electrode reaction by current-reversal chronopotentiometry.^{7,16} Reversibility was verified in the case of all but two compounds studied. Neither 3-acetyl-1,1'-di(ethoxycarbonylamino)ferrocene nor 3-acetyl-1,1'-trimethyleneferrocene gave any distinct chronopotentiometric wave upon current reversal. This probably indicates rapid decomposition of the oxidation product. Data for these compounds are excluded from the subsequent discussion.¹⁷

Preparation of Compounds. Most of the compounds listed in Table IA have been described in a previous publication.¹⁸

- (14) D. D. DeFord, Symposium on Electroanalytical Techniques, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958.
 (15) F. C. Anson, *Anal. Chem.*, **33**, 939 (1961).
 (16) P. Delahay, "New Instrumental Methods in Electrochemistry," Interscience Publishers, Inc., New York, N. Y., 1964.
 (17) More information is available in ref 1a and b concerning chronopotentiometric studies on the two compounds mentioned above, as well as on reversibly oxidized ferrocene compounds not deemed pertinent to the present paper.
 (18) D. W. Hall and J. H. Richards, *J. Org. Chem.*, **28**, 1549 (1963).

Samples used in the present study were of known analytical purity except for the compounds discussed below. These compounds were prepared according to published procedures and carefully purified. A check on sample purity was made by comparing melting points with the corresponding literature values when these were available, and by inspection of the infrared spectra.

1,1'-Di(methoxycarbonylamino)ferrocene¹⁹ was prepared in a manner analogous to Rosenblum's²⁰ preparation of 1,1'-di(ethoxycarbonylamino)ferrocene. The compound was purified by chromatography on alumina followed by recrystallization from petroleum ether (melting point, sealed tube, 152–153°; no melting point cited in ref 19). The infrared spectrum of this material compared favorably with the spectrum of a sample of analytically pure 1,1'-di(ethoxycarbonylamino)ferrocene.

Methoxyferrocene was prepared according to the procedure of Nesmeyanov²¹ and purified by vacuum sublimation. The resulting yellow needles possessed a fairly wide melting range (35–40°; sealed tube), but the upper end of the range was comparable to the reported melting point (39.5–40.5°). The infrared spectrum was in accord with the structure. The chronopotentiometric curves for this material displayed no evidence for the presence of other than a single oxidizable component.

3-Acetyl-1,1'-dimethylferrocene was donated by Hill.²² The purity of the sample was rechecked since it had stood on the shelf for some time. The melting point was unchanged from the value reported originally. The infrared spectrum was in accord with the structure.

1,1'-Dibromoferrocene was prepared according to the procedure of Nesmeyanov²¹ and purified by chromatography on alumina. Recrystallization from petroleum ether gave finely divided yellow crystals (mp 50–52°, sealed tube; lit.²¹ mp 50–51°).

Results

Chronopotentiometric quarter-wave potentials *vs.* the silver–silver perchlorate electrode for reversibly oxidized ferrocene derivatives determined in the present study are listed in Table I, part A. We have followed the precedent set by Little, *et al.*,⁹ and reported the data as $\Delta E^{1/4}$ values relative to the quarter-wave potential of ferrocene. The quarter-wave potential of ferrocene *vs.* the silver–silver perchlorate electrode was found to be 0.063 volts.

Quarter-wave potentials previously reported by other workers are listed in Table I, part B. These are $\Delta E^{1/4}$ values relative to the quarter-wave potential of ferrocene *vs.* the standard calomel electrode. These $\Delta E^{1/4}$ data were taken directly from ref 9, and represent in some instances, as outlined in that reference, averages of $\Delta E^{1/4}$ data determined by several research groups. It has been established⁹ that even though the quarter-wave potential of ferrocene *vs.* the standard calomel electrode varies considerably in the studies reported in ref 7–9, it appears to have been held reproducible for a given set of determinations by each individual research group. Thus, $\Delta E^{1/4}$ data for the same ferrocene derivatives are closely comparable throughout the several sets of studies. We chose the silver–silver perchlorate electrode only after experiencing difficulty in obtaining stable potential measurements with the aqueous calomel electrode.

We measured quarter-wave potentials for several ferrocene derivatives which had already been studied by other workers. We found a close correspondence between our $\Delta E^{1/4}$ data and the previously published data. Complete details of these repetitive studies are to be found elsewhere.^{1b,c} A comparison of our measurement of $\Delta E^{1/4}$ for 1,1'-diacetylferrocene (0.488 v)

(19) G. R. Knox, *Proc. Chem. Soc. (London)*, 56 (1959).

(20) M. Rosenblum, Ph.D. Thesis, Harvard University, 1953.

(21) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Chem. Ber.*, 93, 2717 (1960).

(22) E. A. Hill and J. H. Richards, *J. Am. Chem. Soc.*, 83, 4216 (1961).

Table I. Chronopotentiometric Quarter-Wave Potentials for Reversibly Oxidized Ferrocene Derivatives in Acetonitrile at 25°, Relative to the Quarter-Wave Potential for Ferrocene

No. code	Substituents	$\Delta E^{1/4}$	$\Sigma\sigma_m$	$\Sigma\sigma_p$
A. $\Delta E^{1/4}$ (silver–silver perchlorate electrode ^a)				
1	1,1'-Di(ethoxycarbonylamino)	−0.139	0.204	−0.172
2	1,1'-Di(methoxycarbonylamino)	−0.137	0.204	−0.172
3	Methoxycarbonylamino	−0.070	0.102	−0.086
4	Acetamido	−0.068	0.102	−0.086
5	Methoxy	−0.058	0.115	−0.268
6	3-Acetyl-1,1'-dimethyl	0.148	0.238	0.162
7	1'-Acetyl-1-methoxycarbonylamino	0.157	0.478	0.416
8	1'-Acetyl-1-acetamido	0.171	0.478	0.416
9	2-Acetyl-1-acetamido	0.250	0.478	0.416
10	1,1'-Dibromo	0.317	0.782	0.464
11	Cyano	0.375	0.560	0.660
12	1'-Acetyl-1-bromo	0.406	0.767	0.734
13	1'-Acetyl-1-chloro	0.427	0.749	0.729
14	1,1'-Diacetyl	0.488	0.752	1.004
15	1'-Acetyl-1-cyano	0.598	0.936	1.162
B. $\Delta E^{1/4}$ (standard calomel electrode ^b)				
16	1,1'-Diethyl	−0.115	−0.140	−0.302
17	1,1'-Dimethyl	−0.100	−0.138	−0.340
18	Ethyl	−0.061	−0.070	−0.151
19	Methyl	−0.060	−0.069	−0.170
20	Hydrogen	0.000	0.000	0.000
21	Trimethylsilyl	0.005	−0.040	−0.070
22	1,1'-Di(trimethylsilyl)	0.005	−0.080	−0.140
23	Phenyl	0.028	0.060	−0.010
24	1,1'-Diphenyl	0.055	0.120	−0.020
25	Iodo	0.142	0.352	0.180
26	1'-Ethyl-1-carboxy	0.182	0.300	0.300
27	Carboxy	0.240	0.370	0.450
28	Carbethoxy	0.241	0.370	0.450
29	Benzoyl	0.260	0.343	0.429
30	Acetyl	0.255	0.376	0.502
31	1,1'-Dicarboxy	0.453	0.740	0.900
32	1'-Acetyl-1-carboxy	0.466	0.750	0.950

^a $E^{1/4}$ for ferrocene was determined to be 0.063 v. ^b The $\Delta E^{1/4}$ data cited are taken directly from the appropriate tables in ref 9. In some instances, these data are averages of values reported in ref 7 and 8, as well as in ref 9.

with similar measurements by other workers (0.489 v;⁷ 0.484 v⁹) shows the sort of agreement which is typically observed in these studies.

The substituent constants employed are those tabulated by McDaniel and Brown,¹⁰ unless otherwise indicated. The σ values for the acetamido and benzoyl groups are those reported by White, Schlitt, and Gwynn.²³ The σ constants for the acetamido group differ substantially from those tabulated by McDaniel and Brown, but the discussion to follow does not depend qualitatively on which set is used. The σ constants for the urethano groups were arbitrarily assigned to be the same as those for the acetamido group. Again, the conclusions are qualitatively the same if the derived σ values reported by Kaplan²⁴ for the urethano group are used instead.

Hammett plots of the $\Delta E^{1/4}$ data given in Table I *vs.* $\Sigma\sigma_m$ and *vs.* $\Sigma\sigma_p$ are depicted by Figures 3 and 4, respectively. Figure 5 is a plot of the $\Delta E^{1/4}$ data *vs.*

(23) W. N. White, R. Schlitt, and D. Gwynn, *J. Org. Chem.*, 26, 3613 (1961).

(24) M. Kaplan, *J. Chem. Eng. Data*, 6, 272 (1961).

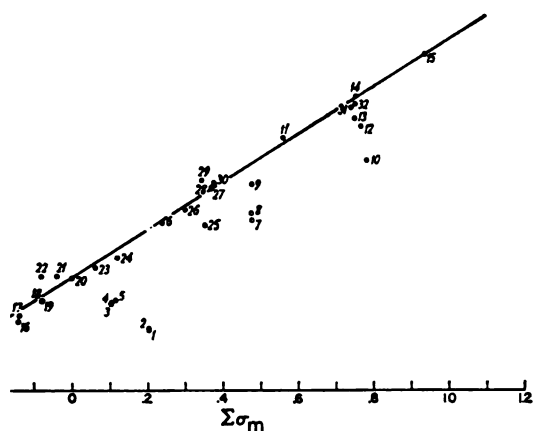


Figure 3. Relationship between $\Delta E^{1/4}$ of ferrocene derivatives and $\Sigma\sigma_m$ constants. Data represented by closed circles were used to determine the regression line. See Table I for list of data.

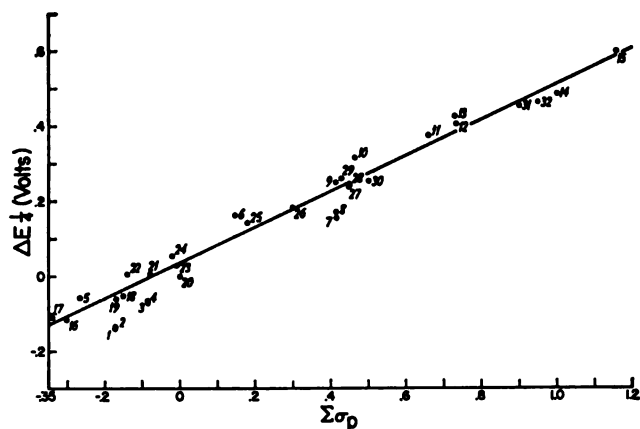


Figure 4. Relationship between $\Delta E^{1/4}$ of ferrocene derivatives and the Hammett σ_p constants. Data represented by closed circles were used to determine the regression line. See Table I for list of data.

any blending of the σ_m and σ_p constants. The constant, $\Sigma(\sigma_m + 2\sigma_p)/3$, is intended to represent effects intermediate in the relative inductive and resonance effects associated with σ_m and σ_p constants. Hill²⁵ has shown that effects in the solvolysis of heteroannularly substituted methylferrocenylcarbonyl acetates^{1b} are related by the calculated constant discussed herein by either σ_m or σ_p . Since it is believed that the α -ferrocenylcarbonium ion formed during solvolysis²² and thereby acquires a degree of positive character, it is perhaps not surprising that substituent effects in the solvolysis resemble substituent effects in the chronopotentiometric oxidation studies discussed here. In fact, it is shown that there is an excellent linear correlation between the solvolysis rate constant data and half-wave potentials of the appropriately substituted ferrocenes.^{1b} This work will be discussed in a future publication.²⁶

Table II lists the results of statistical analyses of the data, which are graphically represented in Figures 3–5.²⁷ These are merely unweighted least-squares treatments of the data. The Hammett equation was used as previously discussed by Jaffé;⁶ therefore, the significance of the statistical parameters is the same as discussed in detail by Jaffé. We have, perhaps, taken liberties from the standpoint of the statistician. We have selectively deleted data for substituents which do not fit a given chemical classification. This was in order to pinpoint sources of substituent effect. We believe these liberties will not lead to incorrect conclusions to be presented. But, they are not so obvious as it is possible inadvertently to omit discussion of statistically significant deviations not falling into our arbitrarily picked classes of substituent effects. However, we can safely say that the orders of magnitude of the deviations are far less than is the case with the data to be discussed.

Although it would be desirable to include in Table II the standard deviations of the data, we have deleted data for the standard deviations of the

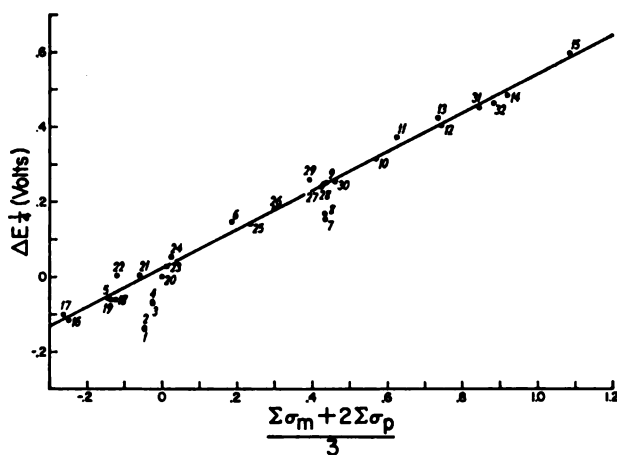


Figure 5. Relationship between $\Delta E^{1/4}$ of ferrocene derivatives and $\Sigma(\sigma_m + 2\sigma_p)/3$. Data represented by closed circles were used to determine the regression line. See Table I for list of data.

quarter-wave potentials, this is not warranted because of limitations on space.²⁸ When it becomes necessary to support a conclusion which cannot be adequately supported by the data presented in Table II, reference will be made to Figures 3–5. Quantitative data for deviations referred to in the Hammett plots will be cited from our files.

Discussion

Comparison of Figures 3 and 4 demonstrates that, as previous researchers have stated, the quarter-wave potentials are better correlated with Hammett's σ_p constants than with the σ_m constants. Discussion of those data which deviate even from the $\Delta E^{1/4}$ vs $\Sigma\sigma_p$ plot will be deferred for the moment.

It is of interest to examine the data given in Figures 3 and 4 in more detail.

Combination of all the previously published data, with but the exception of that for iodoferrocene, and a judicious selection of our data (exclude substituents which can stabilize a positive site by strong conjugation effects) lead to a large set of data which can be correlated very well by the standards listed by Jaffé⁶ with either $\Sigma\sigma_m$ or $\Sigma\sigma_p$. Compare computation numbers 2 and 5 in Table II. For a set of 20 ferrocene deriva-

(28) These data are available upon request.

²⁵ Hill, III, private communication.

²⁶ Hill, D. W. Hill, and J. H. Richards, manuscript in preparation.

We are indebted to D. E. Stephens for writing the programs and for assistance in the least-squares computations on the Marathon Oil Co.'s B-5000

Table II. Statistical Evaluation of the Correlation between $\Delta E^{1/4}$ and Substituent Constants

Computation no.	Subst const	Compds listed in Table I which were omitted	Slope of regression line	Correln coeff, r^a	Std dev	
					s^b	$\Delta E^{1/4}$, v ^b
1	$\Sigma\sigma_m$	None	0.620	0.920	0.084	0.081
2	$\Sigma\sigma_m$	1-5,7-10,12,13,25	0.639	0.995	0.022	0.021
3	$\Sigma\sigma_p$	None	0.493	0.983	0.040	0.039
4	$\Sigma\sigma_p$	1-4,7,8	0.472	0.993	0.025	0.024
5	$\Sigma\sigma_p$	1-5,7-10,12,13,25	0.468	0.995	0.022	0.021
6	$\Sigma(\sigma_m + 2\sigma_p)/3$	1-4,7,8	0.517	0.997	0.018	0.017

^a See discussion of statistical treatment of Hammett equation in ref 6. ^b Refers to the standard deviation of the quarter-wave potentials from the regression line.

tives, covering a magnitude of 1.5 σ units in the $\Sigma\sigma_p$ plot and 1.1 units in the $\Sigma\sigma_m$ plot, there is no difference in the degree of correlation with $\Sigma\sigma_m$ or $\Sigma\sigma_p$. In fact, both correlations are excellent according to standards suggested by Jaffé. The correlation parameters are identical for both computations ($r = 0.995$; $s = 0.022$; and the standard deviation of $\Delta E^{1/4}$ from the regression line is 0.021 v). Of course, in one sense the comparison here also reflects inherent weaknesses of the statistical parameters r and s as a test of goodness of fit. For this reason, visual inspection of the Hammett plots, even with all the known weaknesses of subjective influences of judgment, can sometimes be more rewarding. The same goal is achieved by utilizing the statistical data on standard deviation of quarter-wave potentials from the regression line. Arbitrarily selecting twice the standard deviation as a criterion for rejection, we find only the data point for 1,1'-di(trimethylsilyl)ferrocene anomalous in the $\Sigma\sigma_m$ plot described by computation 2 (0.055 v compared with 0.042-v limit). Since the same $\Delta E^{1/4}$ is reported for 1,1'-di(trimethylsilyl)ferrocene as for trimethylsilylferrocene, this anomalous point may be due to an error in the determination (or tabulation) of the quarter-wave potential. None of the 20 data points was anomalous in the $\Sigma\sigma_p$ plot described by computation 5 according to our arbitrary criterion. Thus, unless one wishes to weigh very heavily rejection of a dubious data point in computation 2, one must conclude that the correlations with either $\Sigma\sigma_m$ or $\Sigma\sigma_p$ discussed above are equally good. When the data point for iodoferrocene⁹ (halogen substituents are among those "key" substituents one should select for an investigation of the type discussed here) is included in the comparison, then one indeed finds a better correlation with σ_p than with σ_m by visual inspection of the Hammett plots or by consideration of the standard deviations of quarter-wave potentials from the regression line. The deviation from the regression line is graphically estimated to be 0.084 v. However, if one considers only the r and s parameters of Jaffé's statistical treatment, one finds the deviation by iodoferrocene in the $\Sigma\sigma_m$ plot is masked, and the correlations still appear to be about equally good. Thus, one would be forced to choose the $\Sigma\sigma_p$ correlation over the $\Sigma\sigma_m$ correlation on the basis of a single previously reported data point.

The problem of comparable correlations of data from a variety of reactions of ferrocene derivatives with either σ_m or σ_p has been a persistent one in our investigations.^{1b}

For example, we found the ionization constants of heteroannularly substituted ferrocenoic acids (litera-

ture values were used) were only slightly better correlated with σ_p than with σ_m . Both correlations were at least "good" by Jaffé's standards.⁶ However, these studies suffered from the fact that too few data were available (4 or 5 data points), key substituents were not included, and the ρ for the reaction was very small, thus making a choice between σ_m and σ_p more difficult for reasons cited by Jaffé.⁶ We found that Nesmeyanov's²⁹ pK_a data for the ferrocenoic acids could be correlated just as well with the quarter-wave potentials of the appropriately substituted ferrocenes as with the Hammett constants.^{1b} What this means is that a sufficiently extensive test of substituent effects has not yet been made for this particular reaction.

The rates of esterification of substituted ferrocenoic acids with diphenyldiazomethane³⁰ have been claimed⁹ to be better correlated with σ_p than with σ_m . However, comparisons were made on the basis of only four data points. In our treatment of the published data, we found no justification for selecting the σ_p correlation over the σ_m correlation. A more extensive study needs to be made before this problem can be resolved. We found the published esterification rate data could be correlated equally well with the appropriate quarter-wave potentials.^{1b} We attach no significance to that observation at the present time.

We believe the problem of equally good correlations of reaction data for ferrocene derivatives with σ_m or σ_p can best be avoided by including larger numbers of compounds in the studies than have generally been used in the past. Substituents should also be more diverse, rather than including only alkyl or carbonyl functions closely related in electronic effects. A study which includes, for example, three or four alkyl derivatives and acetyl, ester, and carboxylic acid derivatives in reality amounts to a study employing only two carefully determined data points.

Returning to the comparison of Figures 3 and 4, we find that $\Sigma\sigma_p$ does correlate more data points than does $\Sigma\sigma_m$ when data for substituents which are electron donating *via* a resonance interaction are considered. Thus, of the 12 compounds not used in computing the regression lines for Figures 3 and 4, six may be included in the $\Sigma\sigma_p$ plot (computation 4 in Table II) without appreciably decreasing the excellent correlation found in the case of the 20 compounds selected for computing the regression line for Figure 4. At least

(29) (a) A. N. Nesmeyanov and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, 115, 518 (1957); (b) A. N. Nesmeyanov and O. A. Reutov, *Izv. Akad. Nauk SSSR*, 926 (1959).

(30) W. F. Little and R. Eisenhal, *J. Am. Chem. Soc.*, 83, 4936 (1961). Table II of this reference inadvertently cites Nesmeyanov's value for the pK_a of ferrocenecarboxylic acid (6.11).

f these six compounds deviate badly in the $\Sigma\sigma_m$ correlation, while in the $\Sigma\sigma_p$ correlation only one of six data points (that for 1,1'-dibromoferrocene) lies by more than two times the standard deviation for the entire group. If one draws the new regression line derived from computation 4 in Table II, by adding to the original 20 data points those for methoxyferrocene, 2-acetyl-1-acetamidoferrocene, and halogen-substituted ferrocenes, a decisive trend in the data is noted.³¹ Data points for those substituents which can donate electrons by a resonance interaction tend to fall consistently on one side of the regression line (except for the alkyl substituents) as points for substituents which cannot stabilize a positively charged site in this manner fall on the other side of the line. Thus, the data points for both methoxyferrocene and 1,1'-dibromoferrocene fall off the line in the same direction and, as pointed out above, the data point for 1,1'-dibromoferrocene is rejected from the correlation according to our arbitrary limit.

We believe this trend indicates that σ_p overestimates the importance of resonance effects in the chronopotentiometric oxidation of ferrocene derivatives. Therefore we have plotted the data vs. the constant intercept between σ_m and σ_p , which Hill found to give the best correlation for rate data obtained for the solutions of methylferrocenylcarbonyl acetates.³⁵ Computation 6 in Table II shows that the correlation for the six data points in question is somewhat improved as compared with the $\Sigma\sigma_p$ correlation. Figure 5 graphically displays the treatment, in which $\Delta E^{1/4}$ is plotted against $\Sigma(\sigma_m + 2\sigma_p)/3$.

Only one compound among the 26 used in computation 6 deviates from the regression line shown in Figure 5 by more than two times the standard deviation; namely, 1,1'-di(trimethylsilyl)ferrocene (0.040 v compared with the arbitrary limit of 0.034 v). It certainly seems that $\Delta E^{1/4}$ for this compound should be redefined. The data point for 1,1'-dibromoferrocene falls almost precisely on the regression line.

We include the correlation of $\Delta E^{1/4}$ with $\Sigma(\sigma_m + 2\sigma_p)/3$ only to point out more strongly that σ_p somewhat overestimates resonance effects in the oxidation of ferrocene derivatives. Since there is already an abundance of σ constants of various types mentioned in the literature, we are not recommending that our calculated constant be added to the list.

Nesmeyanov has stated that formal oxidation potentials of ferrocene derivatives are correlated better with Taft's σ^0 constants than with Hammett's σ_p constants.³² The σ^0 constants place less weight on resonance interactions between the substituents and the reaction center.³³ Therefore, a correlation of these constants implies a decreased resonance effect, just as does correlation with our calculated constant $\Sigma(\sigma_m + 2\sigma_p)/3$.³⁴

We chose not to draw this regression line on Figure 4 since the line would become overly detailed. One may visualize this second regression line as remaining about the same as the line drawn in Figure 4 in the middle of points 16 and 17, but at the other end being shifted upward to pass through points 12 and 13.

A. N. Nesmeyanov and E. G. Perevalova, *Ann. N. Y. Acad. Sci.*, **136**, 103 (1965).

R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

We are indebted to a referee for pointing out ref 32. Although we have not done a statistical treatment on the correlation of $\Delta E^{1/4}$ with σ^0 , a physical examination shows the correlation to be at least as good as that obtained using σ_p .

The most important discovery in the present work is that quarter-wave potentials for several of the compounds listed in Table I deviate uniformly and markedly from the regression lines shown in either Figures 4 or 5. Thus, 1,1'-di(ethoxycarbonylamino)ferrocene, 1,1'-di(methoxycarbonylamino)ferrocene, methoxycarbonylaminoferrocene, acetamidoferrocene, 1'-acetyl-1-methoxycarbonylaminoferrocene, and 1'-acetyl-1-acetamidoferrocene all are much more readily oxidized than would have been expected on the basis of the σ_p constants for the acetamido and urethano groups, approximate as these may be.

Even if there were no linear correlation of quarter-wave potentials with $\Sigma(\sigma_m + 2\sigma_p)/3$, the fact that acetamido and urethano groups behave as more powerful electron donors than the methoxy group in the oxidation reaction would be quite unexpected. There is ample evidence based on reactions of benzene derivatives to indicate that the methoxy group should be the most potent of the three in stabilizing an electron-deficient reaction center.³⁶

Brown³⁶ and Stock³⁷ have shown that in mercuration and bromination reactions of substituted benzenes the methoxy group is about ten times more potent an electron donor than is the acetamido group.

We believe the anomalous behavior observed for the acetamido- and urethano-substituted ferrocenes is due to a direct interaction of the carbonyl oxygen atoms of these substituents with the positively charged iron atom in the oxidized species. This interaction may be viewed as an "internal solvation" effect.

Gubin and Perevalova, in their determination of normal oxidation potentials of monosubstituted ferrocenes in acetic acid-perchloric acid solution, postulated a direct field effect by phenyl, carbomethoxy, carboxyl, and halogen substituents.¹³ They stated that the methoxy, acetoxy, and alkyl groups showed no such effect.

Little, *et al.*,⁹ found no evidence in their work to support the direct field effect postulated by Gubin and Perevalova. In fact, they questioned that the field effect could be the magnitude suggested by the Russian workers for substituents such as the halogens, carboxyl, and carboalkoxy groups and yet be minor in the case of the methoxy and acetoxy groups. Little and co-workers concluded that the correlations observed in their work indicated that a direct field effect was either small or else proportional to the Hammett σ_p constants for the series of substituents studied.

It should be pointed out that 2-acetamido-1-acetylferrocene (compound 9 in Table I) deviates from the regression line only in the σ_m correlation. It appears to behave normally in the two correlations shown in Figures 4 and 5. We have previously shown that the amide hydrogen in this compound is strongly hydrogen bonded to the carbonyl oxygen of the acetyl group.¹⁸ It may be that this hydrogen bond is sufficiently strong so as to restrain the amide group from rotating to a favorable position for interacting with the positive iron atom in the oxidized species. Or, it may be that the energy required to break the hydrogen

(35) Ref 1b, pp 165-170, reviews the pertinent literature available at the time.

(36) H. C. Brown and G. Goldman, *J. Am. Chem. Soc.*, **84**, 1650 (1962).

(37) L. M. Stock and F. W. Baker, *ibid.*, **84**, 1661 (1962).

bond closely approximates that gained through rotation of the amide group and subsequent coordination with the iron atom.

Little, *et al.*, found that both acetoxyferrocene and phenoxyferrocene were not only oxidized more readily than expected, but also were irreversibly oxidized. We suggest that coordination of the acetoxy and phenoxy substituents with the positive iron atom in the oxidized species may have provided a pathway for decomposition. It would seem that more research is indicated to determine why methoxyferrocene is stable and acetoxy- and phenoxyferrocenes unstable under oxidation conditions. Apparently, the urethano- and acetamidoferrocenes do not have a similar pathway for facile decomposition when oxidized.

In conflict with the present study wherein acetamido- and urethanoferrocenes are oxidized at anomalously low quarter-wave potentials, Tirouflet and Komenda observed no unusual behavior for acetamidoferrocene in a polarographic study.¹¹ The data point for this compound fell very nearly on the correlation line in their plot of the oxidation potentials of 17 ferrocene derivatives *vs.* σ_p . Unless the ethanol-water solvent

used in the study of Tirouflet and Komenda minimized the effect of internal solvation by the acetamido group as compared with the effect in acetonitrile, we are at a loss to explain the conflicting results. It is our feeling that a polar hydroxylic solvent system should not completely mask an internal solvation phenomenon. This problem should be investigated further.

Tirouflet and Komenda also reported that their data did not correlate nearly as well with σ_m or Taft's polar constants. It is interesting to note that in their σ_p plot the point for aminoferrocene fell off the correlation line in the same direction that the point for methoxyferrocene did in our own study. Here again it seems that the electron-donating effect of substituents is overestimated by σ_p .

Acknowledgment. We are indebted to Professor J. H. Richards and Professor F. C. Anson for their helpful comments and for financial assistance during the course of this investigation. The financial assistance was derived in part from the U. S. Army Research Office (Durham) under Grant No. DA-ARO(D)-31-124-G315 and in part from the National Science Foundation under Grant No. NSF-GT5190.

Rates and Isotope Effects in the Proton Transfers from 2-Nitropropane to Pyridine Bases¹

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Abstract: The reaction between pyridine bases and 2-nitropropane in the presence of iodine is uncomplicated in *t*-butyl alcohol-water mixtures. In the absence of excess iodide ion and with only a small fraction of the pyridine converted to its conjugate acid, the reversibility can be neglected, and the reaction is apparently free from solvent and lyate ion catalysis. Steric retardation from 2- and 6-alkyl groups in the pyridine is significant, and comparable in magnitude to the acceleration resulting from the increase in base strength. Isotope effects measured when using 2-nitropropane-2-*d* are large and variable, increasing not only with base strength but also with steric hindrance from a value of $k_H/k_D = 9.8$ at 24.88° for pyridine catalysis to $k_H/k_D = 24.2$ for 2,4,6-trimethylpyridine catalysis at the same temperature. Reasons for the unusually large isotope effects are considered; both tunneling and extensive loss of zero-point energy are invoked.

The proton transfer reaction is one of the most important reactions of chemistry, because of the prevalence of hydrogen and also because of the widespread use of hydroxylic solvents, which serve as both proton donors and acceptors. Aliphatic nitro compounds are experimentally desirable as proton donors to bases because the slow reaction is not susceptible to acid catalysis, so that the interpretation of measured rates is simplified. In previous work³ aqueous ethanol was used as a solvent, and complications resulting from the side reactions with iodine were significant. In the present work *t*-butyl alcohol-water was used as a solvent to avoid this difficulty, and the extent of the reverse

reaction, the existence of which has been established,^{3,4} was reduced by minimizing the concentrations of inorganic products, acid, and iodide ion.

Results

The rates of reaction 1 were followed by disappearance of iodine measured spectrophotometrically in a



system containing *ca.* 0.1 *M* pyridine base, *ca.* 0.1 *M* 2-nitropropane, and *ca.* 10⁻⁴ *M* iodine in a solvent consisting of six volumes of *t*-butyl alcohol made up to ten with water. The small amount of perchloric acid used in previous studies^{3,5} is not necessary, but was usually

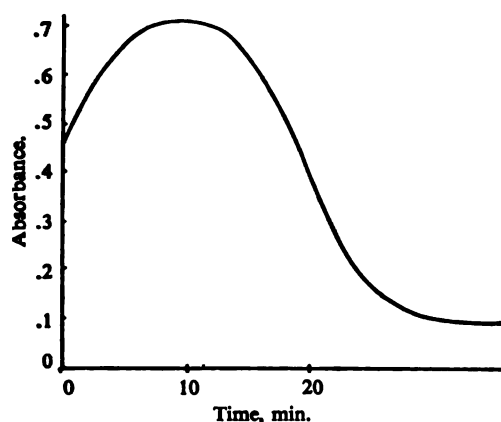
(1) A portion of this work has been published before in preliminary form: L. Funderburk and E. S. Lewis, *J. Am. Chem. Soc.*, **86**, 2531 (1964). From the Ph.D. Thesis of L. H. Funderburk, 1964.

(2) Robert A. Welch Foundation Predoctoral Fellow, 1962-1964. We thank this Foundation for this and other support of this work.

(3) E. S. Lewis and J. D. Allen, *J. Am. Chem. Soc.*, **86**, 2022 (1964).

(4) R. P. Bell and E. Gelles, *Proc. Roy. Soc. (London)*, **A210**, 310 (1952).

(5) R. G. Pearson and F. V. Williams, *J. Am. Chem. Soc.*, **75**, 3073 (1953).



1. The time dependence of absorbance at 360 $m\mu$ for iodine, 2-nitropropane, and 2,4,6-trimethylpyridine in aqueous *t*-butyl alcohol.

The disappearance of iodine follows a zero-order course, but a plot of optical density *vs.* time is not linear, because both the reagent pyridine base and the product iodide ion react reversibly with iodine and the extinction coefficient, but not the kinetics. Earlier work,³ excess iodide ion was used to make the extinction coefficient constant, but in this case the simplification is not worth the added complexity of interpretation introduced by extensive dilution. Figure 1 shows the absorbance plotted against time for a reaction with 2,4,6-trimethylpyridine base. The curvature results entirely from variation of the extinction coefficient, and this one is extreme when it was measured at 360 $m\mu$. Most measurements were made at 468 $m\mu$, where this effect is less marked and is not present. This plot, obtained directly from the reading spectrophotometer, was then converted to a plot of concentration of iodine (including all its components) as a function of time using appropriate extinction coefficients. The plot so obtained from the data in Figure 1 is shown in Figure 2, and the good linearity to large extents of completion is shown. The reaction in this linear portion is thus zero order in iodine. The reversal indicated by the non-zero final concentration of iodine was neglected, since data were not available before the appearance of significant curvature.

Second-order rate constants were obtained by dividing the zero-order rate constant by the product of initial 2-nitropropane and free base concentrations. Since the rate expression has been explored in detail, no searching experiments were done to verify if the results were incompatible with this rate law for the blank reaction mentioned elsewhere, for correction was made. We therefore consider the important term in the rate expression, that in eq 2 (2NP = 2-nitropropane, Py = a pyridine

$$-d(I_2)/dt = k_2(Py)(2NP) \quad (2)$$

and the ionization of nitro compounds is presumably subject to general base catalysis, one should also be concerned about the terms $k_2(OR^-)(2NP)$ and $k_4(OR^-)(2NP)$. Following Pearson and Williams,⁵ we tried to suppress the k_2 term by adding some acid. Lack of important contribution of this term is indicated by an experiment in which the acid was omitted,

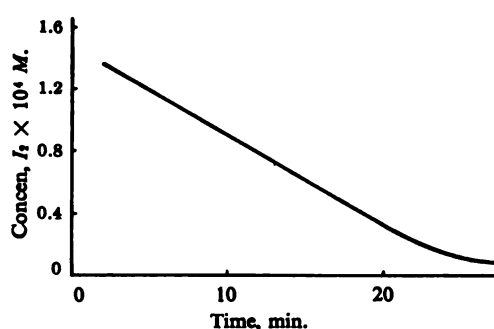


Figure 2. The time dependence of total iodine concentration as measured by the extinction coefficients and the absorbance shown in Figure 1.

using 2,6-dimethylpyridine as the base. No significant change in rate was noted, which suggests that the lyate ion term becomes negligible with only the amount of acid produced in the first few per cent of the reaction of the iodine, which occurred before measurements were started. The absence of the solvent term was not rigorously demonstrated, but if this term had contributed heavily, the rate would not have been proportional to the concentration of free base, and a significant rate in the absence of base would have been noted. The rate constants determined as described above are shown in Tables I and II. The tabulated

Table I. Rates and Isotope Effects for the Iodination of 2-Nitropropane in the Presence of Pyridine Bases

Pyridine subst	pK_a^a	$10^4 k_B^b$ $M^{-1} \text{ min}^{-1}$	$10^4 k_D^{c,d}$ $M^{-1} \text{ min}^{-1}$	k_B/k_D
None	5.17 ^a	1.12 ± 0.02	0.122 ± 0.003	9.8
3-Methyl	5.68 ^a	1.56 ± 0.03	0.153 ± 0.003	10.2
2- <i>t</i> -Butyl	5.76 ^a	0.0585 ^e	<i>f</i>	...
2-Methyl	5.97 ^a	2.70 ± 0.02	0.232 ± 0.001	10.2
4-Methyl	6.02 ^a	2.24 ± 0.06	0.211 ± 0.002	10.6
3,5-Dimethyl	6.19 ^a	2.20 ± 0.02	0.207 ± 0.004	10.6
2,5-Dimethyl	6.48 ^a	4.23 ± 0.10	0.387 ± 0.002	10.9
3,4-Dimethyl	6.53 ^a	3.07 ± 0.09	0.303 ± 0.01	10.1
2,6-Dimethyl	6.75 ^a	1.73 ± 0.04	0.0717 ± 0.002	24.1
2,4-Dimethyl	6.79 ^a	5.93 ± 0.06	0.403 ± 0.005	14.6
2,4,6-Trimethyl	7.59 ^a	4.83 ± 0.07^b	0.199 ± 0.011^b	24.3

^a pK_a of PyH^+ measured in water. ^b The indicated errors are average deviations of several runs made in aqueous *t*-butyl alcohol at 24.88° and measured at 468 $m\mu$. Blank corrections not more than 2%. ^c Corrected for blank reaction of not more than 10%, otherwise as in *b*. ^d Corrected for 1.3% light hydrogen content; the uncertainty of this correction is not included in the figures following \pm . ^e H. C. Brown and X. Mihm, *J. Am. Chem. Soc.*, **77**, 1723 (1955). ^f Too slow for adequate separation from blank reaction. ^g J. M. Essery and K. Schofield, *J. Chem. Soc.*, 3939 (1961). ^h Estimated from the pK_a of pyridinium ion by adding 0.80 for each 2-CH₃ group, 0.51 for each 3-CH₃ group, and 0.85 for each 4-CH₃ group. This estimate reproduces the published values in the table within 0.03 pK_a unit. ⁱ L. Sacconi, D. Paoletti, and M. Ciampolini, *J. Am. Chem. Soc.*, **82**, 3828 (1960). ^j H. C. Brown, S. Johnson, and H. Podall, *ibid.*, **76**, 5556 (1954). ^k Measurements made at both 468 and 360 $m\mu$.

values of the rate constant for deuterated species, k_D , include a correction, suitable when the extent of reaction is small, for contamination by the protonated species by eq 3, in which k_{obsd} is the observed rate constant for the deuterated compound, and *f* is the fraction

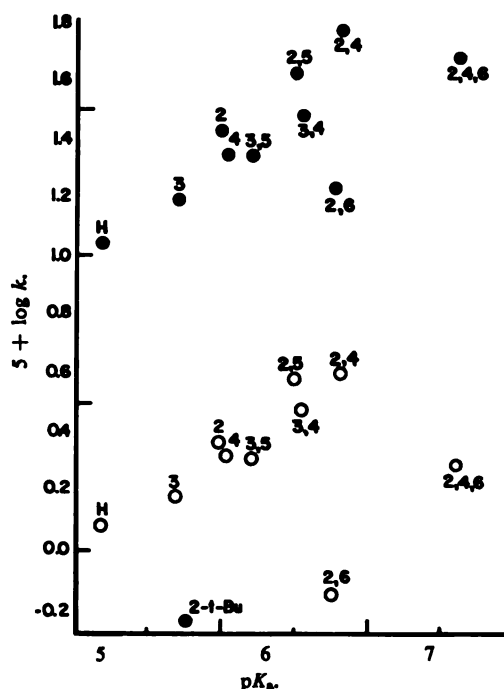


Figure 3. Brønsted plots for the reaction of pyridine bases with 2-nitropropane, ●, and 2-nitropropane-2-d, ○, in aqueous *t*-butyl alcohol. Numbers indicate positions of substituents, methyl except where otherwise stated.

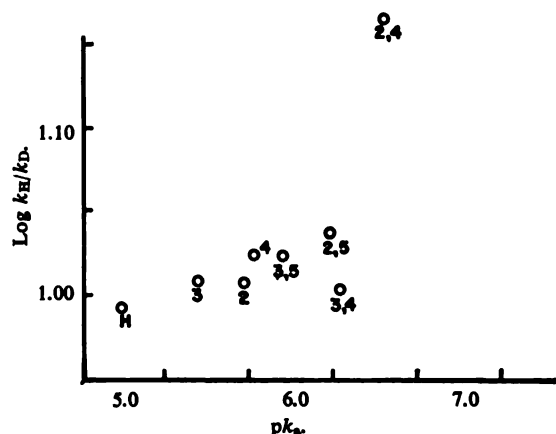


Figure 4. Plot of $\log k_H/k_D$ vs. pK_a for the reactions of substituted pyridines with 2-nitropropane. The points for 2,6-dimethylpyridine and 2,4,6-trimethylpyridine are off scale.

of the protium in this compound. The value used for proton content of the deuterated species was 1.3%.

$$k_D = (k_{\text{obsd}} - f k_H) / (1 - f) \quad (3)$$

Discussion

The results in Table I can be used to show that there is significant steric hindrance in some of these reactions. Brønsted plots of the data for both the protium and deuterium compounds are shown in Figure 3.

The Brønsted correlation is rough, but the deviations of the points for the 2,6-dimethyl-, 2,4,6-trimethyl-, and 2-*t*-butylpyridines (amounting to a factor of about 5 too slow a rate for the first two bases, and about 30 for the third) are clear and can be understood in terms of steric hindrance to proton transfer. There is no obvious deviation with any of the other 2-methyl

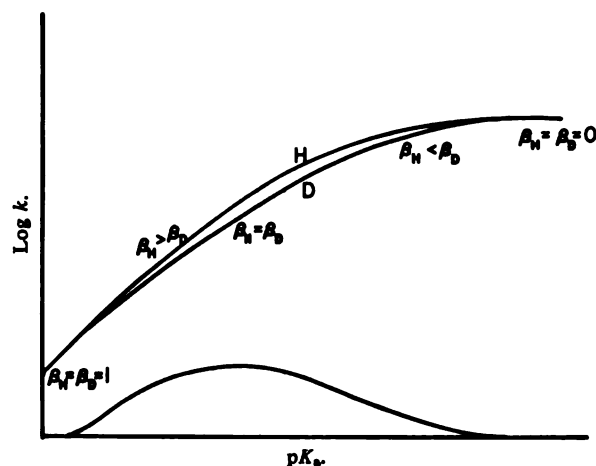


Figure 5. Theoretical plots of $\log k_H$, $\log k_D$, and $\log k_H/k_D$ vs. pK_a for a proton transfer reaction.

substituents. We shall discuss the results with the the apparently unhindered bases first.

The slopes (β) of the Brønsted plots are not well defined, but that for the deuterium compound is about 0.4. A small difference in the Brønsted slope between the hydrogen compound and the deuterium is not obvious from this plot, but is more conspicuous in Figure 4, in which $\log k_H/k_D$ is plotted against pK_a of the pyridinium ion, the bases with serious steric effects being off scale. A correlation with base strength is indicated,

Table II. Temperature Dependence of the Iodination of 2-Nitropropane with 2,4,6-Trimethylpyridine

Temp, °C	$10^4 k_H, ^\circ M^{-1} \text{ min}^{-1}$	$10^4 k_D, ^\circ M^{-1} \text{ min}^{-1}$	k_H/k_D
32.08	9.08 ± 0.02	0.425 ± 0.013	21.4
27.03	6.49 ± 0.27	0.265 ± 0.010	24.5
25.01	4.89 ± 0.05	0.197 ± 0.006	24.8
20.45	3.61 ± 0.20	0.138 ± 0.007	26.2

^a Conditions, corrections, and errors as described in Table I except for temperature.

and most of the 8 points fall reasonably on a line with a slope of 0.04, indicating that the Brønsted β for unhindered cases is perhaps 10% larger for the proton transfer than for the deuterium transfer reaction. This increase in isotope effect with base strength of the attacking species has often been observed before (a few of the many examples are cited in ref 3); it is clear that it cannot continue over a wide range of base strengths, for the isotope effects would become unreasonably large. Thus, this increase of 0.04 in $\log k_H/k_D$ per pK unit would predict $k_H/k_D = 50$ with a hypothetical base with conjugate acid pK_a of 20. Such isotope effects are unreasonable and not in accord with either experience or any theory of isotope effects. The Brønsted relationship runs into a limitation when reactions are diffusion controlled, but for this same base with conjugate acid $pK_a = 20$, the rate constants k_D and k_H predicted by the Brønsted coefficients of 0.40 and 0.44, respectively, are $k_D = 0.2$ and $k_H = 10$ l./mole sec, which are well below the diffusion-controlled limit. In order to reconcile experience and theory with this extrapolation, it is clear that the extrapolation must give way, and the Brønsted relation for either the proton

er, the deuteron transfer, or both must fail over wide range of base strengths. It is absurd to expect a conspicuous failure of the Brønsted relationship for only one isotope; it is more reasonable to expect deviation from the relationship in both reactions.

A reasonable form for the deviation from linearity is illustrated in Figure 5, which shows the limiting behavior of one and zero as described by Eigen.⁶ The same curve is also plotted (with a magnified scale), showing a maximum in k_H/k_D at some intermediate strength associated with a Brønsted slope well removed from either limit.

It is difficult to construct any other dependence of the isotope effect on pK_a that does not lead to a rather tortuous Brønsted plot, especially since the kinetic isotope effect can reasonably be expected to be absent in the uncontrolled reverse reaction at the left-hand

end. There is no obvious analytic form to the curves of Figure 5, so that it is not necessary to assume the value of 0.500 in the neighborhood of a base giving maximum isotope effect. The observed value of $\beta = 0.4$, which is probably near the maximum since the isotope effects are so large, is reasonable. We would expect that the Brønsted β would be large for a reaction with isotope effect increasing with base strength, and small when the isotope effect decreases with base strength.

It should be noted that an imaginative reader can easily see a maximum in the isotope effect in Figure 5 if it is assumed that even the single 2 substituent introduces a steric effect which influences the isotope effect. Then one should exclude these from Figure 4, and the remaining points show a maximum in isotope effect at pK_a about 6.1. If this is real, then this is the observation of such an effect with a closely related set of bases.

It is interesting that this maximum in the isotope effect on changing K_a is a consequence only of the dependence of the isotope effect on K_a . The maximum derived from these considerations may be compared with that predicted by Westheimer⁸ (and in different form by Melander⁹) for the one-dimensional transition state with hydrogen between two heavier particles. They predict a maximum isotope effect when the force constants to the two particles are equal, and k_H/k_D is unity when either one of these force constants is greater than the other. The maximum in the isotope effect may then be expected roughly when the reactant base and product base are equal in strength; the transition state should then be about halfway to the reactants and thus the Brønsted coefficient should be one-half. It is of interest to see to what extent the present situation fits these expectations. Since the nitropropane anion is probably a stronger base than pyridine bases, the ionization reaction is endothermic. Hence, following Hammond,¹⁰ the transition

state is somewhat product-like but would become more symmetric if the attacking base were stronger. This consideration of basicity would lead to the conclusion that we are on the left-hand side of the maximum in Figure 5. The observed coefficient of 0.4 is then adequately close to the predicted value. There are two complicating factors which should be considered in comparing the present results with any theory. First, the proton is attached to carbon in the reagent and to nitrogen in the product, and the reaction leads to separate charges from neutral reagents. There is thus no reason to believe that the upper curves in Figure 5 should have much symmetry. If a transition state has reached the halfway point in charge separation (the condition expected with $\beta = 0.5$), it need not have attained exactly the halfway point in bond strengths, such that the isotope effect is maximized. Second, the reported Brønsted β is based on pK_a 's measured in water, but to use it as a measure of the extent of proton transfer in the reaction under study the pK_a 's should be measured in the same solvent as is used in the reaction.

The rates and the isotope effects with the unhindered cases then present elements of interest, especially with regard to the consequences of an isotope effect that varies with base strength, but do not present any features without precedent from earlier work. The fact that the isotope effects and rates are understood makes them of greater value as a basis for the discussion of the hindered cases, which we shall now consider.

There is no conspicuous evidence for hindrance with only a 2-methyl group. We should then limit this discussion to those bases which deviate markedly from the Brønsted plot, namely 2,6-dimethylpyridine, 2,4,6-trimethylpyridine, and 2-*t*-butylpyridine. In the last case the rate was very low, and the deuterium case was too slow to measure, so that the isotope effect is quite large, but undetermined.

The very large isotope effects with 2,6-dimethylpyridine and 2,4,6-trimethylpyridine are somewhat larger than can be accounted for even by total loss of all the zero-point energy of the C-H and C-D bonds.¹¹

The very large isotope effect ($k_H/k_D = 19.5$ at 25°) has also been reported for the 2-nitropropane-2,6-dimethylpyridine reaction in water solution by Bell and Goodall.¹² They also report work of great pertinence to the problem of variation in isotope effect with acid and base strength.

The temperature dependence of the rate for 2,4,6-trimethylpyridine (eq 4) shows that the preexponential factor ratio A_H/A_D is significantly less than unity, so that the activation energy difference is even more difficult to reconcile with zero-point energy effects alone.

$$k_H/k_D = A_H/A_D e^{\Delta E_a/RT} = 0.15e^{3006/RT} \quad (4)$$

The large isotope effect, the large activation energy difference, and the small A_H/A_D factor all suggest, as

⁶ Eigen, *Angew. Chem.*, **75**, 489 (1963).

⁷ If the reverse reaction has no isotope effect ($k_H/k_D = 1$), then the forward reaction; more strictly, the ratio of the forward and reverse isotope effects is rigorously the equilibrium isotope effect, which is usually very close to unity. This equilibrium isotope effect is plotted in Figure 5.

⁸ H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

⁹ Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, 1962.

¹⁰ I. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(11) Estimates of the isotope effect attainable under these circumstances depend on the values chosen for the bond vibrational frequencies. The largest estimate in print is about 18, and a smaller maximum value of about 12 arises from a calculation based upon the admittedly inadequately resolved infrared spectra of 2-nitropropane and of 2-nitropropane-2-*d*.

(12) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc. (London)*, **A294**, 273 (1966). We are indebted to Mr. Bell for communicating several of these results to us in advance of publication.

discussed by Bell,¹³ that there is a significant tunnel correction, especially to k_H . The existence of a relationship between the steric hindrance and the anomalous isotope effects is strongly indicated, and it is worth considering simple explanations of this relationship.

The simplest picture of the potential barrier to a reaction is a one-dimensional plot of potential energy *vs.* reaction coordinate. The activation energy required is of two sorts; the first is energy required to break bonds or stretch them beyond their equilibrium distance, and the second is that to overcome repulsions between nonbonded atoms. It is clear that steric hindrance falls in the second category. At short interatomic distances, the repulsive energy between atoms, whether bonded or not, rises very rapidly as the distance decreases, so that a potential barrier with an important steric repulsion component can be expected to be very steep in the neighborhood of the maximum. The resulting high barrier, which is difficult to surmount classically, has steep sides and is, therefore, relatively thin at the top; this situation is conducive to significant contribution of tunneling.¹⁴

It has been pointed out by Johnston¹⁵ that one-dimensional barrier is inadequate to understand tunneling. It is interesting that even with a two-dimensional barrier representing a three-atom linear system there is a factor which will also enhance the fraction of tunneling in sterically hindered cases. Let us consider the familiar energy contours in the plot of r_{AH} *vs.* r_{BH} , and consider that there is in the unhindered case a certain fraction of tunneling direct from some point *x* on the reaction coordinate to another point *y* well below the maximum on the other side of the barrier and also on the reaction coordinate. Steric repulsion will raise the entire surface at short interatomic distances, that is, near the origin, but will have little effect when all distances are large. This has a major effect on the transition state but very little effect on the region directly between *x* and *y*, not along the reaction coordinate. Thus this tunneling will be relatively unchanged, but the rate of the classical barrier passage will be greatly reduced, and the fraction of tunneling will be increased by this steric repulsion.¹⁶ These explanations, which are not entirely independent, do not allow us to be quantitative, but they do help make these very large isotope effects qualitatively understandable.

It should be noted that steric repulsions in the transition state can also increase the loss of zero-point energy. The most easy deformation in the A-H-B system to get rid of repulsions between A and B is to stretch the hydrogen bond itself, and as this is stretched, the bending vibrations will become less stiff and there will be substantial loss of bending zero-point energy, leading to an isotope effect approaching the upper limit accessible from zero-point energy effects alone. We now believe in fact that both tunnel effects and large zero-point energy effects are responsible for these very large isotope

effects from results of an independent nature to be published shortly.

No mention has been made of the role of the solvent, nor can we find any evidence of any peculiar feature associated in the solvent in this reaction. Some less precise measurements with somewhat different mixtures of *t*-butyl alcohol and water showed essentially the same large isotope effects. The discrepancy between the isotope effects measured here and those reported in aqueous ethanol solution earlier³ is therefore worthy of comment. The other measured isotope effects show reasonable agreement; for instance for pyridine k_H/k_D is 10.2 in *t*-butyl alcohol and 10.7 in ethanol, whereas for 2,6-dimethylpyridine we now find that k_H/k_D is 24.1 in *t*-butyl alcohol, but only 10.1 was reported in ethanol. We now believe that the values in aqueous ethanol suffer from an experimental error and possibly an error of interpretation, both of which could reduce the isotope effect. The principal experimental error is the existence of a slow iodine-consuming reaction in the absence of nitropropane which is essentially negligible for the faster reactions but which becomes serious with the slowest reactions. It will be seen from Table I in ref 3 that the slowest reactions are those of the deuterated 2-nitropropane with pyridine and with 2,6-dimethylpyridine. Since the blank reaction is faster when pyridine is substituted (either because iodination of the solvent is catalyzed more effectively by the stronger bases or because the blank reaction is in part iodination of the pyridine side chains), this blank correction is largest for the case in question of 2,6-dimethylpyridine. Our blank corrections were made assuming that this side reaction was zero order in iodine; if the reaction is first order, the correction is too big. Thus uncertainty in this blank correction makes the value of k_D for 2,6-dimethylpyridine the least accurate of all the data reported, and the k_H/k_D value the least reliable.

A possible error of interpretation in the earlier work may arise from the assumption that the terms associated with the general base catalysis in solvent and in lyate ion are negligible. In aqueous *t*-butyl alcohol these terms are indeed negligible, but in water solution both a water term and a hydroxide ion term are reported to contribute markedly.¹² It is therefore possible that these terms also contribute in aqueous ethanol. Since they would very likely have smaller isotope effects, the ratio of gross rates of the hydrogen and deuterium compounds would be less. We are grateful to Mr. R. P. Bell for presenting this suggestion to us before publication of this explanation.¹²

The absence of lyate ion term was demonstrated for pyridine solutions by showing that the rate was insensitive to the concentration of pyridinium ions. This experiment was not tried on the more strongly basic 2,6-dimethylpyridine, where the lyate ion concentration is higher. The solvent term was believed to be small, but the evidence is incomplete. The only pertinent data are rate constants measured at two different base concentrations which might be interpreted as differing by virtue of a solvent term in the rate expression instead of a change in iodine extinction coefficients as originally assumed. The data are inadequate to separate the two effects, and the blank error mentioned above makes it unlikely that it will be possible even with more data. Nevertheless, the presence of solvent and lyate ion

(13) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(14) A referee suggests that steric hindrance may hold the extreme atoms of a model triatomic system farther apart throughout, thus effectively making the barrier thicker. We have not become convinced that the barrier thickness is this simply estimated, but we present the above argument as a plausible but by no means rigorous possible explanation of the observed experimental result.

(15) H. S. Johnston and D. Rapp, *J. Am. Chem. Soc.*, **83**, 1 (1961).

(16) This suggestion was made to us by Dr. James M. Perry, whom we thank for this idea.

with smaller isotope effects would reduce the gross effect substantially in the aqueous ethanol. We therefore are inclined to weight the new isotope more heavily than the old in aqueous ethanol and do not feel that a large isotope effect near a factor of 20 in the aqueous ethanol is necessarily excessive. The minimization of all these complications in aqueous *t*-butyl alcohol is doubtless related to the basicity and acidity of this solvent and its resistance to halogenation. It was indeed the unreliability of the lowest rates in the aqueous ethanol solution that led us to reinvestigate this reaction in aqueous alcohol.

Experimental Section

Materials. 2-Nitropropane and 2-nitropropane-2-*d* were prepared as before;³ the protium content of the deuterated species was 2% in the 2 position, as measured by the nuclear magnetic resonance spectrum. The substituted pyridines were prepared as described before, and several new ones were commercially purified by distillation. Impurity by gas chromatography, which was able to resolve all the compounds available, amounted to no more than 1%. 2,4,6-Trimethylpyridine was purified by distillation from its boron fluoride complex as described before for 2,6-dimethylpyridine³ to remove unhindered tertiary butyl alcohol which was a commercial material of boiling point.

Measurements. The solvent was usually made by diluting 0.119 *M* aqueous perchloric acid with 30 ml of *t*-butyl alcohol.

The carefully weighed appropriate amount of pyridine (about 0.4 g) was mixed with the *t*-butyl alcohol solution and then diluted to 50 ml with water, giving a solution about 0.1 *M* in perchloric acid and 0.1 *M* in pyridine.

Reactions were started by adding a concentrated solution of 2-nitropropane to this base solution until the reaction reached a preselected value (about 0.48) and allowed to the thermostat temperature. 2-Nitropropane, about 0.5 g weighed, was diluted to 50 ml with the above base and

iodine solution and the resulting solution was placed in a 10-cm absorption cell placed in a recording spectrophotometer set at 468 mμ as rapidly as possible. Since temperatures in the cell compartment were slightly closer to room temperature than the thermostat, because of heat transfer in the circulating system, the temperature changes in dilution and cell filling were in part compensated and the times taken for the cell to come adequately close to the compartment temperature were in fact rather small.

In order to demonstrate absence of serious error from the conversion of absorbances to concentration, the results for 2,4,6-trimethylpyridine were repeated at 360 mμ, using 1-cm cells instead of 10 to compensate for the higher extinction coefficients. The results agreed within 2%.

Controls showed that uncertainty about the reaction temperature was not a significant source of error. Temperatures were measured with a thermistor in the cell compartment with the thermostat itself used frequently as a reference to compensate for drift. The thermostat temperature was determined with a Bureau of Standards calibrated thermometer. Absolute temperatures are probably not accurate to better than $\pm 0.1^\circ$, but relative temperatures are limited primarily by reading accuracy and by the precision of bore of the thermometer, leading to an error probably $\pm 0.02^\circ$, since the calibration was smooth.

Solutions of known concentration of the base, iodine, and iodide ion in the solvent simulating various extents of reaction were made up, to determine the relation between absorbance and concentration of iodine in all its various complexed states. The record of absorbance vs. time from the rates was then converted to a concentration vs. time plot, which was linear up to large extents of completion confirming the zero order in iodine and its complexes. There was a residual iodine absorption because of the reversibility of the reaction, but this complication was avoided by using only the linear portion of the curve. The reported second-order rate constants are the slopes of these linear plots, less a blank correction amounting in the largest case to 10% of the observed rate (measured in a solution containing everything but 2-nitropropane and not followed to complete consumption of iodine, since it is so slow) and then divided by the base and nitropropane concentrations. Blank runs with the pyridine base omitted showed negligible reaction, and the measured rates were unchanged by the omission of the small amount of perchloric acid, usually added.

The Importance of the "α Effect" in Amine General Base Catalyzed Ionization of Nitroethane

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Contribution from the Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106. Received December 29, 1966

Abstract: The conversion of nitroethane to its ion by amine general-base catalysis ($k_{2,B}$) and the retrograde general-acid neutralization of the anion ($k_{2,A}$) have been investigated. Both $k_{2,B}$ and $k_{2,A}$ are correlated by the Brønsted equations for general-acid and general-base catalysis, respectively. Though the log of the rate constants for tertiary, secondary, and primary amines lie on separate Brønsted plots of parallel slope (presumably due to differences of solvation), hydrazine, *N*-methylhydrazine, hydroxylamine, and methoxylamine show no positive deviations from these plots. Therefore, the so-called α effect does not appear to be operative in the breaking or making of the C-H bond of nitroethane.

The term "α effect" has been used³ to describe the high reactivity of nucleophiles possessing an unpaired pair of electrons adjacent (α) to the nucleophilic

This high reactivity is generally noted as a large deviation of the log k_{rate} for a nucleophile from

a Brønsted plot for nucleophilic displacements by a series of like nucleophiles in aqueous solution. Therefore, the α effect amounts to a nucleophilic (kinetic) parameter not predicted by the thermodynamic affinity of nucleophile for a proton. The various rationales for this kinetic effect have recently been summarized and discussed.⁴ They include intramolecular hydrogen

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² To whom inquiries concerning this paper should be directed.

O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16

(4) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).

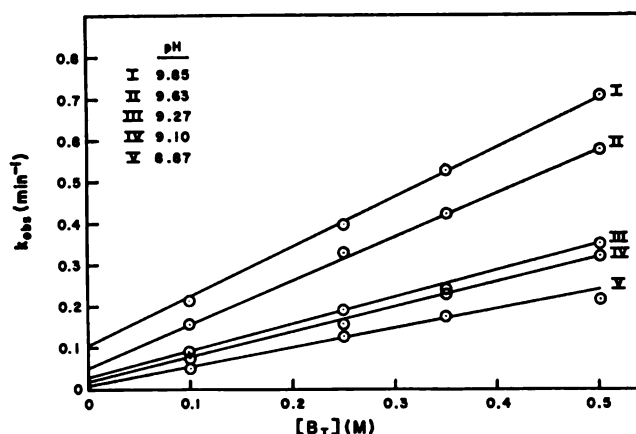


Figure 1. The linear dependence of the pseudo-first-order rate constants for the reaction of glycine with nitroethane on the concentration of glycine at five pH's.

bonding to a carbonyl or similar group,^{5,6} intramolecular general-base catalysis,⁶ stabilization of the transition state due to overlap of the orbitals of the α lone pair of electrons,⁸ lessened solvation of nucleophiles exhibiting the α effect relative to other nucleophiles of the same series,⁷ destabilization of the nucleophile by repulsion of the nonbonding electrons,^{8,9} high polarizability, and stabilization of the products of reaction.

Substrates upon which this effect has been noted to operate are all valence states of carbon, peroxides, and tetrahedral phosphorus (see ref 3). The question arises as to whether the α effect is of importance in nucleophilic displacement on hydrogen (*i.e.*, general-base catalysis). It has been reported¹⁰ that oxime anions show an enhanced effectiveness in the dehydration of acetaldehyde hydrate. The present work is concerned with the neutralization of nitroethane with a series of aliphatic amines. This reaction has received some attention by Pearson and co-workers.¹¹

Experimental Section

Apparatus. Absorbance measurements were made on Gilford Model 2000 or 220 recording spectrophotometers. Kinetic solutions were maintained at $30 \pm 0.1^\circ$ by circulating water at this temperature through Beckman double thermostats. pH Measurements were made with a Radiometer Model 22 pH meter with a PHA 630 scale expander, using a combined glass-calomel electrode (Radiometer G.K. 2021C). The electrode was thermostated at the temperature of the kinetic runs.

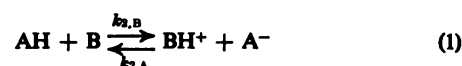
Materials. Nitroethane (Matheson Coleman and Bell) was distilled twice through a 9-in. Vigreux column; bp 113° . Concentrated ammonia solution (Baker and Adamson, CP) and ethylamine (Eastman White Label) were appropriately diluted with water. Diethylamine (Eastman) and piperidine (Matheson Coleman and Bell) were distilled from barium oxide, bp 55 and $103\text{--}104^\circ$, respectively. Morpholine (Eastman) was refluxed over sodium for 24 hr and distilled under nitrogen, bp $125\text{--}126^\circ$. Methoxyamine, glycine ethyl ester (Eastman), and hydrazine (Matheson Coleman and Bell) hydrochlorides were crystallized from ethanol-

ether mixtures. Tris(hydroxymethyl)aminomethane (Matheson Coleman and Bell), glycine (Fisher reagent), and hydroxylamine hydrochloride (Baker Analyzed Reagent) were used without further purification. Methylhydrazine hydrochloride was prepared by passing dry hydrogen chloride into an ethereal solution of the amine (Matheson Coleman and Bell). The precipitate was crystallized from ethanol-ether mixtures.

Kinetics. The rate of disappearance of nitroethane in various buffers was followed by measuring the variation in absorbance at $240\text{ m}\mu$. Stock solutions of nitroethane in peroxide-free dioxane were prepared. One drop of these solutions in 2 ml of buffer gave a solution approximately 10^{-5} to 10^{-4} M in nitroethane. Freshly distilled water was used to prepare buffer solutions and serial dilutions were made with 1.0 M potassium chloride solution stored under nitrogen. The reactions were carried out in T cuvettes. Absorption due to the various buffers was compensated for by using a reference cell containing only the buffer solution. The concentration of buffer was always in large excess over that of nitroethane, resulting in pseudo-first-order kinetics. Reactions were routinely followed to four half-lives or more. The pH's of solutions were determined before and after each run. Pseudo-first-order rates were obtained from the slopes of plots of $\log(\text{OD}_\infty - \text{OD}_t)$ vs. time.

Results¹²

The reaction studied is of the type



If $[\text{B}]$ and $[\text{BH}^+]$ are in large excess over $[\text{A}_T]$, this equilibrium can be treated as a unimolecular equilibrium



(2), for which the rate expression is given by¹³

$$-\ln ([\text{AH}]_0 - [\text{AH}]_e)/([\text{AH}] - [\text{AH}]_e) = (k_{2,B}[\text{B}] + k_{2,A}[\text{BH}^+])t \quad (3)$$

where $[\text{AH}]_0$, $[\text{AH}]$, and $[\text{AH}]_e$ represent concentrations of AH at $t = 0$, at any time t , and at equilibrium, respectively. As the measured absorbance is that of the nitroethane anion, $(\text{OD}_\infty - \text{OD}_t)$ is proportional to $([\text{AH}] - [\text{AH}]_e)$

$$-\ln ([\text{AH}]_0 - [\text{AH}]_e) + \ln (\text{OD}_\infty - \text{OD}_t) = (k_{2,B}[\text{B}] + k_{2,A}[\text{BH}^+])t \quad (4)$$

Thus the slope of a plot of $\log(\text{OD}_\infty - \text{OD}_t)$ vs. t is equal to $0.434(k_{2,B}[\text{B}] + k_{2,A}[\text{BH}^+]) = k_{\text{obs}}$. As the neutralization is also catalyzed by hydroxide ion this term is included in k_{obs} which is then equal to $(k_{2,B}[\text{B}] + k_{2,A}[\text{BH}^+] + k_{\text{OH}}[\text{OH}^-])$. Thus, a plot of k_{obs} vs. $[\text{B}_T]$ is linear, of slope k_2' and intercept $k_{\text{OH}}[\text{OH}^-]$ (Figure 1)

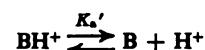
$$k_2' = k_{2,B}([\text{B}]/[\text{B}_T]) + k_{2,A}([\text{BH}^+]/[\text{B}_T]) \quad (5)$$

and

$$k_2' = k_{2,B}[K_a'/(K_a' + a_H)] + k_{2,A}[a_H/(K_a' + a_H)] \quad (6)$$

A plot of $k_2'(K_a' + a_H)$ vs. a_H is linear of slope $k_{2,A}$ and intercept $k_{2,B}K_a'$ (Figure 2). For amines of high

(12) Abbreviations used in this study are: $[\text{B}_T] = [\text{B}] + [\text{BH}^+]$



where B and BH^+ represent amine and its conjugate acid; k_{obs} , pseudo-first-order rate constant at constant pH and $[\text{B}_T]$; k_2' , apparent second-order rate constant at a fixed pH; $k_{2,A}$, $k_{2,B}$, pH-independent second-order rate constants for general acid and general base catalyzed reactions, respectively; a_H , hydrogen ion activity as determined by the glass electrode, $[\text{OH}^-] = 1.48 \times 10^{-14}/a_H$.

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(11) R. G. Pearson and F. V. Williams, *J. Am. Chem. Soc.*, **76**, 258 (1954). This paper gives leading references to previous papers.

Table I. Experimentally Determined Rate Constants and Equilibria Constants for the Reaction of Amines with Nitroethane at 30°, $\mu = 1.0$

Base	Min ⁻¹ M ⁻¹		$K'_{\text{aNE}} \times 10^{-9}$	No. of k_{obsd}	pH range	No. of pH's	Concn range, M	pK _a ' ^a
	$k_{2,A}$	$k_{2,B}$						
1 Ethylamine	...	7.7	...	20	10.26–11.10	5	0.448–0.090	10.69 ^b
2 Ethylenediamine	...	6.7	...	20	9.63–11.18	5	0.5–0.1	10.10 ^c
3 Glycine	0.22	1.71	4.4	24	8.87–10.26	6	0.5–0.1	9.63 ^c
4 Ammonia	...	0.56	...	20	8.64–9.85	5	0.380–0.076	9.33 ^b
5 Methylhydrazine	1.65	1.32	6.3	16	7.36–8.40	4	0.5–0.1	8.14 ^d
6 Hydrazine	0.72	0.35	3.7	20	7.42–8.60	5	0.5–0.1	8.11 ^c
7 Tri(hydroxy-methyl)amino-methane	0.56	0.31	3.7	20	7.52–8.87	5	0.5–0.1	8.15 ^c
8 Hydroxylamine	...	5.7×10^{-3}	...	5	8.95	1	1.0–0.1	6.04 ^c
9 Glycine ethyl ester	1.00	0.23	4.0	20	6.99–8.47	5	0.5–0.1	7.75 ^d
10 Methoxylamine	...	1.35×10^{-3}	...	3	8.80	1	1.0–0.2	4.81 ^c
11 Diethylamine	...	49.5	...	16	10.61–11.27	4	0.3–0.06	11.08 ^d
12 Piperidine	...	39.2	...	16	10.20–11.32	4	0.5–0.04	11.10 ^c
13 Morpholine	1.38	3.45	6.4	20	8.28–9.67	5	0.5–0.1	8.59 ^c
14 Hydroxide	...	990	...	11	9.63–11.18	11

$\mu = 1.0$, 30°. ^b See ref 4. ^c See T. C. Bruice, J. J. Bruno, and W. S. Chou, *J. Am. Chem. Soc.*, **85**, 1659 (1963). ^d This study, by half-neutralization.

the acid-catalyzed rate constant is small and $K_a' + a_H$ was a constant equal to $k_{2,B}K_a'$. Kinetic studies using methoxylamine and hydroxylamine were carried out in 0.1 M borate buffer to maintain constant pH. Rate constants for these amines were determined from the slopes of plots of k_{obsd} vs. $[B_T]$. In all other cases the nucleophile and its conjugate acid were used to maintain a constant pH.

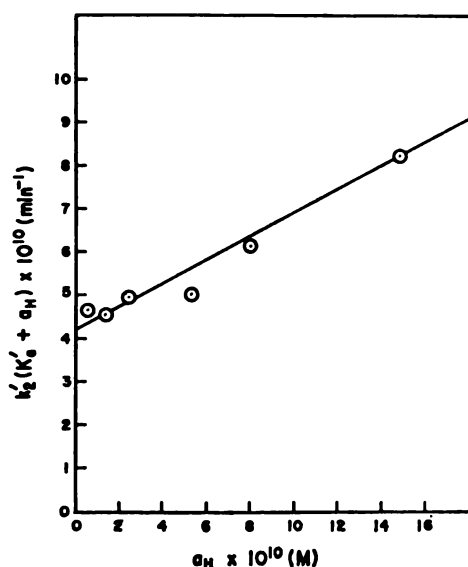


Figure 2. The linear dependence of the product $k_2'(K_a' + a_H)$ on hydrogen ion activity for the reaction of glycine with nitroethane.

The rate constants for the reaction of 13 amines with nitroethane derived by these methods are given in Table I. The rate constant for hydroxide was obtained by plotting the intercepts at $[B_T] = 0$ from buffer dilution plots vs. $[OH^-]$. The buffers used were ethylamine, glycine, and ammonia.

The equilibrium constants K_a for (1) are given by

$$K_a = k_{2,B}/k_{2,A} = [BH^+][A^-]/[AH][B] \quad (7)$$

where the concentration terms refer to equilibrium concentrations

$$K_a = [A^-]_e a_H / [AH]_e K_a' = K'_{aNE} / K_a' \quad (8)$$

and K'_{aNE} is the calculated dissociation constant of nitroethane. The calculated constant as obtained for each amine is given in Table I.

Discussion

The rate constants for the general-base neutralization of nitroethane by 13 amines are given as a Brønsted plot in Figure 3. Comparison of this Brønsted plot with that of Pearson and Williams¹¹ shows that the behavior of the various classes of amines are essentially the same, the only difference being in the slope used for primary amines (0.50 vs. 0.65 for Pearson and Williams' estimate).

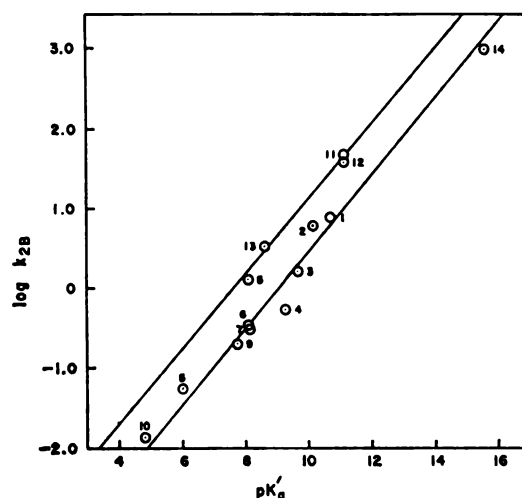


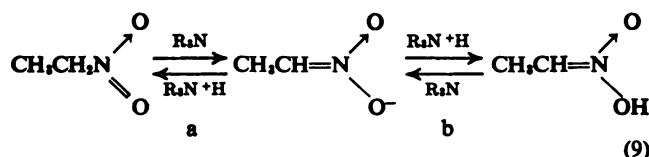
Figure 3. Brønsted plot for the reactions of 14 bases with nitroethane. The numbers refer to the compounds in Table I. No statistical corrections have been made.

The dissociation constants (K'_{aNE}) for nitroethane determined from the rate constants for primary amines are in good agreement with that found by half-neutralization (3.6×10^{-9} at 30°).¹⁴ However, the values derived from rate constants with secondary amines differ considerably from those obtained by half-

(14) D. Turnbull and S. H. Maron, *J. Am. Chem. Soc.*, **65**, 212 (1943).

neutralization. This is believed to be due to a statistical factor, and that the true equilibrium constant should be expressed in terms of the number of equivalent protons on the conjugate acid of the amine. In order to correlate the equilibrium constants found with secondary amines (two protons) with those for primary amines and hydronium ion (three protons), the former constants were multiplied by a factor of $2/3$. This correction gave a value for the K_a' of nitroethane of 4.1×10^{-9} , which is close to the value found with primary amines (3.9×10^{-9}).

The possibility that the rates obtained were for reaction of the amine species with the tautomeric *aci*-nitro forms of nitroethane and its anion (9) was discounted, as the pK_a' obtained from the kinetic data is that for nitroethane whereas the pK_a' of *aci*-nitroethane is approximately 5. In the pH range studied (7–11) the



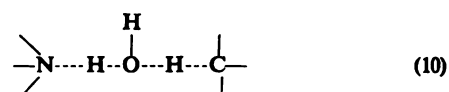
equilibrium concentration of *aci*-nitroethane would be so small that equilibrium 9b can be ignored.

The order of catalytic efficiency for amines in this reaction (*i.e.*, tertiary > secondary > primary) has been attributed to solvation effects by Pearson and Williams.¹¹ The same order of nucleophilicity of amines (*i.e.*, tertiary > secondary > primary) has also been noted with phosphate¹⁶ and sulfate¹⁶ esters and has also been attributed to solvation effects. It is interesting to note that these substrates are sensitive to the α effect. However, toward phenyl acetate primary and secondary amines lie on a single Brønsted plot whereas tertiary amines exhibit a negative deviation from this plot.⁴ A possible explanation for this apparent anomaly is found in the fact that the bond from nucleophile to substrate is little formed in the transition states for substrate equals phosphate or sulfate esters whereas when the substrate is phenyl acetate the bond is much more completely formed. This suggestion is supported by the small Brønsted α constants for the former substrates (0.20 and 0.13, respectively) as compared to the large value for the latter substrate (1.05). Therefore, steric effects outweigh solvation effects for phenyl acetate while steric effects are of little importance for phosphate and sulfate esters. This contention finds support in the much greater nucleophilicity of azetidines and aziridine toward phenyl acetate as compared to acyclic secondary amines.¹⁷

The rate constants for the general base catalyzed reactions of hydrazine, hydroxylamine, and methoxylamine with nitroethane do not deviate significantly from the Brønsted plot for primary amines (Figure 3). The rate constant for methylhydrazine lies on the Brønsted plot for secondary amines, in agreement with Condon's¹⁸ suggestion that protonation of alkylhydrazines occurs at the nitrogen bearing the greater number of

alkyl groups. We can therefore find no evidence for an α effect for hydrazine, methylhydrazine, hydroxylamine, or methoxylamine in this reaction. The value of 0.5 for the slope of the Brønsted plot suggests that the proton has moved considerably in the transition state, and that any effect operating on the ground state of either products or reactants should be observable. This confirms that the reactivity in proton abstraction of these amines is adequately related to their pK_a 's.

General base catalyzed proton abstraction differs from nucleophilic displacement reactions on other elements on two points. Whereas the latter must involve direct attack of the nucleophile on the substrate molecule or capture of carbonium ion, etc., the former may operate through a water molecule in a manner analogous to proton transfer in water.¹⁹ Regardless of the mechanism of the proton abstraction, the un-



shared pair of electrons of the base are not considered⁸ to be greatly perturbed in the transition state, whereas considerable perturbation of these electrons occurs in other nucleophilic displacements. Thus proton abstraction and nucleophilic displacements are not strictly analogous in that proton abstraction is insensitive to polarizability of the nucleophile.

As amines which exhibit the α effect are similar in polarizability (as measured by molar refractivity) to those which do not, the α effect must be a kinetic parameter which is not described by the E_n or P terms of Edwards.²⁰ Our results eliminate such ground-state phenomena as diminished solvation as a cause of the α effect in amines such as hydrazine since amine-catalyzed ionization of nitroethane is sensitive to solvation changes at the basic nitrogen.

The attribution of the high reactivity of oxime anions in the dehydration of aldehyde and ketone hydrates to an α effect³ is probably not valid, as this too could be caused by solvation differences between these anions and the carboxylate and phenolate anions used as references. This is supported by the fact that water exhibits an equally great positive deviation from the Brønsted plot. However, for the general base catalyzed hydrolysis of ethyl trifluorothiolacetate²¹ and the self-assisted general base catalyzed aminolysis of phenyl acetate⁴ the α effect is probably of importance and for the latter process of greater kinetic significance than for simple nucleophilic attack of amine on ester. These reactions differ from the neutralization of nitroethane in that they involve an actual nucleophilic attack on an unsaturated center and in addition proton transfer from nitrogen or oxygen rather than from carbon. It is possible that work in process may provide a rationale for these observations.

Acknowledgment. This research was supported by a grant from the National Institutes of Health.

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A Kinetic and Isotopic Study of the Decomposition of Monoperoxyphthalic Acid

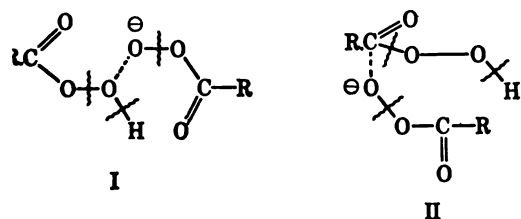
R. E. Ball,^{1a} J. O. Edwards,^{1a} M. L. Haggett,^{1b,c} and Peter Jones^{1b}

Contribution from the Metcalf Chemical Laboratory of Brown University, Providence, Rhode Island, and the Department of Physical Chemistry of the University of Newcastle, Newcastle upon Tyne, England. Received January 10, 1967

Abstract: The mechanism of the decomposition of monoperoxyphthalic acid has been investigated. The rate law is analogous to those found for other monosubstituted peroxides (second order in peroxide with a maximum rate at pH equal to pK_a of peroxidic proton). The isotope data are consistent with previously observed cases in that the data are explicable in terms of two competing transition states of identical composition but different configuration.

The thermal decomposition of peroxy acids in aqueous solution to form the parent acid and oxygen has been the subject of a number of recent investigations. Edwards, *et al.*,²⁻⁴ have studied the kinetics of the decomposition of two aliphatic peroxy acids and the cyclic peroxy acids Caro's acid and peroxymonophosphoric acid. Goodman and Robson^{5,6} have studied the decomposition of peroxybenzoic acid and a series of substituted peroxybenzoic acids. The latter workers have also investigated Caro's acid and have obtained results in agreement with those reported by Edwards. Independent data on peroxybenzoic acids are also in good agreement.⁷

In all cases it has been found that the rate of peroxy acid decomposition is second order in total peroxy acid concentration, with a maximum rate constant at a pH equal to the pK of the proton bound to the peroxide group. The results are consistent with the idea that decomposition occurs by nucleophilic attack of the peroxy acid upon the undissociated peroxy acid molecule, where there has been some question as to the electrophilic site at which this attack occurs. Whereas Edwards and Robson advanced arguments which led them to conclude that attack was at the carbonyl carbon of the peroxy acid (II) (sulfur or phosphorus in the case of Caro's acid and peroxymonophosphoric acid, respectively). These two activated complexes can be distinguished by a tracer technique. Mechanism I



predicts that, from a mixture of doubly oxygen-18-labeled peroxy acid and unlabeled peroxy acid, some scrambled molecular oxygen (mass 34) should be obtained. Mechanism II predicts that under the same condition no scrambling should occur. Two cases have so far been investigated. In the case of peroxyacetic acid Edwards and co-workers³ found a distribution of isotopic label in product oxygen corresponding to 83% of the reaction occurring *via* II. Studies of Caro's acid⁴ yield the result that 91% of the reaction occurs *via* I. Thus it appears likely that the two mechanisms, which yield identical kinetic form and differ only in the conformation of the transition state, are operating simultaneously.

The double-labeling method has not yet been applied to the case of substituted peroxybenzoic acids, but the experiments cited above suggest that if the carbonyl carbon electrophilic site is sterically hindered, then attack at outer peroxidic oxygen (I) may be favored. Monoperoxyphthalic acid is a most suitable peroxy acid to test this idea since the pK of the peroxy acid proton is 8.2, and the pK of the carboxylic acid proton is -0.5 ,⁸ so that around pH 8 decomposition would arise from attack of the dinegative ion upon the mononegative ion. Thus the electrostatic situation is similar to that with Caro's acid (attack of SO_5^{2-} on HSO_5^-) and additional steric hindrance is provided by the *o*-carboxylate group.

This paper describes the results of our investigation of the decomposition of monoperoxyphthalic acid. Studies of the hydrolysis of monoperoxyphthalic acid are reported elsewhere.⁸

Experimental Section

Monoperoxyphthalic acid was prepared according to the method of Bohme.⁹ The product was a mixture of peroxy acid and phthalic acid. Various preparations yielded samples containing 40–60% w/w monoperoxyphthalic acid. The preparation of doubly oxygen-18-labeled monoperoxyphthalic acid followed the same procedure except that, to the hydrogen peroxide used, was added sufficient $H_2O_2^{18}$ to give a mole fraction of $H_2O_2^{18} \approx 0.04$. $H_2O_2^{18}$ was prepared from water containing 97 atom % O^{18} (Yeda Research and Development Co., Ltd., Rehovoth, Israel) by the electric discharge method.¹⁰

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(a) Metcalf Chemical Laboratory, Brown University, Providence, Rhode Island. (b) Department of Physical Chemistry, University of Newcastle, Newcastle upon Tyne, England. (c) Exploratory Research Laboratory, Chemical of Canada, Ltd., Sarnia, Ontario, Canada.

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(6) J. Curci and G. Modena, *Tetrahedron Letters*, 1749 (1963); *chim. Ital.*, 94, 1257 (1964).

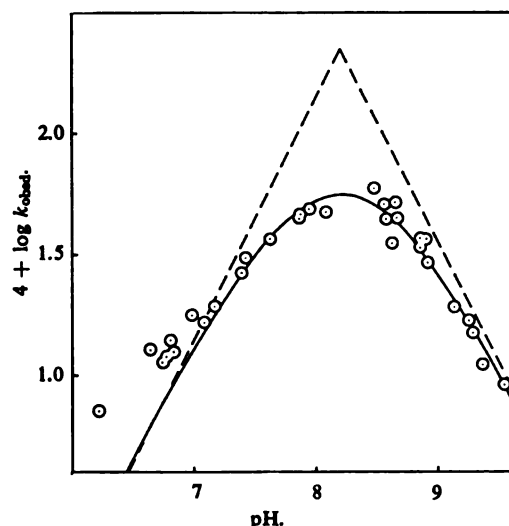


Figure 1. Second-order rate constant for decomposition of peroxyphthalic acid as a function of pH, temperature 24.6°.

Buffer Components. Analar Na_2CO_3 , NaHCO_3 , Na_2HPO_4 , and KH_2PO_4 were used. Reagent grade phosphates were found to give an enhanced decomposition rate (about 8%) compared with Analar materials. Analar 72% perchloric acid and 1 M NaOH (diluted to suitable concentrations) were used to adjust pH where necessary. EDTA, which was added to sequester trace metal cations, was recrystallized as described by Blaedel and Knight.¹¹ Laboratory distilled water was further purified, either by using a mixed-bed ion exchanger, or by two further distillations from alkaline KMnO_4 and dilute phosphoric acid, respectively. Other reagents were of Analar grade where possible.

Procedures. For the decomposition kinetic studies about 0.5 g of peroxyphthalic acid-phthalic acid mixture was weighed directly into a flask and the required volume of 1 M NaOH added to neutralize the phthalic acid and also the carboxylic acid proton of the peroxy acid. Buffer solution (50 ml) consisting of x ml of 0.33 M Na_2HPO_4 (or 0.67 M NaHCO_3) + $(60 - x)$ ml of 0.33 M KH_2PO_4 (or 0.67 M Na_2CO_3) + 0.65 ml of 0.1 M EDTA solution was added, the solid dissolved, and the solution allowed to come to thermostat temperature. Samples (5 ml) were withdrawn by pipet, quenched in 30 ml of acetate buffer (pH \approx 3) containing KI, and titrated with 0.1 N sodium thiosulfate using starch indicator.

Second-order graphs of the results were linear for at least two half-lives. Deviations at longer reaction times were observed, and the experiments at pH \leq 7 were less satisfactory because hydrolysis of the peroxy acid occurred. Two other buffers were tried out near pH 8. Tris buffer ($\text{pK} = 8.1$) was very rapidly oxidized. With $\text{NH}_4\text{-NH}_4\text{H}_2\text{PO}_4$ buffers, the reaction became first order in peroxyacid. Botvinnik¹² has reported a reaction between ammonia and peroxybenzoic acid.

The apparatus and technique used in the isotopic-labeling experiments was the same as that described previously.^{3,4}

Results

Figure 1 shows the experimental values of the second-order rate constants for the decomposition reaction at 24.6° as a function of pH. The points lie on a curve with a maximum rate constant of $5.6 \times 10^{-3} \text{ l. mole}^{-1} \text{ sec}^{-1}$ at pH 8.2. The proton bound to the peroxide group in peroxyphthalic acid has a $\text{pK} = 8.2 \pm 0.1$ at 25°.⁸ Since the dissociation of the carboxylic acid proton in peroxyphthalic acid has $\text{pK} \approx 0.5$, the decomposition reaction may be formulated, following Ball and Edwards,² as an attack of the dianion $-\text{O}_2\text{CC}_6\text{H}_4\text{CO}_3^-$ upon the monoanion $-\text{O}_2\text{CC}_6\text{H}_4\text{CO}_2\text{H}$. The curve in Figure 1 was constructed using this model and the numerical values noted above. At pH \leq 7, the experimental rate constants deviate appreciably

from the theoretical curve. In this region the decomposition and hydrolysis reactions⁸ overlap so that kinetic data for the decomposition reaction alone become much less reliable.

Table I shows the results of isotopic-labeling experiments carried out at pH 8.5 and room temperature ($\approx 20^\circ$). The composition of the hydrogen peroxide used in the preparation of labeled peroxyphthalic acid was determined by mass spectrometric analysis of the evolved oxygen from reaction with ceric ammonium sulfate in acid solution. The values quoted are the means of four experiments. Some samples were analyzed on a Consolidated-Electronics 21-103 mass spectrometer at Harvard University; the remainder on a

Table I. Isotopic Tracer Results for Peroxyphthalic Acid Decomposition

Source of oxygen	Composition of oxygen gas, mole %		
	O_2^{12}	O_2^{14}	O_2^{16}
H_2O_2	95.8 ± 0.1	0.6 ± 0.1	3.6 ± 0.1
Peroxyphthalic acid decomposition (pH 8.5 phosphate buffer)	93.6 ± 0.2	5.4 ± 0.3	1.0 ± 0.1
H_2O_2 from hydrolysis of peroxyphthalic acid	95.2	0.8	3.9

Hitachi-Perkin-Elmer mass spectrometer. The results from the two instruments were in good agreement. As a check that scrambling did not occur during synthesis of peroxyphthalic acid, a sample of the labeled peroxy acid was hydrolyzed in phthalate buffer solution at pH 4 in the presence of 10^{-2} M EDTA, and the hydrogen peroxide produced was then allowed to react with acid ceric ammonium sulfate solution. The results of the check experiment are shown in the third line of Table I. It must be concluded from the data in the second line that the amount of scrambling (indicated by per cent O_2^{14}) is extensive but not complete, and that this scrambling occurred during the process of decomposition.

Discussion

The kinetic data conform well to the pattern found for other peroxy acids and are described equally well by either mechanism I or II. The isotopic tracer results cannot be explained by either mechanism alone. If it is assumed that both mechanisms contribute to the total reaction, then a statistical analysis, in which it is assumed that peroxy acid species of all isotopic distributions will react with each other at a rate unaffected by isotopic mass, yields the result that $74 \pm 4\%$ of the product oxygen molecules derive from mechanism I. Thus, in this reaction, decomposition *via* displacement on oxygen by oxygen (I) predominates over decomposition *via* attack at the alternative carbonyl carbon electrophilic center (II). This result was expected since, in peroxyphthalic acid, we have chosen a molecule in which the latter reaction path would be disfavored. It must be concluded that the decomposition of derivatives of peroxycarboxylic acids will not generally occur exclusively by attack at carbonyl carbon. Indeed the present results reinforce the idea⁴ that peroxy acid decompositions occur by two competing pathways having identical rate laws and differing only in the conforma-

(11) W. J. Blaedel and H. T. Knight, *Anal. Chem.*, **26**, 741 (1954).

(12) M. M. Botvinnik, *J. Gen. Chem. USSR*, **16**, 863 (1946).

of the transition state. In no case so far investigated does either mechanism alone completely satisfy kinetic and isotopic tracer results.

The investigation of the decomposition of a series of substituted peroxybenzoic acids by Goodman, *et al.*⁶

present the most complete study of a group of structurally closely related acids and the data suggest the contribution of decomposition by path I may be inappreciable in this series. For this series of reactions there is no simple Hammett $\sigma\rho$ relationship between the logarithm of the rate constant and σ since substituents in the aromatic ring affect both substrate and nucleophile instead of only the substrate and also the two mechanisms should have different ρ values. Indeed it was found⁶ that the decomposition constants exceeded that for peroxybenzoic acid whether electron-releasing or -attracting groups were introduced in the benzene ring.

The convenience and the usefulness of the doubling method for study of peroxide decompositions are exemplified well by the present investigation. Some systems to which this technique is being applied

at present are the paramagnetic peroxyborates,¹³ the tetraperoxychromate ion,¹⁴ and peroxyphthalic acid.¹⁵ A combined kinetic and isotope study of the decompositions of substituted peroxybenzoic acids would give data of considerable value in understanding the factors which govern the reactivities of carbonyl carbon and peroxide oxygen to peroxyanions.

Acknowledgments. This work was supported in part by U. S. Air Force Grant AF-AFSOR-1027-66 and by the ARPA agency of the Defense Department. We thank the Leverhulme Trust Fund for a fellowship (to M. L. H.), Laporte Chemicals, Ltd., for financial assistance, the University of Newcastle upon Tyne for a leave of absence to Dr. Peter Jones, and Dr. G. O. Dudek of Harvard University for mass spectrometer facilities.

(13) K. Watters, private communication; *cf.* R. Bruce, J. O. Edwards, D. Griscom, R. A. Weeks, L. R. Darbee, W. DeKleine, and M. McCarthy, *J. Am. Chem. Soc.*, **87**, 2057 (1965).

(14) S. B. Brown, private communication; *cf.* D. Quane and J. E. Earley, *ibid.*, **87**, 3823 (1965).

(15) E. Koubek, private communication.

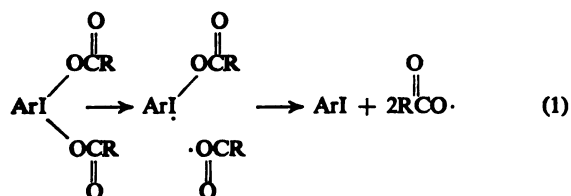
The Decomposition of Aryl Iodine Diacetates

J. E. Leffler and L. J. Story¹

Contribution from the Department of Chemistry, Florida State University, Tallahassee, Florida 32306. Received December 2, 1966

Abstract: The decomposition of aryl iodine diacetates takes place by three mechanisms: nucleophilic displacement within an ion pair to give aryl acetate and iodine acetate (the major reaction), homolysis to aryl iodide and acetoxy radicals, and induced homolysis. The intermediate iodine acetate decomposes rapidly to carbon dioxide and methyl iodide, but may be trapped completely by cyclohexene. The radical chain homolysis of phenyl iodine diacetate is enhanced by di-*t*-butyl peroxide.

The decomposition of phenyl iodine dibenzoate² in aromatic solvents gives clear indications of the presence of phenyl radicals,^{3a,b,c} and it was at one time generally presumed to consist entirely of homolysis to acetoxy radicals, in a process such as eq 1 or the corresponding single-step mechanism. However, a detailed study of the products and kinetics re-



vealed a reaction of considerable complexity.^{3a} One of the products, in 8–25% yield, is phenyl benzoate. Kinetic experiments established that the phenyl moiety of that ester comes exclusively from the aryl

iodine moiety of the dibenzoate and not at all from benzyloxy-derived phenyl radicals. This suggested that at least part of the reaction goes by way of an internal nucleophilic displacement (eq 2), closely analogous to a well-established major route for the decomposition of diaryliodonium compounds.⁴ Kinetic and other evidence indicated that the intermediate iodine benzoate interacted with additives such as benzoic anhydride or benzaldehyde to induce a radical chain decomposition of the dibenzoate, but the details of the mechanism remained conjectural. The behavior of the diacetate, as reported in the present paper, appears to be simpler and more amenable to mechanistic interpretation.

The Ion Pair Process. Table I and Figure 1 show the products and typical kinetic behavior of the decomposition of phenyl iodine diacetate in chlorobenzene under anhydrous conditions.⁵ The second yield col-

(4) See, for example, F. M. Beringer and R. A. Falk, *ibid.*, 4442 (1964).

(5) Unless otherwise noted, the solvent is chlorobenzene containing 0.1 M acetic anhydride to reactylate any diacetate that may be hydrolyzed by traces of water. Within experimental error, the presence of this amount of acetic anhydride has no effect on the decomposition rate. Although the direct reaction between traces of water and acetic anhydride in chlorobenzene at 126.8° is very slow, the indirect reaction in the presence of phenyl iodine diacetate is extremely fast. Unless

¹ Petroleum Research Foundation Predoctoral Fellow.

The Chemical Abstracts name is (dihydroxyiodo)benzene diacetate.

(a) J. E. Leffler, W. J. M. Mitchell, and B. C. Menon, *J. Org. Chem.*, **31**, 1153 (1966); (b) B. M. Lynch and K. H. Pausacker, *Austral. Chem.*, **10**, 329 (1957); (c) D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.*, 1475 (1956).

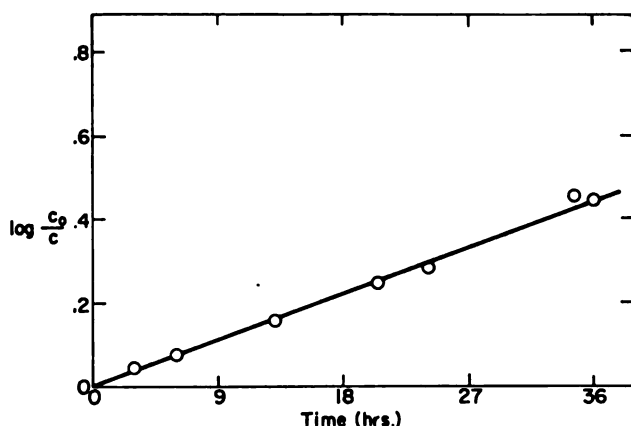


Figure 1. Typical phenyl iodine diacetate decomposition in chlorobenzene (0.1 *M* added acetic anhydride) at 126.8°. Initial concentration 0.02 *M*.

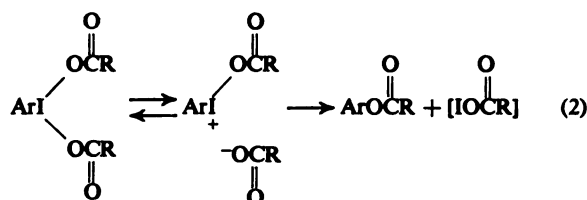
umn of Table I and the curves of Figure 2 show the effect of adding cyclohexene. The yield of methyl iodide is reduced drastically from 70 to 1% or less while the initial rate is left unchanged. The most plausible intermediate capable of giving methyl iodide in high

Table I. Products of Decomposition of Phenyl Iodine Diacetate in Chlorobenzene^a at 126.8°^b

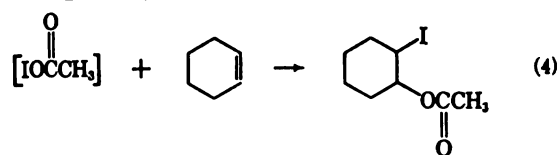
Product	Mole % per mole of diacetate	
	No cyclohexene	0.222 <i>M</i> cyclohexene
Methyl iodide	70.4	1
Iodobenzene	26.0	81.2
Phenyl acetate	74.6	20.0
Acetic acid	22.7	121.4
Chlorotoluenes ^c	10.8	2
Carbon dioxide	72.5	13.4
Methane	0	2
Benzene	0	22.3
2-Iodocyclohexyl acetate	...	≥7.7 ^d
<i>trans</i> -1,2-Diacetoxycyclohexane ^d	...	0.8

^a Containing 0.1 *M* acetic anhydride. ^b Product yields are ±3%. Results are the average of two experiments. Initial diacetate concentrations 0.0662 and 0.0732 *M* in the absence of cyclohexene, 0.0790 and 0.0765 *M* in the presence of cyclohexene. ^c 63% *ortho*, 24% *meta*, and 13% *para*. ^d 0.08 mole % of the *cis* isomer also believed to be present. See Experimental Section. ^e 2-Iodocyclohexyl acetate partly decomposes during vapor chromatography.

yield yet capable of reacting still more rapidly with cyclohexene is undoubtedly iodine acetate. The expected diversion product, 2-iodocyclohexyl acetate, is indeed isolated, although in low yield. Reactions 2 and 3 account for 70–75% of the decomposition in the absence of cyclohexene.



water is carefully excluded or removed in this way the rates are not reproducible.



Iodine acetate has never been isolated, but has been postulated as an intermediate in the Hunsdiecker and Simonini reactions, the reaction of lead tetraacetate, iodine, and carboxylic acids,^{6,7} the reaction of iodine and peracetic acid with cyclohexene⁸ or with aromatic compounds,⁹ in the decomposition of iodine triacetate,¹⁰ and the decomposition of acetyl peroxide in chlorobenzene in the presence of iodine.¹¹

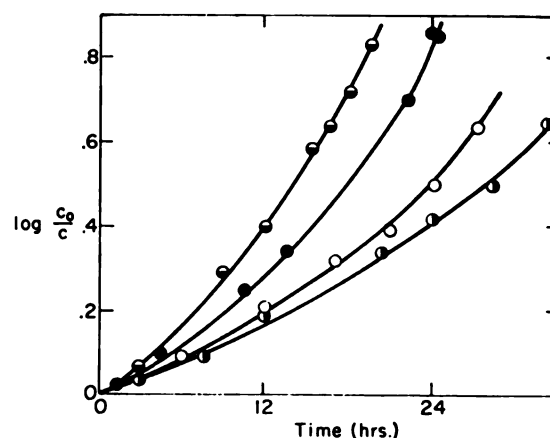


Figure 2. Effect of varying cyclohexene concentration on the rate of decomposition of 0.034 *M* phenyl iodine diacetate in chlorobenzene at 126.8°: ●, 0.181 *M* cyclohexene; ●, 0.0678 *M*; ○, 0.0271 *M*; ○, 0.013 *M*.

The decomposition of phenyl iodine diacetate in the presence of cyclohexene is complicated in its later stages by a secondary reaction between phenyl iodine diacetate and 2-iodocyclohexyl acetate. This reaction accelerates the decomposition of the diacetate as 2-iodocyclohexyl acetate accumulates in the latter part of each run, and increases the yield of iodobenzene and acetic acid at the expense of phenyl acetate. Experiments in which 2-iodocyclohexyl acetate was added initially gave a very fast decomposition of the phenyl iodine diacetate from the beginning of the reaction. These rates were not readily reproducible, however, and in view of the instability of 2-iodocyclohexyl acetate and the difficulty in obtaining pure samples of known stereochemical composition the reaction was not investigated further. Judging from the yield data in Table I, the accelerated part of the decomposition in the presence of cyclohexene gives iodobenzene, acetic acid, and benzene as the major products. Since

(6) D. H. R. Barton, H. P. Faro, E. P. Serebrayakov, and N. F. Woolsey, *J. Chem. Soc.*, 2438 (1965).

(7) G. B. Bachman and J. W. Wittman, *J. Org. Chem.*, **28**, 65 (1963).

(8) Y. Ogata, K. Aoki, and Y. Furuya, *Chem. Ind. (London)*, 304 (1965).

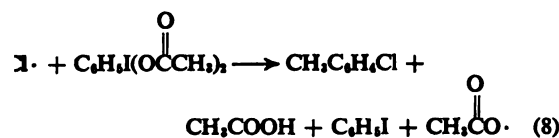
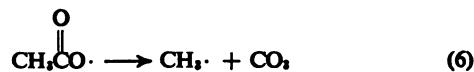
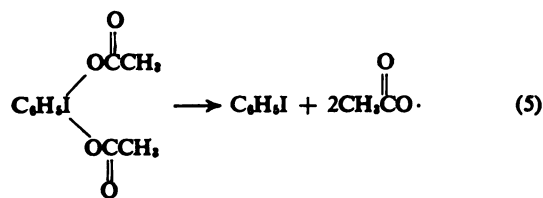
(9) Y. Ogata and K. Nakajima, *Tetrahedron*, **20**, 2751 (1964).

(10) J. W. H. Oldham and A. R. Ubbelohde, *J. Chem. Soc.*, 368 (1941).

(11) G. S. Hammond and G. Moses, private communication.

nal phenyl groups are otherwise accounted for, mole % of benzene probably comes from the ene. A direct chain transfer between acetoxy and cyclohexene to give radicals responsible induced decomposition of the phenyl iodine is unlikely in view of the slowness of the initial position. A similar chain transfer between radicals and 2-iodocyclohexyl acetate, however, the delayed acceleration produced by added ene, the immediate acceleration produced by iodocyclohexyl acetate, and also the formation ene and acetic acid. We envisage a process the attacking radical, derived from 2-iodocyclohexyl acetate, supplies a hydrogen atom and the decomposition of the phenyl iodine into a molecule of acetic acid, a molecule of ene, and a new chain-carrying acetoxy radical. hydrogenated radical could then react further to ene by disproportionation, elimination, or donation of hydrogen to phenyl iodine or to acetoxy radicals.

Free-Radical Reaction. The other products in Table I, phenyl iodide, isomeric chloro-, and acetic acid, could be assigned to homolytic cleavages such as eq 5-8. The presence of free

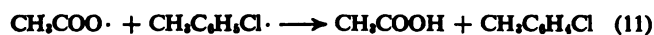
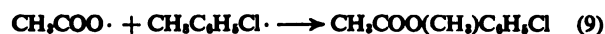


is indicated by the initiation of acrylonitrile polymerization, the presence of methyl radicals in it by the chlorotoluene isomer ratios which are close to those observed when di-*t*-butyl peroxide¹² or ethylmercuric iodide¹³ is used as the radical

source. The homolysis of phenyl iodine diacetate to give two acetoxy radicals (eq 5) is superficially like the first step in the homolysis of acetyl peroxide,¹⁴ but the higher temperature required and the greater initial distance between the acetoxy radicals should greatly reduce the rate of geminate recombination. The total absence of ethane and methyl acetate is, therefore, in no way remarkable and does not necessarily mean that the acetoxy radicals are formed in separate steps.

Radical-Induced Decomposition. The substantial amount of acetic acid formed in the decomposition of phenyl iodine diacetate is very unlikely to come from

reaction of acetoxy radicals with the solvent. In the decomposition of acetyl peroxide in isooctane, no more than 1% of the acetoxy radicals react in that way.^{14d} Alternative explanations for the acetic acid are induced decomposition *via* eq 8,¹⁵ eq 9-10, or eq 11. Induced



decomposition according to the sequence 5-8 with either eq 9-10 or 11 as the chain-breaking steps would give a first-order and kinetically undetectable contribution to the rate law. The first-order rate constants in Table II do not appear to be very sensitive to the initial concentration of phenyl iodine diacetate, but since the total participation of homolytic processes is only 25%, a small contribution from reactions of other than first order could easily escape detection.

Table II. Effect of Initial Concentration of Phenyl Iodine Diacetate on Rate in Chlorobenzene^a at 126.8°

$10^3 \times$ C_0, M	$10^3 \times$ k, sec^{-1}	$10^3 \times$ C_0, M	$10^3 \times$ k, sec^{-1}
3.05	7.16	25.76	7.46
7.39	7.38	36.44	6.67
16.72	7.70	45.31	6.61
20.96	7.68	23.02	7.57 ^b

^a With 0.1 *M* acetic anhydride. With less acetic anhydride the rates are not reproducible unless elaborate precautions are taken to ensure dryness. Runs in ordinary solvent without added anhydride start with a very high rate constant, decreasing later in the run to that obtained in the presence of anhydride. The initial fast reaction is also suppressed by added acetic acid. The rate constant is the same as that for the reaction in the presence of acetic anhydride.

^b With 0.2 *M* acetic anhydride.

The potential chain inhibitors, trinitrobenzene and iodine, appeared to accelerate the decomposition slightly,¹⁶ though only by 15% or less. Styrene, like cyclohexene, caused an increased rate late in the run but had no effect on the initial rate. Diethyl ether (0.14 *M*) had no effect. On the other hand the addition of di-*t*-butyl peroxide as an independent source of methyl radicals gave a pronounced acceleration (Figure 3).

Benzoic anhydride in chlorobenzene causes an accelerated first-order decomposition of phenyl iodine diacetate after a short delay during which the reaction apparently proceeds at about its normal rate (Figure 4). This behavior is very much like the effect of benzoic anhydride on the decomposition of phenyl iodine dibenzoate^{3a} except that the final value of the rate constant is $19.0 \times 10^{-6} \text{ sec}^{-1}$ instead of the $61 \times 10^{-6} \text{ sec}^{-1}$ obtained in the case of the dibenzoate. In the latter investigation it was demonstrated that benzoic anhydride trapped some intermediate quantitatively, eventually producing a critical concentration of a chain-transfer agent responsible for the accelerated reaction. A possible explanation for the acceleration of the decomposition of the diacetate by benzoic anhydride is

(15) A similar explanation has been suggested by Lorand for the formation of acetic acid (23 mole %) in the decomposition of *t*-butyl peracetate in chlorobenzene at 140°: J. P. Lorand, Dissertation, Harvard University, 1964.

(16) Aromatic nitro compounds accelerate the decomposition of benzoyl peroxide: B. B. Gill and G. H. Williams, *J. Chem. Soc., Phys. Org.*, 880 (1966).

R. Cowley, R. O. C. Norman, and W. A. Waters, *J. Chem. Soc.*, 1959.

F. Williams and G. E. Corbett, *Proc. Chem. Soc.*, 240 (1961); *ibid.*, 3437 (1964).

J. W. Taylor and J. C. Martin, *J. Am. Chem. Soc.*, 88, 3650 (1966).

J. L. Herk, M. Feld, and M. Szwarc, *ibid.*, 83, 2998 (1961);

Loenig and W. D. Brewer, *Tetrahedron Letters*, 2773 (1965);

γ and M. Szwarc, *J. Am. Chem. Soc.*, 76, 5981 (1954).

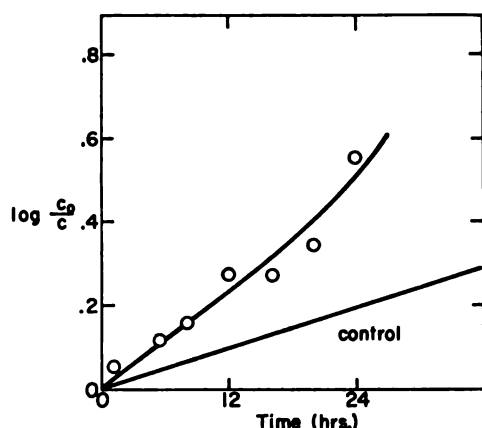


Figure 3. Effect of added di-*t*-butyl peroxide ($3.55 \times 10^{-3} M$) on the rate of decomposition of phenyl iodine diacetate ($21.9 \times 10^{-3} M$) in chlorobenzene at 126.8° .

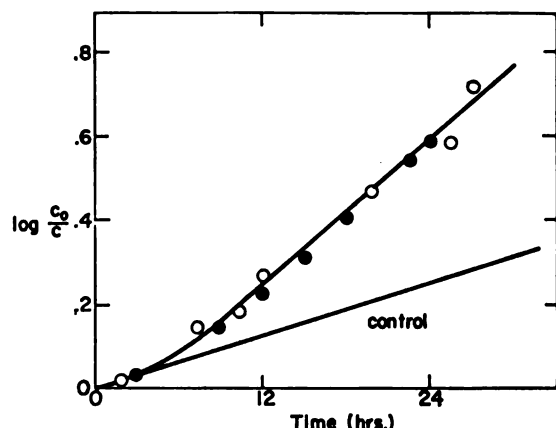


Figure 4. Effect of added benzoic anhydride on the rate of decomposition of phenyl iodine diacetate at 126.8° : ●, C_0 0.0241 *M*, benzoic anhydride 0.050 *M*, ordinary solvent; ○, C_0 0.0216 *M*, benzoic anhydride 0.070 *M*, very carefully dried solvent.

again the trapping of some intermediate, presumably iodine acetate, with the formation of a slightly different chain-transfer agent. However, exchange of acetate and benzoate groups cannot be ruled out.¹⁷

Another probable instance of induced decomposition is the rapid reaction at room temperature between the diacetate and cyclohexene in undegassed chlorobenzene solutions. This reaction takes place with or without acetic anhydride, and loss of oxidizing titer is complete within 48 hr. Phenyl acetate is no longer detectable, and the major products are acetic acid, iodobenzene (100%), 2-cyclohexen-1-one (42% based on the phenyl iodine diacetate), 2-cyclohexen-1-ol (16%), and cyclohexene oxide (3.6%).¹⁸

Substituent Effects. Table III shows the effects of *meta* and *para* substituents on the rate of decomposition of phenyl iodine diacetate at two temperatures. Log *k* is correlated with σ , the ρ value being about 0.8 at 126.8° ,

(17) A reverse experiment by W. J. Mitchell (this laboratory) in which a 0.005 *M* solution of phenyl iodine dibenzoate was decomposed in the presence of 0.01 *M* acetic anhydride in chlorobenzene at 126.8° gave an initial fast reaction consuming about 10% of the oxidizing titer, then a first-order rate constant of $13 \times 10^{-4} \text{ sec}^{-1}$. The reaction was followed to 50% completion, well past the usual time for acceleration in an ordinary run using phenyl iodine dibenzoate in the presence of 0.01 *M* benzoic anhydride.

(18) These yields are from an experiment with 0.125 *M* phenyl iodine diacetate and 4.88 *M* cyclohexene in benzene as solvent to facilitate separation of the cyclohexene oxide.

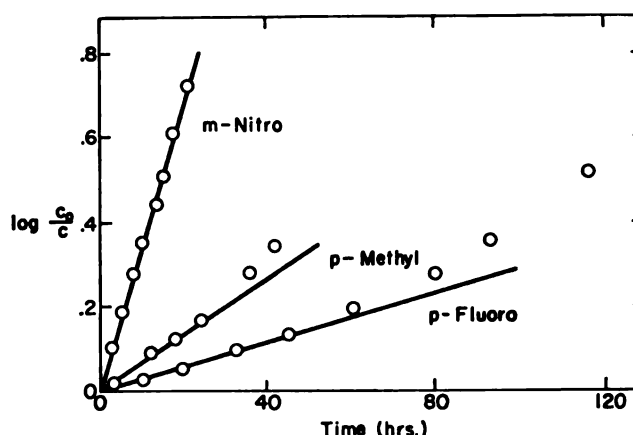


Figure 5. Decomposition of three aryl iodine diacetates illustrating curvature of first-order rate plots when electron-releasing substituents are present.

but even this rather rough correlation requires the exclusion of *para* substituents capable of strong resonance interactions, whether electron donating or electron withdrawing. Neglecting the contribution from the homolytic part of the reaction for the moment, the observed first-order rate constants should be functions of k_1 and k_{-1} , rate constants for the ionization and recombination steps of eq 1, and k_2 , the rate constant

Table III. Rate Constants^a for the Decomposition of Substituted Phenyl Iodine Diacetates in Chlorobenzene^{b,c}

Substituent	$10^4 \times k, \text{ sec}^{-1}$	
	126.8°	150.1°
<i>p</i> -Methoxy	1.59	13.6
<i>p</i> -Fluoro	1.78	
<i>p</i> -Methyl	4.20	30.5
<i>p</i> -Phenyl	4.35	52.5
Hydrogen ^d	7.24 ^d	60.9
<i>m</i> -Chloro	10.5	106
<i>p</i> -Chloro	6.19	49.5
<i>m</i> -Nitro	21.1	201
<i>p</i> -Carbomethoxy	42.3	389

^a In view of the complexity of the reaction, the activation parameters are of no theoretical significance. ^b The solvent contained acetic anhydride, 0.1 *M*. ^c Initial concentrations were usually in the range 0.02–0.03 *M*. ^d Mean of seven runs in Table II.

for the nucleophilic displacement step. Since the iodine–oxygen bonds in the diacetate are already quite

$$k_{\text{obsd}} = k_1 k_2 / (k_2 + k_{-1}) \quad (12)$$

polar, only a small negative value of ρ is expected for the ionization equilibrium. The net effect should be dominated by the positive ρ of the nucleophilic displacement.¹⁹ A further source of complexity in the substituent effects is variation in the relative rate of the homolytic part of the reaction. As can be seen in Figure 5, runs in which the substituent is electron releasing show a distinct increase in first-order rate constant in the latter part of the reaction.²⁰ The electron-releasing substituents may not decelerate the homolytic reaction,

(19) A different relative importance of inductive and resonance effects in the two steps would seriously perturb any simple free-energy relationship involving k_{obsd} : J. E. Leffler and E. Grunwald "Rates and Equilibria of Organic Reactions," Interscience Publishers, Inc., New York, N. Y., 1963.

(20) In such cases the tabulated rate constants are initial values.

particularly the induced part, to the same extent as the ion-pair reaction. If the homolytic reaction gives rise to any cyclohexadienes,²¹ their reaction with iodine acetate should give an efficient chain-transfer agent comparable to 2-iodocyclohexyl acetate. Whatever the explanation for the autocatalysis, the products from the *p*-fluoro derivative clearly indicate a decreased relative rate for the ion-pair part of the reaction. The yields per mole of diacetate were as follows: methyl iodide, 37.4%; acetic acid, 27.6%; *p*-fluoroiodobenzene, 54.1%; and *p*-fluorophenyl acetate, 48.0%.

Experimental Section

Chlorobenzene was stirred with three portions of sulfuric acid and washed with water and sodium bicarbonate solution. After successive 24-hr periods of drying with CaCl_2 , anhydrous CaSO_4 , and P_2O_5 , it was distilled from P_2O_5 through a 35-in. column packed with 0.25-in. glass helices. A middle fraction, bp 131.1–132.1°, was collected.

Acetic anhydride was distilled through the glass helices column. After a large forerun, a middle fraction, bp 139.0°, was collected.

Cyclohexene (bp 83.1–83.5°) was refluxed over Na in a nitrogen atmosphere. Samples were taken off as needed by distillation through a 1-ft glass helices column. Cyclohexene exposed to the air for 2 days gave a positive peroxide test.

Benzoic anhydride (mp 40.0–41.5°) was twice recrystallized from benzene and petroleum ether (bp 60–70°). It was shown by infrared spectroscopy to be free from benzoic acid.

Aryl Iodine Diacetates. The substituted phenyl iodine diacetates were prepared by a procedure like that given for *m*-chlorophenyl iodine diacetate (see Table IV for melting point data).

Table IV

Subst	Mp, °C	Subst	Mp, °C
<i>p</i> -F ^{a,b}	177.0–179.8 ^d	<i>m</i> -NO ₂ ^{f,g}	151.0–154.2 ^d
<i>p</i> -COOCH ₃ ^{a,c}	150.0–153.3 ^d	<i>p</i> -C ₆ H ₅ ^h	141.0–144.1
<i>o</i> -OCH ₃ ^a	146.9–150.1	<i>p</i> -Cl ^{d,i}	109.8–113.2 ^d
<i>p</i> -CH ₃ ^{d,e}	106–110 ^d	<i>m</i> -Cl ^{f,i}	153.1–154.7 ^d
<i>p</i> -CH ₃ O ^f	92.4–96.0	H ^h	161.1–162.2 ^d

^a This paper. ^b Oxidizing titer 99 and 99.5% of theoretical. The bis(trideuterioacetate) melts at 183.7–185.8°. It exchanges carboxylate groups rapidly with acetic acid solvent. ^c Oxidizing titer 102 and 102% of theoretical. ^d K. H. Pausacker, *J. Chem. Soc.*, 107 (1953). ^e Lit.⁴ gives 107°. ^f C. H. C. Willgerodt, "Die Organischen Verbindungen mit Mehrwertigem Jod," F. Enke, Stuttgart, 1914. ^g Lit.⁷ gives 155°. ^h Lit.⁷ gives 140°. J. G. Sharefkin and H. Saltzman, *Anal. Chem.*, 35, 1428 (1963). ⁱ Lit.⁴ gives 104°. ^j Lit.⁷ gives 155°. ^k Lit. gives 158°. I. Lillien, *J. Chem. Soc.*, 4498 (1962).

***m*-Chlorophenyl Iodine Diacetate.** To 23.8 g (0.1 mole) of *m*-chloroiodobenzene was added dropwise with stirring 31 ml (0.24 mole) of 40% peracetic acid. The flask was chilled with an ice-water bath during the slow addition (1 hr). Two phases separated, but on continued stirring the solution became homogeneous. The solution was stirred for an additional hour at 20–25° and then cooled in an ice-salt bath. The white crystals which formed were washed quickly with ice-cold water. (Warm water may cause hydrolysis of the diacetate to the aryl iodine oxide, particularly in the case of the *p*-methoxy-substituted compound.) The crystals were pressed dry and dried overnight *in vacuo* over P_2O_5 . (The use of CaCl_2 instead of P_2O_5 caused the crystals to turn yellow.) Recrystallization was effected from a minimum amount (1.5 ml/g) of 1:4 acetic anhydride–acetic acid, yield, 22.5 g (63%); mp 154.5–156.5° (lit.²² 154°). Pure dry benzene (10 ml/g) could also be used for the recrystallization.

Kinetic Procedure. At no time was the purity of the aryl iodine esters used in the kinetic runs less than 98.5%. Standard solutions

in chlorobenzene were checked by iodometric titration before a run was started.

Kinetic runs were made in 18 × 150 mm test tubes fitted with a standard taper, ground glass joint. The tubes were cleaned with hot chromic acid cleaning solution and rinsed repeatedly with water, dilute ammonium hydroxide, water, and distilled water. The tubes were oven dried and a constriction was added for sealing. Before use, the tubes were fitted to a vacuum system and leak tested with a Tesla coil.

The tubes were flushed with prepurified²³ nitrogen, and aliquots of the diacetate solution were added to each tube from a calibrated pipet. Each tube was then attached to the vacuum system and put through a four-cycle freeze–degas–thaw procedure. The final pressure in the vacuum system was less than 0.005 mm. The tubes were sealed and removed for use or storage at 5°. Kinetic runs using tubes degassed fewer than three times were usually not reproducible.

For the experiments with "carefully dried solvent" aliquots of diacetate solutions were pipetted into standard constricted tubes. These tubes and unconstricted tubes containing phosphorus pentoxide were attached to the vacuum line. The chlorobenzene was degassed three times, distilled into the phosphorus pentoxide tube, allowed to stand for 1 hr at room temperature, and redistilled into the original tube. After one more degassing cycle, the tube was sealed. For experiments with cyclohexene, the constricted tubes were fitted with a rubber serum cap and the cyclohexene was injected with a syringe just before the last degassing cycle.

Normally, eight tubes were used in each kinetic run. Since the half-life for the decomposition of phenyl iodine diacetate at 126.8° in chlorobenzene is about 24 hr, the warm-up period for the tubes is insignificant and the zero point was determined from an aliquot of the prepared solution. This also provided a constant check on diacetate purity.

For short runs (ca. 6 hr or less), all tubes were placed in the bath and the zero-point tube was removed when the temperature of the bath returned to equilibrium. An accurate account of the temperature was kept by a thermistor–Wheatstone bridge–recorder arrangement.²⁴ During the shorter runs, tubes were quenched in ice water.

For analysis the contents of the tubes were decanted and rinsed out with two 1-ml portions of pure chlorobenzene. The concentration of diacetate was determined by iodometric titration:²⁵ (1) add 10 ml of fresh acetic acid (acetic acid left exposed to the air gives high blank values), (2) add pellets of carbon dioxide to the flask and at the same time to 25 ml of distilled water, (3) prepare a fresh solution of saturated potassium iodide and add 3 ml to the flask, (4) swirl the flask and add the deaerated water, (5) titrate immediately to a starch–iodine end point with approximately 0.015 to 0.10 *N* sodium thiosulfate using a magnetic stirrer for mixing. This titration occurs in a two-phase system; however, excellent results have been obtained with both benzene and chlorobenzene solutions of the diacetate. The use of acetic acid as a solvent for iodometric titrations has been criticized²⁶ but titrations of benzene solutions of freshly recrystallized benzoyl peroxide showed purities greater than 99%.

Product Analysis. Phenyl iodine diacetate was weighed into a modified Pyrex hydrogenation bomb (A) and the constriction rinsed clean with a few milliliters of chlorobenzene. Approximately 300 ml of purified chlorobenzene was added to a second bomb (B) along with several grams of phosphorus pentoxide and a magnetic stirring bar. The entire apparatus was attached to a vacuum system and bomb B was degassed using a three-cycle freeze–degas–thaw procedure. The solution was stirred for 1 hr at room temperature at the end of the third cycle. Bomb A was then cooled with liquid nitrogen and the chlorobenzene in bomb B allowed to distil into bomb A. Stirring was continued to prevent bumping. After all the liquid had been distilled, the system was degassed twice more and the constriction sealed with a flame. The bomb was then placed in the thermostated bath.

After about ten half-lives, the bombs were removed, cooled, wiped clean, and attached to the vacuum system. After the system was evacuated, the capillary tip was broken, and the gases were allowed to distil into the liquid nitrogen trap. The bomb was re-

(23) Minimum purity: 99.997%; dew point: –85°F, contains 8 ppm oxygen.

(24) This apparatus was designed and built by Mr. Vern Champeaux.

(21) See, for example, the decomposition of benzoyl peroxide in aromatic solvents: D. F. DeTar and R. A. J. Long, *J. Am. Chem. Soc.*, 80, 4742 (1958).

(22) A. R. Fox and K. H. Pausacker, *J. Chem. Soc.*, 295 (1957).

(25) J. P. Wibaut, H. B. vanLeeuwen, and B. van der Waal, *Rec. Trav. Chim.*, 73, 1033 (1954).

(26) R. D. Mair and A. J. Graupner, *Anal. Chem.*, 36, 194 (1964).

frozen with Dry Ice-isopropyl alcohol and the pressure of the non-condensable gases recorded. The liquid nitrogen bath was removed and the total gas pressure recorded.

The gases were thoroughly mixed using a Toepler pump and then forced by external pressure into a gas sampler fitted with a rubber serum cap. A gas-tight Hamilton syringe was used to transfer the gas mixture to a F & M Model 700 gas chromatograph with a thermal conductivity detector.²⁷ Air, methane, ethane, and carbon dioxide are easily resolvable and a check was made of their separation before an unknown was measured.

After the sample had been removed, the system was evacuated and the bomb degassed a second time. The pressure was measured and added to the first pressure reading. The system was reevacuated and the total volume calculated by admitting a known volume of gas at atmospheric pressure and observing the final pressure.

The Dry Ice-isopropyl alcohol trap was rinsed with chlorobenzene and the washings were added to the main solution. For qualitative identification the solution was distilled and three fractions were collected; a 5-ml forerun, bp 25–130°; ca. 300 ml of chlorobenzene, bp 130°; and a high boiling residue (ca. 20 ml). Each of the fractions was subjected to gas chromatography (10 ft × 0.25 in. SF-96 silicone oil, 7 ft × 0.25 in. DEGS,²⁸ 7 ft × 0.25 in. PPE,²⁹ and 7 ft × 0.25 in. FFAP³⁰ columns). Peaks were collected

(27) Conditions: 12 ft × 0.25 in. copper column; 30–60 mesh silica gel; oven, 70–90°; detector, 80°; injector, 52°; helium, 37 cc/min; sample, approximately 30 μ l.

(28) Diethylene glycol succinate.

(29) Polyphenyl ether.

(30) A specially modified Carbowax obtained from Wilkins Instrument and Research Corp., Walnut Creek, Calif.

and identified by comparing their infrared and nmr spectra and gas retention times with those of authentic samples.

Quantitative measurements were performed using standard solutions of known compounds. Each peak was bracketed by injecting enough of the standard solutions so that both a smaller and a larger peak than that of the unknown compound was obtained. Analyses were made using the same chromatographic conditions. All analyses were made in duplicate.

No low-boiling compounds other than methyl iodide were observed. Methyl acetate was found to be completely resolved from methyl iodide at 35° using a 7 ft × 0.25 in. DEGS column; it was not present in the product mixture.

No high-boiling compounds other than those mentioned were detected. Biphenyl, phenol, *o*- and *m*-iodochlorobenzene, *o*-iodophenyl benzoate, *p*-chlorobenzyl acetate, and *p*-chlorophenyl acetate were shown to be absent (or if present, in less than 1% yield) by control experiments.

Determination of Chlorotoluene Isomer Ratios. The chlorotoluene isomer ratios were determined by gas chromatography, using the liquid crystal technique recently developed by Dewar and Schroeder³¹ and an F & M Model 700 flame ionization chromatograph at 125°. Peak height-to-composition conversion factors were determined experimentally for each isomer.

Acknowledgments. We are happy to acknowledge support of this research by the Petroleum Research Foundation and by the National Science Foundation.

(31) M. J. S. Dewar and J. P. Schroeder, *J. Am. Chem. Soc.*, **86**, 5235 (1964).

Decarbonylation of Aromatic Carbonyl Compounds Catalyzed by Rhodium Complexes

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Abstract: The catalytic decarbonylation of aroyl chlorides, bromides, and cyanides with chlorotris(triphenylphosphine)rhodium(I) has been investigated; particular attention has been paid to polycyclic aroyl halides. A theory of the mechanism of decarbonylation has been suggested which accounts for the observations made in this study. The essential features of the theory are the formation of V, its isomerization to VI, and the loss of carbon monoxide from the latter. Several new rhodium complexes are described.

A previous communication from this laboratory² reported that chlorotris(triphenylphosphine)rhodium(I) catalyzes the decarbonylation of aroyl chlorides to the corresponding aryl chlorides. Almost simultaneously, Tsuji and Ohno observed that aliphatic acyl chlorides are converted, under the same conditions, into olefins.³ In both cases, the analogous response of acyl bromides was briefly mentioned.^{3,4}

The Japanese authors suggested a mechanism for these decarbonylation reactions. This mechanism will have to be somewhat modified in view of the more extensive studies reported in the present paper.

In Table I, the results obtained with a number of benzoyl chlorides are summarized. This table also

contains some examples for the decarbonylation of benzoyl and naphthoyl bromides. The last two examples in this table indicate that carbon monoxide can be extruded also from benzylic carbonyl chlorides without difficulty.^{2,3} It is obvious from these data that the reaction is practically unaffected by electronic or steric influences of substituents; the seemingly accelerating effect of the α -naphthoyl residue (compare benzoyl and α -naphthoyl bromide) is most probably due to the higher temperature at which the reaction with α -naphthoyl bromide is carried out.

The behavior of the three isomeric phthaloyl chlorides deserves some comment. *o*-Phthaloyl chloride does not react at all, possibly because it has the structure of α,α -dichlorophthalide.⁵ The other two isomers decompose in two distinct steps, *via* the chlorobenzoyl chlorides, into the dichlorobenzenes. This is in

(1) To whom inquiries should be addressed at the Department of Organic Chemistry, Hebrew University, Jerusalem.

(2) J. Blum, *Tetrahedron Letters*, 1605 (1966).

(3) J. Tsuji and K. Ohno, *ibid.*, 4713 (1966).

(4) Cf. J. Blum, *ibid.*, 3041 (1966).

(5) F. B. Garner and S. Sugden, *J. Chem. Soc.*, 2877 (1927).

Table I. Decarbonylation of Aromatic Acid Chlorides and Bromides ("Distillation Technique")

Acid halide	Reaction time, hr	Yield of pure aryl halide, %	Acid halide	Reaction time, hr	Yield of pure aryl halide, %
$C_6H_5COBr^a$	6	80	$4-(CH_3CONH)C_6H_4COCl$	0.25	Low
$3-CH_3C_6H_4COCl^b$	20	74	$1,2-C_6H_4(COCl)_2$	10	0
$4-C_6H_4C_6H_4COCl$	15	82	$1,3-C_6H_4(COCl)_2^d$	3.5	78 + 17
$4-CH_3OC_6H_4COCl$	10	50	$1,4-C_6H_4(COCl)_2^d$	4.5	79 + 5
$4-C_6H_4OC_6H_4COCl$	5	59	$3,4-Cl_2C_6H_3COCl^e$	5	76
$3-BrC_6H_4COBr$	2	85	$2,4,6-(CH_3)_3C_6H_2COCl$	2	55
$4-BrC_6H_4COBr$	0.25	95	$\alpha-C_{10}H_7COBr^a$	0.5	84
$4-NCC_6H_4COCl^a$	4	90	$C_6H_5CH_2COCl^{a,b}$	0.25	97
$4-O_2NC_6H_4COCl^c$	8.5	79	$(C_6H_5)_2CHCOCl$	0.25	94

^a Compare ref 3. ^b Under nitrogen. ^c A 25-cm-long Vigreux column was used. ^d The first yield figure corresponds to the chlorobenzoyl chloride, the second to the dichlorobenzene. ^e The acid bromide was prepared by refluxing α -naphthoic acid with twice its weight of phosphorus tribromide for 30 min; bp 195–196° (30 mm). This method is superior to that of Yu. A. Ol'dekop and A. M. Kalinina, *Zh. Obshch. Khim.*, **34**, 3473 (1964).

Table II. Decarbonylation of Polycyclic Aroyl Halides (without distillation)

Aroyl halide ^a	Reaction temp, °C	Yield of ArX, %	Aroyl halide ^a	Reaction temp, °C	Yield of ArX, %
Acenaphthene-5-COCl	300	81	Phenanthrene-9-COBr	300	95
Fluorene-2-COCl	280	60	Fluoranthene-3-COCl	235	84
Anthracene-2-COCl	310	81	Chrysene-6-COCl	280	48
Anthracene-9-COCl	310	24 ^b	Pyrene-1-COCl	250	94
Phenanthrene-2-COCl	235	95	Pyrene-1-COBr	290	89
Phenanthrene-9-COCl	260	60	Benzo[c]phenanthrene-6-COCl	260	89

^a "Ring Index" numbering. ^b And 30% of ketone X.

marked contrast to the behavior of the benzenedisulfonyl chlorides.⁴

The very low yields obtained with *p*-acetamidobenzoyl chloride are due to the very pronounced instability of the aroyl halide at the required elevated temperature.

In the decarbonylation of relatively low-boiling aroyl chlorides it has proven essential to distil off the aryl chloride as it is formed; otherwise the reaction comes to a standstill after a given period, which varies from compound to compound. As examples, *o*-, *m*-, and *p*-chlorobenzoyl chlorides, heated with a small amount (100 mg/9.9 g) of I at 217°, cease to react after 300, 40, and 10 min, respectively (the yield of the three dichlorobenzenes after these periods was 8.0, 15.3, and 1.7%, respectively). Here an influence of the distance of the carbonyl group from the substituent appears to exist. Following the theoretical concept outlined below, we assume that a rhodium complex is formed which does not participate in the decarbonylation reaction. Whatever the structure of the complex is, it must be assumed that it is stable in the presence of aroyl halides.

The "distillation technique" is not applicable to the preparation of the otherwise difficultly obtainable halogenated polycyclics in which we were particularly interested in connection with other projects of this laboratory. This is due to the relative instability of the polycyclic acid halides at elevated temperatures and the difficulty in obtaining these halides free from impurities, e.g., hydrogen halide. We shall return to this point later on; here it may be said that an easy technique has been developed for the polycyclic acyl halides. They are heated at about 260° for 1–3 min in the presence of I, and the product is purified by chromatography on alumina. The results are summarized in Table II, from which it can be seen that this technique gives, e.g., for 1-pyrenoyl chloride a yield of 94%, while the

"distillation technique" at 230° (8–10 min) gave only 40% of 1-chloropyrene.

Table III shows some experiments with aroyl cyanides which are also decarbonylated by heating with I, yielding the nitriles of aromatic acids. This is perhaps not surprising in view of the "pseudo-halogen" character of the cyano group. Table III contains, for comparison, also two examples for the decarbonylation of aldehydes. The stoichiometric decarbonylation of aldehydes by the reaction with I has, of course, been known before.⁶

Table III. Decarbonylation of Aroyl Cyanides and Aldehydes

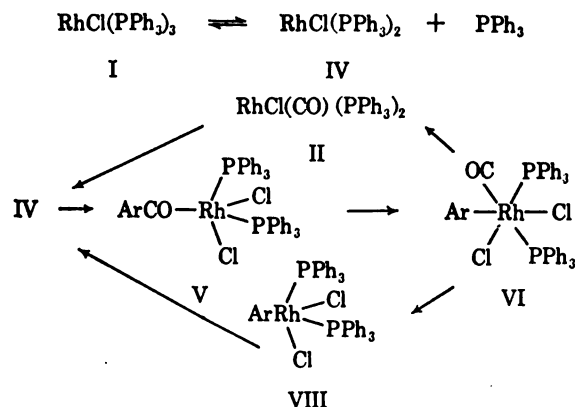
Aromatic carbonyl compd	Reaction time, hr	% Yield of nitrile or hydrocarbon
C_6H_5COCN	^a	^a
$4-ClC_6H_4COCN$	3.5	95
$\alpha-C_{10}H_7COCN$	1	87
$\alpha-C_{10}H_7CHO$	2	88
$\beta-C_{10}H_7CHO$	2.5	77

^a Very slow decarbonylation. After 7 hr, 8% of benzonitrile and 91% of unchanged starting material were obtained.

Tsuji and Ohno³ have assumed that the essential intermediate in the decarbonylation reaction is chlorocarbonylbis(triphenylphosphine)rhodium(II). As we shall show, this complex has a part in the scheme of the reaction, but it cannot always be an essential intermediate; it is often much less reactive as a decarbonylation catalyst than I. α -Naphthoyl chloride is converted at 290° into α -chloronaphthalene by II in 30, and by I

(6) J. Tsuji and K. Ohno, *Tetrahedron Letters*, 3969 (1965).

in 7 min. Furthermore, one would have to assume that II is converted, at least initially, into a complex of type III; however, we have not been able to isolate such a complex or even detect its temporary appearance by its characteristic infrared spectrum.



We propose that compound I is first converted into the dimeric tricoordinate complex IV described by Bennett and Longstaff.⁷ This complex reacts with the aroyl chloride to give V, which isomerizes to VI. The next step is normally the loss of carbon monoxide, leading to VII, followed by the elimination of aryl chloride. Thus IV is regenerated and the catalytic activity of IV (and, therefore, I) is explained. As a side reaction, the steps of the decomposition of VI can be reversed: elimination of the aryl chloride leads to II and subsequent liberation of carbon monoxide back to IV. This would be the mechanism proposed by Tsuji and Ohno³ and, as already pointed out, cannot be the major component of the scheme.

In no case have we been able to isolate and identify all the intermediary stages demanded by the proposed reaction mechanism. It seems, however, supported by the observations described in the following paragraphs. When some of the substituted benzoyl chlorides, e.g., *p*-chlorobenzoyl chloride, were heated very briefly with I, yellow rhodium complexes were obtained (not isolated in analytical purity) which did not show any carbonyl absorption in the infrared and are, very likely, of type VII. Benzoyl, *m*-toluoyl, and *m*-chlorobenzoyl chloride as well as *p*-bromobenzoyl bromide gave at 80 and at 200° the same type of complex, which showed no absorption characteristic of an aroyl group, but metal carbonyl peaks (in Nujol) at 2068, 2058, 2070, and 2055 cm⁻¹, respectively, indicating that the complexes are of formula VI. In analogous cases^{4,8} such carbonyl peaks have been observed at 2080 and 2072 cm⁻¹. On the other hand, α -naphthoyl chloride forms, even at 250°, a complex (or rather a mixture of two isomeric complexes) which shows carbonyl absorption at 1670 and 1685 cm⁻¹, α -naphthoyl bromide gives a complex with a peak at 1675 cm⁻¹, and *o*-chlorobenzoyl chloride, a rather unstable complex with carbonyl bands at 1675 and 1715 cm⁻¹. These complexes represent examples for type V.

In one case—using β -naphthoyl chloride in boiling benzene—we have followed the transition from an iso-

meric mixture of pentacoordinate complexes of type V (aryl carbonyl absorptions at 1665 and 1680 cm⁻¹) to VI (Ar = β -C₁₀H₇), showing a characteristic metal carbonyl band at 2062 cm⁻¹.

We have also observed transitions from complexes V and VI to II, though these transitions have often been erratic in their reproducibility. When hexane or ethanol was added to a benzene solution of VI (Ar = C₆H₅),⁸ II precipitated often, but not always, in quantitative yield.² Heating of VI (Ar = C₆H₅) *in vacuo* (20 mm) for 4.5 hr at 144° did not produce any changes, while refluxing with xylene for 3 min caused complete conversion into II.

In many experiments leading to II, the latter was isolated as a mixture of two isomeric forms, exhibiting carbonyl absorption at 1965 and 1978 cm⁻¹; the melting points of the isomers were 204–205° and 209–210°, respectively. Previous authors^{6,9} reported for II an unsharp melting point around 195° and a carbonyl absorption at 1980 cm⁻¹. As the compound absorbing at 1965 cm⁻¹ predominates in these mixtures it is assumed—in accord with similar cases studied previously^{9,10}—that it has the *trans* structure (mp 209–210°), while the minor isomer is assigned the *cis* configuration. Recently Chatt and Shaw reported that the *trans* isomer of II absorbs at 1961 cm⁻¹, but indicated a melting point of 189–190.5°.¹¹ The pure *trans* form was isolated from α -naphthaldehyde and I, the pure *cis* form, from 9-anthroyl chloride and I (after chromatography on neutral alumina); the former is partially isomerized to the latter by heating with chlorobenzene at 220° in a sealed tube. Incidentally, Tsuji and Ohno's³ theory would imply that under these conditions II is converted into VI, which is, however, not the case.

Let us return to the reactions of polycyclic aroyl halides. It has been pointed out that their transformations are affected adversely by impurities. Moisture and hydrogen chloride may form the hydrido complex VIII⁸ or compound IX (see Table IV) from I. VIII may also originate from V, by reaction with moisture: $\text{V} + \text{H}_2\text{O} \rightarrow \text{ArCOOH} + \text{VIII}$.

Both these complexes may catalyze formation of hydrocarbons from the aroyl chlorides; they may, alternatively, lose hydrogen chloride and cause Friedel-Crafts reactions. Such a reaction has, indeed, been observed in the case of 9-anthroyl chloride. Together with the expected 9-chloroanthracene, a ketone, C₂₀H₁₇ClO, was formed, showing a strong carbonyl absorption at 1645 cm⁻¹. It is assigned structure X on the strength of two independent syntheses: from 9-chloroanthracene and 9-anthroyl chloride, or from anthracene and 10-chloro-9-anthroyl chloride.

It is noteworthy that 9-anthroyl chloride could only be decarbonylated with catalytic amounts of I above 300°. Below this temperature, a yellow complex of formula XI was obtained, which was also formed when the two reactants were refluxed in decalin for 1 hr. The structure is in accord with the existence of two carbonyl absorptions: 1680 cm⁻¹ (acyl carbonyl) and 2055 cm⁻¹ (metal carbonyl).

The analyses and some other data for the metal complexes isolated in this study are summarized in Table IV.

(9) L. Vallarino, *J. Chem. Soc.*, 2287 (1957).

(10) L. Vaska and J. W. DiLuzio, *J. Am. Chem. Soc.*, **83**, 2784 (1961).

(11) J. Chatt and B. L. Shaw, *J. Chem. Soc., A*, 1437 (1966).

(7) M. A. Bennett and P. A. Longstaff, *Chem. Ind. (London)*, 846 (1965). See also J. F. Young, J. A. Osborn, F. H. Jardine, and G. Wilkinson, *Chem. Commun.*, 131 (1965).

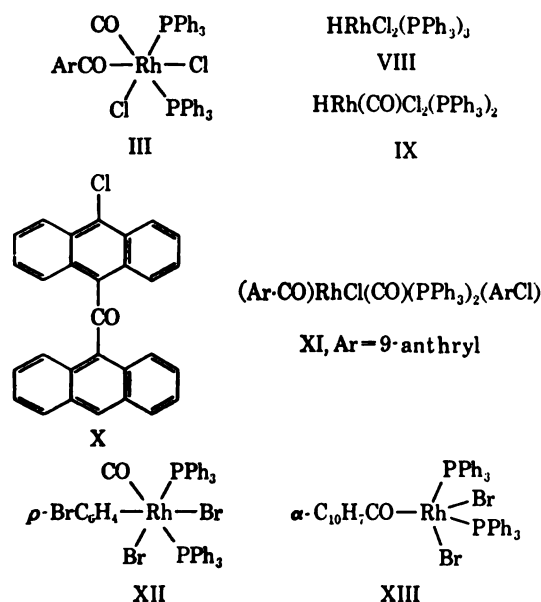
(8) M. C. Baird, D. N. Lawson, J. T. Mague, J. A. Osborn, and G. Wilkinson, *ibid.*, 129 (1966).

Table IV. Analytical Data for Rhodium Compounds

Compd	Mp (dec), °C	Carbon, %		Hydrogen, %		Cl, Br, %	
		Found	Calcd	Found	Calcd	Found	Calcd
$C_{27}H_{30}ClOP_3Rh$ (cis-II)	204–205	64.3	64.3	4.4	4.3	5.4	5.1
$C_{27}H_{30}ClOP_3Rh$ (trans-II)	209–210	64.4	64.3	4.6	4.3	5.4	5.1
$C_{27}H_{31}OP_3Rh$ (IX) ^a	Softens at 195	61.2	61.1	4.4	4.3	9.5	9.8
$C_{13}H_{14}Br_2OP_3Rh$ (XII)	185–186	53.1	53.2	3.7	3.5	25.1	24.7
$C_{13}H_{13}Cl_2OP_3Rh$ (VI, Ar = C_6H_5) ^b	215–218	64.1	64.3	4.4	4.4	9.2	8.8
$C_{17}H_{17}Br_2OP_3Rh$ (XIII)	174–176	60.2	59.9	4.3	3.9	17.5	17.0
$C_{17}H_{17}Cl_2OP_3Rh$ (V, Ar = α - $C_{10}H_7$)	220–222	65.9	66.1	4.6	4.3	8.3	8.3
$C_{17}H_{17}Cl_2OP_3Rh$ (V, Ar = β - $C_{10}H_7$) ^c	145	66.2	66.1	4.4	4.3	8.5	8.3
$C_{17}H_{17}Cl_2OP_3Rh$ (VI, Ar = β - $C_{10}H_7$) ^d	177–180	66.2	66.1	4.6	4.3	8.3	8.3
$C_{16}H_{16}Cl_2O_2P_3Rh$ (XI) ^e	195	71.4	71.6	4.0	4.3	6.0	6.4

^a Rh–H absorption at 2095 cm^{-1} ; carbonyl band at 1960 cm^{-1} . Cf. L. Vaska, *J. Am. Chem. Soc.*, **88**, 4100 (1966). ^b Cf. ref 8. ^c Not isomerically pure; contaminated with VI (Ar = β - $C_{10}H_7$); carbonyl bands at 1665 (vs), 1680 (vs), and 2062 (w) cm^{-1} . ^d ν_{CO} 2062 (vs) cm^{-1} . ^e Recrystallized from a mixture of benzene–hexane.

In conclusion, some comment is due on the reaction of aryl bromides (Tables I, II) with the chloro complex I. Experiments at relatively low temperatures have shown that in these reactions the original metal chlorine atom is partly or completely replaced by bromine. For example, *p*-bromobenzoyl bromide gave with I in boiling benzene (30 min) a complex which could be recrystallized from benzene–hexane, absorbed at 2055 cm^{-1} , and had thus the structure XII, which is confirmed by the analysis. XII is thus an analog to the complex of type VI. α -Naphthoyl bromide, under the same conditions, on the other hand, gave an orange five-coordinate complex, which after recrystallization from benzene showed aromatic carbonyl absorption (at 1675 cm^{-1}) and was thus XIII, corresponding to V.



Experimental Section

The different techniques used for the decarbonylation reactions are illustrated by the following examples.

***m*-Dibromobenzene from *m*-Bromobenzoyl Bromide.** A mixture of 14.0 g of *m*-bromobenzoyl bromide (Eastman Organic Chemicals) and 50 mg of I was heated in a Claisen flask equipped with a 25-cm-long Vigreux column, so as to permit distillation of the dibromobenzene formed at 214–216°. After 1 hr the evolution of carbon monoxide practically ceased, and an additional portion of 15 mg of I was added to the reaction mixture. This process was repeated four times in intervals of 15 min (until decarbonylation was

complete). The crude distillate was washed with alkali, neutralized, and dried in the usual manner and redistilled at 215–216°, yielding 10.6 g (85%) of pure *m*-dibromobenzene.

α -Naphthonitrile from α -Naphthoyl Cyanide. A mixture of 9.0 g of α -naphthoyl cyanide (mp 101–102°; prepared by refluxing α -naphthoyl chloride with an equal amount of cuprous cyanide at 190° for 1 hr) and 0.1 g of I was heated for 45 min in a Claisen flask, so that the product distilled off as formed (bp 294°). The product was distilled again (during 10 min) with 0.02 g of I. Thus 6.6 g (87%) of α -naphthonitrile (mp 37°) was obtained. The nitrile was identical with an authentic sample.

α -Chlorodiphenylmethane from Diphenylacetyl Chloride. A quantity of 6.5 g of freshly distilled diphenylacetyl chloride [bp 185–187° (20 mm)] and 0.1 g of I were placed in a Claisen flask mounted with two thermometers and connected to a variable vacuum system. The mixture was heated at 210–230° (internal temperature), and a suitable vacuum was applied, so that the product distilled off during 15 min. On redistillation at 137–138° (2 mm) there was obtained 5.4 g (94%) of colorless α -chlorodiphenylmethane, identical with a product prepared from benzhydrol.¹²

6-Chlorobenzo[c]phenanthrene. A mixture of 1.45 g of 6-benzo[c]phenanthroyl chloride¹³ and 0.1 g of I was heated in a test tube, under exclusion of moisture, at 260° (internal temperature) for 1–3 min. After this time the evolution of carbon monoxide had ceased. Chromatography on alumina, *n*-hexane serving as eluent, yielded 1.15 g (89%) of 6-chlorobenzo[c]phenanthrene from *n*-hexane as colorless needles, mp 85–86°, λ_{max}^{EtOH} ($m\mu$ (log ϵ)) 219 (4.71), 232 (4.38), 245 (4.15), 276 (4.71), 285 (4.79), 310 (4.00), 318 (4.02), 330 (3.57), 361 (2.57), and 380 (2.38). Anal. Calcd for $C_{18}H_{11}Cl$: C, 82.4; H, 4.2; Cl, 13.4. Found: C, 82.2; H, 4.1; Cl, 13.5.

Decarbonylation of 9-Anthroyl Chloride. A quantity of 2.34 g of 9-anthroyl chloride was heated, in a test tube, with 0.1 g of I at 310° for 3 min. Chromatography on alumina, benzene serving as eluent, yielded, as the first fraction, 0.49 g (24%) of pale yellow 9-chloroanthracene (mp 102–104°) identical with the product prepared from anthracene and cupric chloride.¹⁴

A second fraction from the chromatography afforded, on recrystallization from benzene and ethanol, 0.60 g (30%) of X as deep yellow crystals, mp 260–262°. Anal. Calcd for $C_{20}H_{17}ClO$: C, 83.6; H, 4.1; Cl, 8.5; mol wt, 416. Found: C, 83.8; H, 4.1, Cl, 8.9; mol wt, 416 (mass spectrum).

9-Anthryl 10-Chloro-9-anthryl Ketone (X) by Friedel–Crafts Acylation. a. Following the known route for the preparation of 9-benzoylanthracene, 2.8 g of 9-chloroanthracene, 3.5 g of 9-anthroyl chloride, 1.8 g of aluminum chloride, and 50 ml of carbon disulfide were refluxed for 48 hr. After the usual work-up, the oily residue was chromatographed on alumina, yielding 0.8 g of X, mp 260–262°.

b. In a similar manner, anthracene and 10-chloro-9-anthroyl chloride were treated with aluminum chloride in carbon disulfide, giving X in 21% yield, identical with the samples obtained by the two preceding methods.

(12) A. M. Ward, *J. Chem. Soc.*, 2285 (1927).

(13) M. S. Newman and J. Blum, *J. Am. Chem. Soc.*, **86**, 1835 (1964).

(14) D. C. Nonhebel, *Org. Syn.*, **43**, 15 (1963).

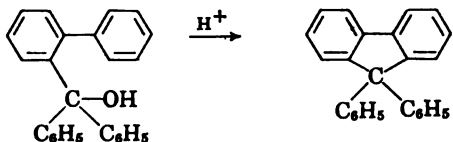
Mechanism of Cyclodehydration of 2-Phenyltriarylcarbinols

Harold Hart and Edward A. Sedor

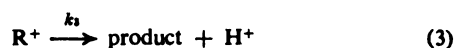
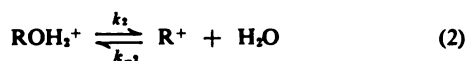
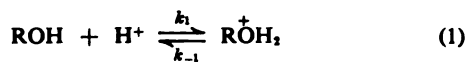
Contribution from the Department of Chemistry, Michigan State University, East Lansing, Michigan 48823. Received January 19, 1966

Abstract: A kinetic study of substituent effects on the acid-catalyzed cyclodehydration of 2-phenyltriarylcarbinols to the corresponding 9,9-diarylfluorenes reveals that the rate-determining step depends on the nature of the substituents. A Hammett plot shows a sharp concave downward break. One group of carbinols have rates which correlate best with σ , have a large negative ρ (-2.51), and show a strong rate dependence on solvent acidity, a threefold rate enhancement in deuterated solvent, and an activation entropy near zero or slightly positive. The remaining carbinols have rates which correlate best with σ^+ , have a large positive ρ ($+2.77$), are insensitive to the solvent acidity, show no marked rate effect in deuterated solvent, and have a rather large negative activation entropy. These observations are rationalized by a three-step mechanism: (1) rapid and reversible protonation of the carbinol, (2) dissociation to the corresponding triarylcarbonium ion, and (3) intramolecular electrophilic substitution on the 2-phenyl ring. Step 2 is rate determining for carbinols on the negative ρ correlation line; step 3 is rate determining for carbinols on the positive ρ correlation line.

Attempts to convert triarylcarbinols with a 2-phenyl substituent in one of the aryl rings to the corresponding carbonium ion by dissolution in acid generally lead instead to a substituted fluorene, by cyclodehydration.¹ An analogous reaction has been observed with diaryl-² and monoaryldialkylcarbinols,³ as well as with 2-benzyl-,⁴ 2-phenoxy-,⁵ or 2-thiophenoxytriarylcarbinols.⁶ For example, Clarkson and Gomborg,¹ who were the first to isolate pure, crystalline 2-phenyltriphenylcarbinol, found that all attempts to convert it to the corresponding chloride gave instead a quantitative yield of 9,9-diphenylfluorene. Although this type of reaction has been known for over 60 years, its mecha-



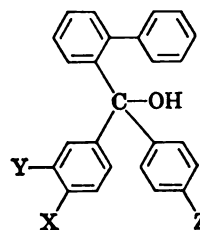
nism has not been examined in detail. Presumably a reaction sequence such as 1-3 is followed, but the



kinetics have not been studied. The reaction has interesting aspects. For example, if k_2 were rate

determining, the reaction would be analogous to an $\text{S}_{\text{N}}1$ solvolysis, with the aromatic ring serving as a built-in nucleophile. On the other hand, if k_3 were rate determining, the reaction would be comparable to other electrophilic aromatic substitutions, but with the electrophile and substrate built into the same reactive intermediate. Substituents might be expected to alter the relative rates of the various steps.

With a view to examining these alternatives, we synthesized a number of carbinols of the type shown (1-12) and found suitable conditions for carrying out



1-12
(for X, Y, and Z see Table I)

the cyclizations at measurable rates. The reaction rates were followed spectrophotometrically. A study of the effect of substituents on the reaction rates, of activation parameters, of effect of solvent acidity on the rates, and of solvent deuterium isotope effects allows a fairly complete mechanistic picture to be presented.

Results

The required carbinols were prepared either by reaction of a substituted phenyl Grignard reagent with 2-benzoylbiphenyl, or by reaction of the Grignard reagent from 2-bromobiphenyl with a disubstituted benzophenone. Formulas of the 12 carbinols studied and their relative rates of cyclodehydration are given in Table I listed in order of decreasing σ values of the substituents. Physical constants of the carbinols are given in Table VI and complete rate data are given in Table VIII in the Experimental Section.

Required samples of the cyclodehydration products were obtained by adding a few drops of strong acid to a refluxing solution of the carbinol in acetic acid. Upon cooling, nearly quantitative yields of the crystalline disubstituted fluorenes were obtained. They are

(1) F. Ullman and R. von Wursterberger, *Ber.*, **38**, 4105 (1905); E. Khotinsky and R. Patzewitch, *ibid.*, **42**, 3104 (1909); P. G. Sergeev, *J. Russ. Phys. Chem. Soc.*, **61**, 1421 (1929); R. G. Clarkson and M. Gomborg, *J. Am. Chem. Soc.*, **52**, 2881 (1930); E. P. Kohler and L. W. Blanchard, *ibid.*, **57**, 367 (1935); G. Wittig and G. Fuhrman, *Ber.*, **73B**, 1197 (1940); J. H. Weisberger, E. K. Weisberger, and F. B. Ray, *J. Am. Chem. Soc.*, **72**, 4250 (1950); H. Gilman and R. D. Gorsich, *ibid.*, **78**, 2218 (1956).

(2) E. Bergmann and A. Bondi, *Ber.*, **64**, 1477 (1931); J. R. Dice, T. E. Watkins, and H. L. Schuman, *J. Am. Chem. Soc.*, **72**, 1738 (1950); C. F. Koelsch, *ibid.*, **56**, 480 (1934); H. H. Hatt, *J. Chem. Soc.*, 478 (1941); H. Suzuki, *J. Chem. Soc. Japan*, **72**, 825 (1951).

(3) M. Anchel and A. H. Blatt, *J. Am. Chem. Soc.*, **63**, 1948 (1941).

(4) E. Barnett, J. W. Cook, and I. G. Nixon, *J. Chem. Soc.*, 504 (1927); F. F. Blicke and R. A. Patelski, *J. Am. Chem. Soc.*, **58**, 559 (1936); F. F. Blicke and R. J. Warzynski, *ibid.*, **62**, 3191 (1940); C. F. Koelsch, *J. Org. Chem.*, **3**, 456 (1938).

(5) Fourth reference in footnote 1.

(6) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Am. Chem. Soc.*, **85**, 2279 (1963).

Table I. Substituted 2-Phenyltriarylcarbinols, and Their Relative Cyclodehydration Rates^a

Compd	X	Y	Z	$k_{rel}^{25^\circ}$	σ^b	$\sigma^+{}^b$	E_a^c	$\Delta H^\ddagger{}^c$	$\Delta S^\ddagger{}^d$
1	Cl	H	Cl	0.096	0.454	0.228	23.7	22.8	1.60
2	H	CF ₃	H	0.052	0.42	0.52	21.3	22.8	4.4
3	H	Cl	H	0.100	0.373	0.399	22.8	21.7	2.7
4	Cl	H	H	0.30	0.227	0.114	21.3	20.1	-0.8
5	H	OCH ₃	H	0.74	0.115	0.047	25.3	21.1	4.3
6	H	H	H	1.00	0	0	19.2	18.9	-2.6
7	H	CH ₃	H	1.48	-0.069	-0.066	24.0	19.8	1.4
8	CH ₃	H	H	3.27	-0.170	-0.311	21.7	18.6	-1.0
9	OCH ₃	H	H	0.56	-0.268	-0.778	18.3	15.0	-16.7
10	CH ₃	H	CH ₃	5.80	-0.34	-0.622	15.4	14.9	-12.3
11	CH ₃	H	OCH ₃	1.76	-0.438	-1.089	18.3	15.0	-16.7
12	OCH ₃	H	OCH ₃	0.0090	-0.536	-1.556	21.8	20.7	-4.9

^a In 80% aqueous acetic acid containing 4% sulfuric acid. ^b Values are taken from H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958). When two substituents are present, the sums of σ 's are used. ^c Kcal/mole. ^d Cal/mole°.

listed, with their properties, in Table VII in the Experimental Section.

The cyclization rates of the carbinols were determined in 80% aqueous acetic acid containing 4 wt % of sulfuric acid. The choice of this rather unconventional medium was dictated by the need to strike a balance between measurable rates and solvents in which both the starting carbinol and the product hydrocarbon were soluble. For some carbinols, the amount of sulfuric acid was varied (4–6%). The reactions were studied at five temperatures between 15 and 35°. Progress of each reaction was followed by the appearance of a band in the vicinity of 308 m μ which was present in the fluorenes, but absent in the carbinols. In several cases (2, 6, and 10) a comparison of the product isolated from a kinetic run with that synthesized independently showed that the reaction proceeded quantitatively to completion, without formation of side products.

All of the reactions followed precise first-order kinetics through at least 88% reaction. The rate data are given in Table VIII in the Experimental Section, and the derived activation parameters are listed in Table I. The reaction rates were independent of initial carbinol concentration, tested with two different substrates (Table II).

Table II. Effect of Initial Carbinol Concentration on Cyclodehydration Rates^a

Compd	Initial concn, moles/l. $\times 10^4$	$k \times 10^4$, sec ⁻¹
4	7.05	7.96 \pm 0.04
	14.10	8.06 \pm 0.05
	25.00	7.78 \pm 0.02
8	3.30	87.6 \pm 0.2
	5.71	86.8 \pm 0.2
	9.53	86.6 \pm 0.2

^a In 80% aqueous acetic acid containing 4% sulfuric acid, at 25°.

Certain of the carbinols (9–12) gave colored solutions in the reaction medium. In these cases, it was possible to follow not only the appearance of product (at \sim 308 m μ) but also the disappearance of the visible peak (at \sim 470 m μ) due to the carbonium ion. The rates of the two processes were identical within experimental error (Table III).

Table III. Comparison of Cyclodehydration Rates Measured by Product Appearance and by Carbonium Ion Consumption^a

Compd	$k \times 10^4$, sec ⁻¹	$k' \times 10^4$, sec ⁻¹	λ_{max} , m μ (ϵ)
9	14.2	14.3	474 (53,000)
10	153	159	458 (53,000)
11	4.67	4.72	487 (79,000)

^a In 80% aqueous acetic acid containing 4% sulfuric acid, at 25°; k = rate constant measured by appearance of 308-m μ peak for the appropriate fluorene; k' = rate constant measured by disappearance of the peak in the visible region, at the wavelength shown in the last column.

Discussion

Hammett Correlations. It is clear from the data presented in Table I that substituents markedly affect the cyclodehydration rates, but that their effect does not follow a single Hammett plot. The fastest reaction occurred with two *p*-CH₃ substituents, and the slowest with two *p*-OCH₃ substituents, whereas compounds with one or two *p*-Cl substituents reacted at intermediate rates. The substituents in fact fall into two groups. One of these is best correlated by Hammett σ values, the value of ρ at 25° being -2.51 . The correlation coefficient is 0.990, as contrasted with 0.955 if σ^+ values are used.⁷ A plot of $\log k$ vs. σ for these substituents is shown in the right portion of Figure 1. Those carbinols which have a *p*-OCH₃ substituent fall nowhere near the correlation line, and in fact fall into the second group of substituents, which are best correlated by σ^+ , with a value of ρ at 25° of $+2.67$ and a correlation coefficient of 0.976.⁸ Carbinol 10, with two *p*-methyl substituents, occupies an ambiguous position at the apex of Figure 1. The two points shown for this carbinol correspond to the use of σ or σ^+ constants, and the compound falls reasonably close to both correlation lines.

The activation parameters (Table I) also fall into two groups. For those substituents on the negative ρ correlation line, the activation enthalpies decrease as the electron-donating power of the substituents increases, and the activation entropy is on the whole near zero or slightly positive. Conversely, for those substituents on the positive ρ correlation line, the activation enthalpies increase as the electron-donating power of substituents increases, and the activation entropy is moderately

(7) Using σ^+ , ρ was -1.94 .

(8) Using σ , the correlation coefficient was 0.801 and $\rho = +7.79$.

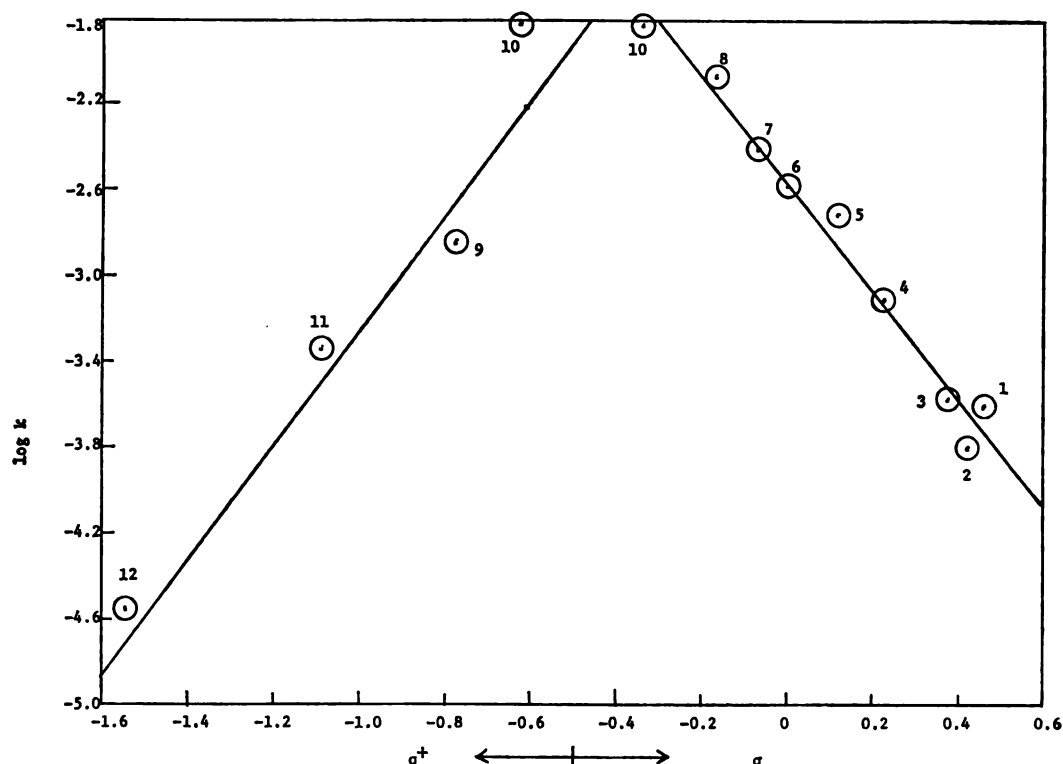


Figure 1. Hammett plot for the cyclodehydration of 2-phenyltriarylcarbinols in 80% aqueous acetic acid containing 4% sulfuric acid at 25°. Numbers refer to the formulas in the text.

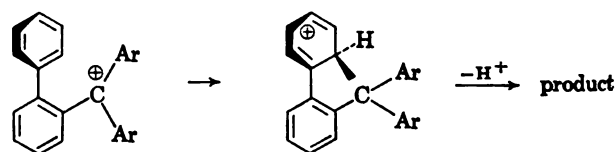
large and negative. A plot of ΔH^\ddagger vs. ΔS^\ddagger for either set of substituents shows a rather large degree of scatter. The best straight lines drawn through each set lead to isokinetic temperatures well above the temperatures of the kinetic measurements.

Mechanism. Leffler and Grunwald⁹ have pointed out that a Hammett plot which shows a concave downward break (Figure 1) is caused by a change in the rate-determining step of an otherwise constant mechanism. This is consistent with sequence 1–3, in which step 2 is rate determining for those substituents which appear on the right side of Figure 1, and step 3 is rate determining for those substituents which appear on the left side of Figure 1. Thus the ionization step is normally rate determining, but when the substituents stabilize the intermediate carbonium ion sufficiently, ring closure becomes rate determining.

The signs and magnitudes of the ρ values, the substituent correlations (i.e., σ or σ^+), and the activation parameters are in accord with this interpretation. When step 2 is rate determining, the transition state will be electron deficient with respect to the ground state, and a negative ρ is expected. However, since formation of R^+ is undoubtedly not complete at the transition state, ρ should be less negative than -3.64 , the value observed¹⁰ for the equilibrium ionization of triarylcarbinols. The observed ρ of -2.51 is thus reasonable. The better agreement with σ rather than σ^+ indicates that direct resonance interaction of the substituents in 1–8 with the cationic center is small. Actually the correlation is not highly sensitive to the difference between σ and σ^+ (0.990 vs. 0.955), possibly because the sub-

stituents are mainly electron withdrawing on the right side of Figure 1. Also, because of the 2-phenyl substituent, the transition state may be sufficiently non-planar as to minimize the importance of a resonance effect. The small, slightly positive activation entropy is consistent with decreased crowding accompanying the change from sp^3 to sp^2 hybridization at the ionization site.

For those substituents on the left side of Figure 1, the reaction solutions became red almost instantly, and the red color disappeared as the reaction proceeded. Extrapolation to zero time gave the λ_{\max} (ϵ) values shown in the last column of Table III. These are nearly identical with reported values for the similarly substituted triphenylcarbinols¹¹ and support the conclusion that the corresponding carbonium ions of 9–12 form rapidly and undergo a slow, rate-determining ring closure (step 3). In accord with this interpretation and the expectation that positive charge is more dispersed in the transition state than in the ground state, one finds a rather large positive ρ value. The far better correlation with σ^+ than with σ is to be expected, since the ground state is in fact a carbonium ion. Finally, the large negative activation entropy is consistent with the requirement that the 2-phenyl group and the carbonium carbon atom be rather specifically oriented for the reaction



(9) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 189.

(10) N. C. Deno and W. L. Evans, *J. Am. Chem. Soc.*, **79**, 5804 (1957).

(11) W. N. White and C. A. Stout, *J. Org. Chem.*, **27**, 2915 (1962).

onsequent restriction in degrees of freedom should in a large entropy effect.

Other Tests of the Mechanism. During any given experiment, acid consumed in step 1 is regenerated in step 3, so that good pseudo-first-order kinetics should be (and were) observed. However a difference effect of acidity on the observed rate constants is noted, depending upon whether step 2 or 3 is rate determining. In the former instance, the rate depends on the concentration of ROH_2^+ which, in turn, depends on equilibrium 1. An increase in the acidity of the medium should increase the equilibrium concentration of ROH_2^+ and accordingly increase the observed cyclodehydration rate. On the other hand, if step 3 is rate determining, all of the carbinol will be rapidly converted to carbonium ion, and should be relatively little effect of acidity on the observed rate.

Accordingly, the cyclodehydration rates of several carbinols which follow each of the Hammett correlations were measured as a function of the per cent acetic acid in the reaction medium, with the results in Table IV. The variation in per cent acid

V. The Effect of Acid Strength on the Cyclodehydration of 2-Phenyltriarylcarbinols

Compd	$k_r \times 10^4 \text{ sec}^{-1} \text{ a}$		
	4%	5%	6%
1	2.53	4.16	6.58
3	2.64	4.53	6.75
4	7.88	14.40	21.88
5	19.5	31.3	
6	26.4	47.6	73.5
9	14.7	15.7	14.8
10	153	169	
11	4.64	4.88	

measured in 80% aqueous acetic acid at 25°, with the indicated percentages of sulfuric acid.

rather limited, in order to keep the rates in a suitable range; it was sufficient, however, to establish essential correctness of the prediction. Cyclization rates for the carbinols on the right of Figure 1 show a strong dependence on acidity, the rate ratios k_6/k_4 and k_8/k_4 being 1.72 ± 0.08 and $2.68 \pm$ respectively. On the other hand, these ratios for carbinols for which step 3 is thought to be rate determining are only 1.07 ± 0.02 and 1.01 (only one determination).

An alternative explanation for the increased rates with increased acidity for carbinols on the $-\rho$ correlation would be that step 1 rather than step 2 is rate determining. Although the protonation of oxygen is usually considered to be exceedingly rapid,¹² there is a remote possibility that the environment around hydroxyl group in 2-phenyltriarylcarbinols was entirely crowded with hydrophobic groups that reaction might be slow. This possibility was subject to experimental test. It is well known that many catalyzed reactions proceed more rapidly in D_2O than H_2O , and this effect has been used as a criterion for rate-determining equilibrium protonation.^{12,13}

For a discussion, see F. A. Long and M. A. Paul, *Chem. Rev.*, (1957).

For a discussion, see K. Wiberg, *ibid.*, 55, 718 (1955).

Accordingly, the cyclodehydration rates of several carbinols on both sides of Figure 1 were determined in 80% $\text{CH}_3\text{COOD}-\text{D}_2\text{O}$, with the results given in Table V. A nearly constant rate enhancement of about 3

Table V. Solvent Isotope Effect on Cyclodehydration Rates*

Compd	k_D/k_H
4	2.91
6	3.10
8	2.88
9	0.94
10	1.55

* Rates in deuterated solvent were measured in 80% $\text{CH}_3\text{COOD}-\text{D}_2\text{O}$ containing 4% H_2SO_4 , at 25°. Total deuterium enrichment of acidic hydrogen was 97.3%.

is observed for three carbinols (4, 6, and 8) on the $-\rho$ correlation line which vary by a factor of over 10 in their absolute cyclodehydration rates. On the other hand, carbinol 9 shows almost no solvent deuterium isotope effect, since step 3 is rate determining.

Carbinol 10, which is at the apex of Figure 1, occupies an ambiguous position. It seems likely that here k_2 and k_3 are of comparable magnitude, with the result that an intermediate solvent deuterium isotope effect is observed. Although the rates for cyclodehydration of 10 as measured by product appearance and by carbonium ion disappearance agree well (Table III), it must be pointed out that this carbinol dehydrates so rapidly that it was impossible to get initial rate readings until reaction was already 45% complete at 25°. Attempts to slow the reaction down by lowering the temperature were frustrated by limited solubility of the product, so it was not possible, as hoped, to observe both the appearance and decay of R^+ .

In summary, all of the data seem to substantiate schemes 1-3 as the correct cyclodehydration mechanism; step 1 is rapid in all cases, but step 2 or 3 may be rate determining, depending on the substituents.

Experimental Section¹⁴

Preparation of 2-Phenyltriarylcarbinols. One of three procedures was used, depending on the number and type of substituent. These procedures, designated A, B, and C, will be illustrated with examples, to indicate some of the ways in which the problem of isolating pure carbinols was overcome. The results of all the preparations are summarized in Table VI.

Procedure A. 3-Methoxy-2'-phenyltriphenylmethanol (5). To the Grignard reagent prepared from 0.643 g (0.0267 g-atom) of high purity magnesium and 5.0 g (0.0267 mole) of 3-bromoanisole in 90 ml of anhydrous tetrahydrofuran there was added (N_2 atmosphere) dropwise a solution of 3.0 g (0.0166 mole) of 2-phenylbenzophenone in 50 ml of the same solvent. The solution turned blue immediately, but became yellow after 30-hr reflux. After 48-hr reflux, 100 ml of distilled water was added dropwise. Extraction with ether (three 100-ml portions), drying over MgSO_4 , and evaporation of the solvent gave 6.1 g of a viscous oil. A sample (3.5 g) of the oil was chromatographed on 100 g of Woelm neutral alumina, activity 1, using 50% carbon tetrachloride-benzene as eluent. The major component (1.1 g, 31.1%) was an oil which showed one spot on tlc plates. Remaining fractions yielded 1.8 g of a complex mixture (tlc). The major product crystallized on standing, and was recrystallized from pentane, mp 104-105.5°. Its nmr spectrum (CCl_4) showed singlets at τ 7.28 (1 H) and 6.42 (3 H) and a multiplet at τ 3.50-2.68 (18 H).¹⁵

(14) Melting points are uncorrected. Analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

(15) Infrared and nmr spectra of all compounds are given in the appendix of the Ph.D. Thesis of E. A. S., Michigan State University, 1965.

Table VI. Preparation and Properties of 2-Phenyltriarylcarbinols

Compd	Conditions ^a	Yield, ^b %	Mp, ^c °C	Calcd, %		Found, %	
				C	H	C	H
1 ^d	B,EB,24	28	118–118.5(p)	74.08	4.48	74.24	4.52
2	A,T,24	52	Oil ^e	77.23	4.74	77.46	4.99
3 ^f	A,EB,5	14.5	101.5–102(p)	81.00	5.16	81.07	5.14
4 ^g	A,EB,2 ^h	5	105.0–106.5(b)	81.00	5.16	81.02	5.15
5	A,T,48	31.1	104–105.5(p)	85.22	6.05	85.07	6.09
6	B,E,4 ⁱ	28	91–92(p) ⁱ				
7	A,T,2	55.8	Oil ^j	89.11	6.33	88.68	6.41
8	C,E,1	37	72.5–74.5(h)	89.11	6.33	89.27	6.25
9	C ^k E	16	87.5–89(h)	85.22	6.05	85.02	6.04
10	B,T,1	25	162–164(b)	88.97	6.64	88.97	6.56
11	B,T,48	28	126–127.5(p)	85.23	6.36	85.19	6.36
12	B,T,24	22	123–124(b)	81.79	6.10	81.62	6.01

^a The first letter refers to the procedure used: A, arylmagnesium bromide + 2-phenylbenzophenone; B, 2-biphenylmagnesium bromide + an appropriately substituted benzophenone; C, aryllithium + 2-phenylbenzophenone. The second letter refers to the solvent: E, ether; T, tetrahydrofuran; EB, ether for preparation of Grignard reagent, replaced by benzene for the subsequent reaction. The number refers to the reflux time in hours after addition of the reactants. Unless otherwise stated, work-up hydrolysis was with H₂O alone. ^b Purified product. ^c Uncorrected; recrystallization solvents are given in parentheses: p, pentane; h, hexane; b, benzene-petroleum ether. ^d Calculated for Cl: 17.50. Found: Cl, 17.56. ^e Purified by chromatography on basic alumina (50% benzene-CCl₄ eluent) and silica gel (benzene eluent) gave a single tlc spot. ^f Calculated for Cl: 9.56. Found: Cl, 9.44. ^g Calculated for Cl: 9.56. Found: Cl, 9.54. ^h Hydrolysis with ammonium chloride. ⁱ Lit. mp 87–88° (Clarkson and Gomberg, ref 1). ^j Purified by chromatography on basic alumina (benzene eluent) and Woelm neutral alumina, grade 1 (CCl₄ eluent); gave a single tlc spot. ^k Inverse addition at 0°.

Table VII. Preparation and Properties of 9,9-Diarylfluorenes

Compd ^a	Procedure ^b	Mp, ^c °C	Composition, ^d %		$\lambda_{\max}^{85\% \text{ EtOH}}$ (ε) ^e
			C	H	
1F ^f	A(5 min)100	165–166.5	77.53 77.39	4.17 4.10	308 (6780), 296 (4410), 284s (9160), 279.2s (11,500), 272.4 (15,000), 269.3s (14,300), 263.2s (13,400), 240 (31,500)
2F	B(3 days)60	127.5–129.5	80.81 80.79	4.44 4.43	307.2 (7870), 295.4 (5050), 282.3s (10,800), 278s (12,800), 271.0 (17,200), 267.0 (16,300), 263s (15,600), 236.7 (26,600), 228.2 (33,400)
3F ^g	A(1 min)100	154–155	85.09 85.13	4.86 4.85	307.2 (7730), 295.6 (4900), 283.2s (10,200), 278.7 (12,400), 271.7 (16,200), 267.3 (15,000), 261.5s (14,400), 238.5 (27,800), 229.6 (34,100)
4F ^h	A(5 min)100	142.5–144.0	85.09 84.78	4.86 4.81	307.9 (7470), 295.9 (7070), 284.2s (8710), 271.6 (15,100), 267.5s (21,140), 264.0s (13,680), 237.5 (28,400), 230.0 (34,700), 228s (33,700)
5F	A (10 min)95	150.5–151.5	89.62 89.54	5.79 5.69	307.8 (8380), 295.7 (5200), 283.7s (12,200), 270.0 (17,500), 267.5s (16,700), 263s (15,100), 237s (27,200), 228s (38,100)
6F	<i>i</i>				307.8 (8230), 296 (4970), 283s (8820), 279s (11,500), 271.5 (15,000), 267.5 (14,600), 263s (13,700), 238 (26,100), 230 (34,000), 224s (33,500)
7F	A(1 min)90	150.0–150.5	93.94 94.05	6.06 6.02	308 (8340), 296 (5200), 283s (9520), 278.5s (12,100), 271.6 (15,700), 267.5 (15,400), 263.3s (14,500), 238.2 (27,100), 230 (35,800)
8F	A(30 sec)100	134–134.5	93.94 93.82	6.06 6.18	308.1 (8310), 296.2 (5040), 284.1s (8140), 279s (11,500), 271.3 (15,120), 267.3 (14,960), 261.9s (13,910), 237.5s (27,400), 229.1 (36,050), 224.5s (35,900)
9F	B(50 min)100	165.5–166.0	89.62 89.41	5.79 5.84	308.6 (8780), 296.5 (5130), 279.5s (14,200), 273.0 (17,600), 268.2s (17,300), 264.1s (16,470), 236.9s (12,600), 230.0 (17,700)
10F	A(1 min)70	160.0–160.5	93.60 93.51	6.40 6.49	308.6 (8500), 296 (5090), 284s (8160), 279.6s (11,320), 271.8 (14,500), 267.5 (14,500), 263.5s (44,800), 238.8 (28,000), 228.3 (40,300)
11F	B(10 hr)96	129–130	89.47 89.39	6.12 5.94	308.8 (10,400), 297 (5970), 278.9s (16,300), 271.5 (22,600), 268 (21,800), 230 (50,300)
12F	B(4 days)85	120–122	85.69 85.42	5.86 5.90	309.8 (10,800), 297.5 (5620), 279.6s (19,000), 271 (24,400), 268 (24,800), 263 (24,800), 230 (79,800)

^a Compounds are numbered to correspond to the carbinols from which they were prepared (see Table I). ^b Although precise procedures varied, they can in general be grouped into two categories: A, 0.1–0.5 g of the carbinol was dissolved in 10–15 ml of glacial acetic acid, the solution brought to reflux, and three to five drops of concentrated HCl added; the reaction mixture became colored (yellow to red), then clear. On cooling, and addition of a few drops of water, crystals appeared; B, 0.1–0.3 g of the carbinol was dissolved in 15–20 ml of 80% aqueous acetic acid containing 4% H₂SO₄, allowed to stand at room temperature until the red color faded to yellow, warmed to 80°, then cooled, water added, and the crystals were collected. Reaction times are given in parentheses, and followed by the per cent yield. ^c Methanol was the recrystallization solvent in all cases. All products showed a single tlc spot. ^d Upper figures calculated, lower figures found. ^e In mμ; s, shoulder. ^f Calculated for Cl: 18.31. Found: Cl, 18.40. ^g Calculated for Cl: 10.05. Found: Cl, 10.00. ^h Calculated for Cl: 10.05. Found: Cl, 10.13. ⁱ Prepared according to Clarkson and Gomberg (ref 1).

Procedure B. 4,4'-Dichloro-2''-phenyltriphenylmethanol (1). Grignard reagent was prepared from 1.35 g (0.0563 g-atom of high purity magnesium and 13.1 g (0.0563 mole) of 2-bromobiphenyl in 50 ml of anhydrous ether. To the refluxing orange solution was added dropwise a solution of 5.5 g (0.0219 mole) of 4,4'-dichlorobenzophenone (Dow Chemical Co.) in 25 ml of anhydrous benzene and 10 ml of ether. After addition, the mixture was refluxed for 24 hr, then allowed to stand at room temperature for 48 hr. The white precipitated complex was filtered through glass wool and washed with anhydrous ether (two 20-ml portions). The complex and glass wool were stirred with 75 ml of ether and decomposed by dropwise addition of distilled water (20 ml). The ether layer

was separated and dried (MgSO₄) and the solvent removed on a rotary evaporator. The oily residue, when stirred with 20 ml of pentane, gave 2.48 g (28%) of the desired carbinol, mp 116.5–117.0°. Recrystallization from pentane raised the melting point to 118–118.5°. The mother liquors gave 4.8 g of a complex mixture (tlc) containing some of the desired carbinol. The nmr spectrum of 1 in CCl₄ had a singlet at τ 7.22 (1 H) and a complex multiplet at τ 4.42–2.67 (16.9 H).¹³

Procedure C. 4-Methyl-2''-phenyltriphenylmethanol (8). *p*-Tolylolithium was prepared (N₂ atmosphere) from 0.40 g (0.057 g-atom) of lithium and 10.0 g (0.0585 mole) of *p*-bromotoluene in 75 ml of anhydrous ether. To the gray solution was added drop-

III. Rate Constants ($\text{sec}^{-1} \times 10^4$) for Cyclization of 2-Phenyltriarylcarbinols in 80% Aqueous Acetic Acid Containing Sulfuric Acid^a

compd	15°	20°	25°	30°	35°
1	(0.295)	1.26 ± 0.03	2.53 ± 0.12	4.93 ± 0.03	8.89 ± 0.15
2	(0.257)	(0.631)	1.36 ± 0.01	2.25 ± 0.02	$13.5 \pm 0.1^*$
3	(0.646)	1.54 ± 0.02	$2.64 \pm 0.02^*$	5.06 ± 0.08	9.94 ± 0.27
4	1.87 ± 0.15	3.90 ± 0.09	7.88 ± 0.17	$12.2 \pm 0.1^*$	23.8 ± 0.9
5	6.39 ± 0.13	9.88 ± 0.02	19.5 ± 0.2	33.0 ± 0.3	(57.5)
6	9.66 ± 0.38	15.5 ± 0.1	26.4 ± 0.6	50.4 ± 1.6	76.2 ± 1.6
7	12.3 ± 0.1	21.8 ± 0.1	39.2 ± 0.1	66.2 ± 1.3	(148)
8	23.3 ± 0.3	44.5 ± 0.2	$86.3 \pm 0.5^*$	$137 \pm 1^*$	(283)
9	5.6 ± 0.05	8.82 ± 0.04	14.7 ± 0.1	24.4 ± 0.6	36.0 ± 0.7
10	53.4 ± 0.1	99.2 ± 0.7	153 ± 5	(282)	(363)
11	(2.04)	2.79 ± 0.01	4.64 ± 0.2	$8.00 \pm 0.05^*$	(12.3)
12		(0.12)	$0.238 \pm 0.003^*$	(0.417)	0.701 ± 0.007

Values in parentheses are estimated from Arrhenius plots. All values are the average of three or more runs, except those marked with an asterisk, which are the average of only two runs.

After 15 min a solution of 4.0 g (0.0155 mole) of 2-phenylhexanone in 100 ml of anhydrous ether. The mixture was stirred for 1 hr, then decomposed with 50 ml of water. Separation of the ether layer, drying, and evaporation afforded 6.0 g of yellow oil which was chromatographed on silica gel (Baker's) with CH_2Cl_2 as eluent. The first three fractions (150 ml) yielded 3.0 g of pure alcohol; the remaining fractions (350 ml) gave 2.5 g of a red oil which became a glass when final traces of solvent were removed. The glass resisted crystallization from pentane or benzene, but on standing for 2 months deposited a few crystals (mp 60–75°) which were used to seed a hexane solution of the oil. In this way, 2.0 g (37%) of 8, recrystallized from hexane, 5–74.5°, were obtained. The product gave a single tlc spot, $R_f = 0.79$, and an nmr spectrum with singlets at τ 7.35 and 7.70 (3H) and a multiplet at τ 3.38–2.66 (18H).¹⁵

Preparation of 9,9-Diarylfluorenes. Preparation of these compounds in pure form offered no difficulties, and the procedures described briefly in footnote b of Table VII should suffice for duplicate results.

Analytical Procedure. Reactions were carried out in 1-cm, 3-ml, red, rectangular, silica cells in the thermostated cell compartment of a Beckman DB spectrophotometer, using a Tecam circulating unit to control the temperature to $\pm 0.1^\circ$. Most reactions were run in a solvent containing $4.000 \pm 0.001\%$ by weight sulfuric acid in 80% aqueous acetic acid. The solvent was prepared by placing 5 g of $100 \pm 0.1\%$ sulfuric acid in a stoppered weighing flask and diluting with 80.0% by weight aqueous acetic acid until the desired percentage was obtained.

This volume of solvent was usually sufficient to run the reactions of all the compounds at a single temperature. To minimize deterioration of the acid solution¹⁶ the solvent was replaced within 5 days.

Solutions of the carbinols were prepared in 5-ml volumetric flasks using anhydrous benzene as the solvent. Aliquots (5 μ l) of solutions (using a 10- μ l Hamilton syringe for measurement) were placed in 2-ml volumetric flasks and thermostated until use. Diluted to 2 ml with solvent, the solutions were about 9×10^{-4} M carbinol.

A solution of each 9,9-diarylfluorene was prepared by diluting 5 μ l of a benzene stock solution of the hydrocarbon with the reaction solvent. This solution was then used to set the exact λ_{max} wavelength position of the "308-m μ " band on the instrument wavelength selector.

Aliquots of stock carbinol solution were diluted with thermostated sulfuric acid–acetic acid solution, mixed by six inversions, and poured into the thermostated silica cells, and the recorder was started. Elapsed time was 30 sec at most; time of mixing was taken as zero reaction time. The recorder was then allowed to record the appearance of product as a function of time, measured to an accuracy of 1 sec/hr.

Rate constants were obtained from the expression $kt = 2.303 \log [A_\infty / (A_\infty - A_t)]$ where A_t is the absorbance of the hydrocarbon at time t and A_∞ is its absorbance at infinite time. For those reactions in which carbonium ion was observable (9–12) the expression was modified to $kt = 2.303 \log [C_0(\epsilon_p - \epsilon_c) / (A_\infty - A_t)]$ where C_0 was the initial concentration of carbonium ion, ϵ_p and ϵ_c were the molar extinction coefficients of the product and the carbonium ion at 308 m μ , and other terms are as defined above, to correct for the finite absorbance of the carbonium ion at "308 m μ ." The rates were also followed, in these cases, by the decrease in absorbance at the λ_{max} of the carbonium ion (Table III). Plots of $\log [1 / (A_\infty - A_t)]$ were linear in all cases. Rate constants were checked with solvent and stock solutions prepared at different times, and gave excellent agreement. The data are summarized in Tables VIII, IV, and V.

Preparation of the Deuterated Solvent. For the results described in Table V, solvent was prepared as follows: to 16.1908 g (0.3202 mole) of D_2O (Merck, Canada) was added dropwise 2.0367 g of $100 \pm 0.1\%$ H_2SO_4 . The flask was fitted with a condenser, and 32.6937 g of acetic anhydride was added dropwise. Initial additions caused warming and slight sputtering at the surface. After complete addition, the system was closed and mixed well, then allowed to remain at 25° for 20 hr before use. The final percentage was 4.00% H_2SO_4 in 80.0% DOAc and 20.0% D_2O .

Acknowledgment. We are indebted to the Army Research Office (Durham) for generous support of this research (DA-31-124-ARO(D)-157).

B. M. Tolbert and G. E. K. Branch, *J. Am. Chem. Soc.*, **69**, 1083 (1947).

Carbanions. X. The Preferential Migration of *p*-Biphenyl in 2-*m*-Biphenyl-2,2-bis(*p*-biphenyl)ethylolithium^{1,2}

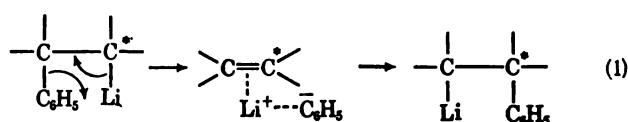
Erling Grovenstein, Jr., and Gary Wentworth

Contribution from the School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332. Received January 3, 1967

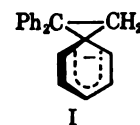
Abstract: Reaction of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane with lithium in tetrahydrofuran at -65° yields 2-*m*-biphenyl-2,2-bis(*p*-biphenyl)ethylolithium as shown by carbonation to give 3-*m*-biphenyl-3,3-bis(*p*-biphenyl)propanoic acid. When the solution of 2-*m*-biphenyl-2,2-bis(*p*-biphenyl)ethylolithium is warmed to 0° and held at this temperature 3 hr before carbonation, the crude acid obtained consists of at least $98.6 \pm 0.4\%$ of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid. The much higher migratory aptitude of *p*-biphenyl than of *m*-biphenyl is taken to indicate that migration of an aryl group in such organolithium compounds occurs in a carbanion by way of a cyclic or bridged transition state or intermediate such as I. Analogies are pointed out to certain related rearrangements involving 1,2 shifts of vinyl, carbonyl, and trimethylsilyl groups, and it is suggested that the area of carbanion rearrangements is more general than usually supposed.

In a previous paper³ it was shown that 2,2,2-triphenylethylolithium in tetrahydrofuran solution undergoes rearrangement to 1,1,2-triphenylethylolithium in the presence of benzylolithium or phenyllithium-C¹⁴ without detectable incorporation of benzyl or radioactive phenyl groups. These experiments demonstrate that the 1,2 shift of phenyl occurs without the formation and readdition of kinetically free phenyl radical, phenyl anion, or phenyllithium.⁴ The rearrangement was thereby concluded to occur by an intramolecular process. These experiments, however, did not eliminate the possibility⁵ that 2,2,2-triphenylethylolithium undergoes elimination of phenyl anion (or radical) but that phenyl anion (or radical) and 1,1-diphenylethene (or corresponding radical anion) exist in a solvent "cage" and recombine before radioactive phenyllithium or benzylolithium can diffuse into the "cage." The possibility that ordinary phenyllithium and 1,1-diphenylethene could exist in such a solvent "cage" and combine before radioactive phenyllithium or benzylolithium could diffuse into the "cage" can be dismissed since phenyllithium was found³ to add to 1,1-diphenylethene only slowly under the reaction conditions. An attractive variation⁶ of the cage-recombination mechanism is that rearrangement of 2,2,2-triphenylethylolithium occurs with elimination of phenyllithium as an ion pair to which 1,1-diphenylethene is bound as a ligand of the lithium ion; the ion pair-olefin complex then collapses to final product before an external organolithium compound can attack the 1,1-diphenylethene in the complex (eq 1).

While such elimination-readdition mechanisms may appear attractive in light of the proof^{3,5} of occurrence of an intermolecular elimination-readdition mecha-



nism for rearrangement of 2,2,3-triphenylpropyllithium, in earlier work it was proposed that phenyl migration⁷ proceeded by way of a cyclic transition state or reaction intermediate such as I for rearrangement of 2,2,2-triphenylethylolithium; similar transition states



of intermediates were proposed by Zimmerman and Zweig⁸ for migration of phenyl in 2,2-diphenylpropyllithium and phenyl or *p*-tolyl in 2-phenyl-2-(*p*-tolyl)propyllithium.

The present investigation was undertaken in order to try to distinguish between the proposed intramolecular elimination-readdition mechanisms of phenyl migration and the intramolecular cyclic mechanism of migration by way of an intermediate or transition state such as I. Such a distinction appears possible since in the elimination-readdition process the unshared electron pair in the phenyl anion or the unpaired electron in the phenyl radical is in an sp^2 orbital which is orthogonal to the aromatic π orbitals of the migrating phenyl group; hence the presence of a substituent at the *meta* or *para* position of the phenyl group would not be expected to greatly affect the rate of elimination of that group as an anion or radical. For comparison, Streitwieser and Lawler⁹ have found that the rate of deuterium exchange in biphenyl with lithium cyclohexylamide in cyclohexylamine is for a *para* position only 2.3 times that of a single position in benzene and for a *meta* position 3.7 times that of a position in benzene; similar partial rate factors were reported by Shatenshtein¹⁰ for exchange with potassium amide in

(1) Abstracted from the Ph.D. thesis of G. Wentworth, Georgia Institute of Technology, 1966.

(2) Presented in part before the Division of Organic Chemistry at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 13, 1966.

(3) Part IX: E. Grovenstein, Jr., and G. Wentworth, *J. Am. Chem. Soc.*, **89**, 1852 (1967).

(4) By "kinetically free" we mean that the phenyl radical, phenyl anion, or phenyllithium had sufficient lifetime to diffuse into the surrounding solvent away from the 1,1-diphenylethene (or 1,1-diphenylethene radical anion). It is assumed here that kinetically free phenyl radicals (or anions) would undergo very rapid lithium atom (or lithium cation) transfer reactions with benzylolithium or phenyllithium-C¹⁴.

(5) E. Grovenstein, Jr., and G. Wentworth, *ibid.*, **85**, 3305 (1963).

(6) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 237.

(7) E. Grovenstein, Jr., and L. P. Williams, Jr., *J. Am. Chem. Soc.*, **83**, 2537 (1961).

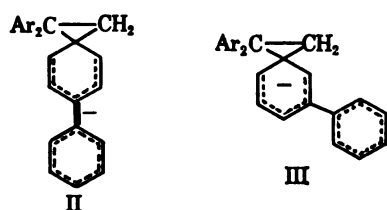
(8) H. E. Zimmerman and A. Zweig, *ibid.*, **83**, 1196 (1961).

(9) A. Streitwieser, Jr., and R. G. Lawler, *ibid.*, **85**, 2854 (1963); **87**, 5388 (1965).

(10) A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, **1**, 187 (1963).

ammonia. For rearrangement of a 2,2,2-triaryllithium proceeding by elimination of an aryl (cf. eq 1), a *m*-biphenyl anion would be expected eliminated somewhat more readily than a *p*-nylyl anion and thus *m*-biphenyl should migrate what more readily than *p*-biphenyl.

the other hand if rearrangement of 2,2,2-triaryllithium proceeds by way of an intermediate such a *p*-biphenyl group should migrate more readily a *m*-biphenyl group because the intermediate in *p*-biphenyl migration should have greater delocalization than that of III from *m*-biphenyl



tion since the mesomeric effect of the substituent /l group is not conveyed nearly as effectively from a as from a *para* position. In a system of somewhat r electrical demand, *m*- and *p*-phenyl as substituent s increase the ionization constant of phenol¹¹ ding to the usual linear Hammett relationship if ituent constants of +0.124 and +0.205, respec-, are assigned¹² these groups.

ordingly 2-*m*-biphenyl-2,2-bis(*p*-biphenyl)ethyl-m was prepared by reaction of 2-chloro-1-*m*-nyl-1,1-bis(*p*-biphenyl)ethane with lithium, and relative migratory aptitude of *m*-biphenyl *vs.* enylyl was determined.

ts

Synthesis of 2-Chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane. Initially it was intended to prepare compound from chloro-*m*-biphenylbis(*p*-biphenyl)methane according to the procedure used for ration¹³ of 2-chloro-1,1,1-triphenylethane from triphenylmethane. *m*-Biphenylbis(*p*-biphenyl)binol was prepared by reaction of 3-lithiobiphenyl 4,4'-diphenylbenzophenone in tetrahydrofuran; ver attempts to convert this carbinol to the chlo- reaction with acetyl chloride according to the dure¹⁴ for conversion of triphenylcarbinol to triphenylmethane gave a halogen-free product. : reaction of the carbinol with thionyl chloride and ine¹⁵ gave a chlorine-containing product, the ial in our hands proved difficult to purity. Ac- ngly the procedure in Scheme I was adopted.

duction of 4,4'-diphenylbenzophenone by the ied Wolff-Kishner procedure of Huang-Minlon¹⁶ an almost quantitative yield of bis(*p*-biphenyl)-ne, whereas Clemmenson reduction under either cidic or alkaline conditions of Martin¹⁷ resulted

F. Kieffer and P. Rumpf, *Compt. Rend.*, **238**, 360 (1954).

These σ values were calculated from the reported¹¹ pK_a values of *o*- and *p*-phenylphenol and a plot of pK_a *vs.* σ for other phenols Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **85**, 3397 (1963); ion and R. W. Matthews, *Australian J. Chem.*, **16**, 401 (1963).

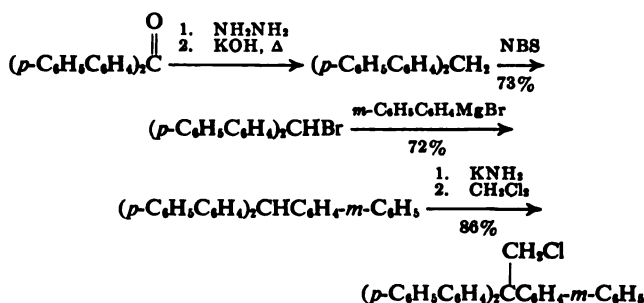
E. Grovenstein, Jr., *J. Am. Chem. Soc.*, **79**, 4985 (1957).

W. E. Bachmann in "Organic Syntheses," Coll. Vol. III, E. C. g. Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p

R. H. Clark and H. R. L. Streight, *Trans. Roy. Soc. Canada*, **17**, [3] 23, 77 (1929).

Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

Scheme I



in almost quantitative recovery of unreacted ketone (possibly because of the very low solubility of the ketone in aqueous media). Bromobis(*p*-biphenyl)methane was prepared by reaction of bis(*p*-biphenyl)methane with N-bromosuccinimide according to a general procedure of Zervas and Dilaris¹⁸ except that benzoyl peroxide was employed as catalyst. A preliminary attempt to couple bromobis(*p*-biphenyl)methane with 3-lithiobiphenyl in tetrahydrofuran solution resulted in a 74% yield of 1,1,2,2-tetrakis(*p*-biphenyl)ethane, possibly by way of a halogen-metal interchange.¹⁹ The reaction of bromobis(*p*-biphenyl)methane with 3-*m*-biphenylmagnesium bromide in tetrahydrofuran also gave 1,1,2,2-tetrakis(*p*-biphenyl)ethane in some 84% yield. While halogen-metal interchange in reactions of Grignard reagents has been reported²⁰ to be more facile in tetrahydrofuran than in ethyl ether, the high yield of symmetrical coupling product under the present conditions is unusual. When the coupling of bromobis(*p*-biphenyl)methane with 3-*m*-biphenylmagnesium bromide was run in ethyl ether, the desired *m*-biphenylbis(*p*-biphenyl)methane was obtained; the best yield of this compound (some 72%) was obtained in ethyl ether-benzene solution²¹ along with 18% yield of 1,1,2,2-tetrakis(*p*-biphenyl)ethane. Reaction of *m*-biphenylbis(*p*-biphenyl)methane with potassium amide in ammonia-ether solution gave a deeply colored solution of the corresponding triarylmethylpotassium which reacted readily with an excess of methylene chloride to give 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane. The over-all yield of this chloride from 4,4'-diphenylbenzophenone was about 43%.

Synthesis of Carboxylic Acids. In order to characterize the products of carbonation of the organolithium compounds from 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane, it was necessary to synthesize all of the likely carboxylic acids.

3-*m*-Biphenyl-3,3-bis(*p*-biphenyl)propanoic acid was prepared by reaction of *m*-biphenylbis(*p*-biphenyl)carbinol with malonic acid. This reaction is modeled after the procedure of Hellerman²² for preparation of 3,3,3-triphenylpropanoic acid from triphenylcarbinol; however in the present case after the reactants were heated at a bath temperature of 220° for 12 hr, the starting carbinol was recovered almost quantitatively. Also heating of the reactants with acetic anhydride according to the modification of Hellerman's procedure

(17) E. L. Martin, *ibid.*, **58**, 1438 (1936).

(18) L. Zervas and I. Dilaris, *ibid.*, **77**, 5354 (1955).

(19) Cf. R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 350 (1951).

(20) L. I. Zakharkin, O. Yu. Okhlobystin, and K. A. Bilevitch, *J. Organometal. Chem.* (Amsterdam), **2**, 309 (1964).

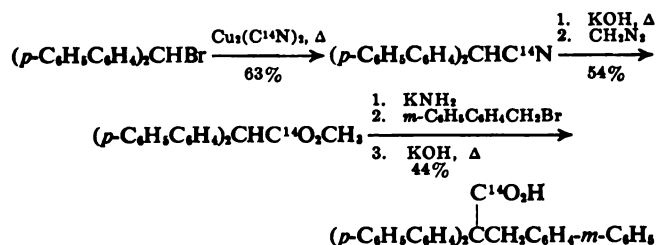
(21) Cf. W. E. Bachman, *J. Am. Chem. Soc.*, **55**, 2135 (1933).

(22) L. Hellerman, *ibid.*, **49**, 1735 (1927).

suggested by Gagnon²³ failed to give any of the desired carboxylic acid. Evidently because of the high melting point of *m*-biphenylbis(*p*-biphenyl)carbinol, malonic acid decomposes before an effective melt of the reactants can be obtained even in presence of acetic anhydride (bp 140°); however in the presence of higher boiling *n*-butyric anhydride (bp 198°), 3-*m*-biphenyl-3,3-bis(*p*-biphenyl)propanoic acid was obtained though in only 17% yield.

3-*m*-Biphenyl-2,2-bis(*p*-biphenyl)propanoic acid-1-C¹⁴ was synthesized according to the method of Scheme II. Reaction of bromobis(*p*-biphenyl)-

Scheme II

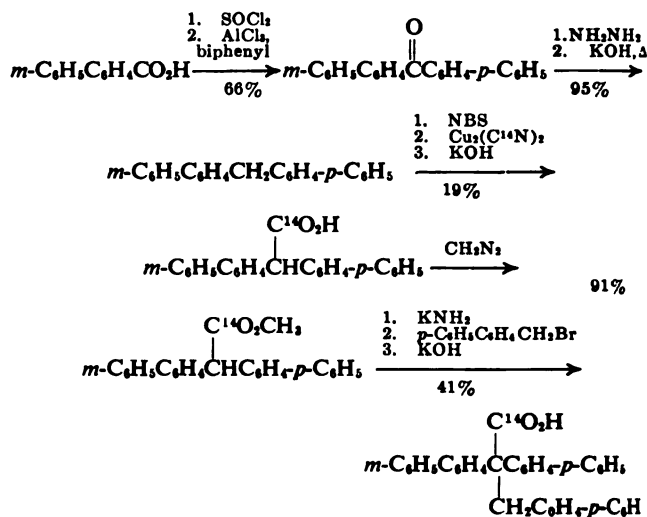


methane with cuprous cyanide at 160° gave the expected nitrile; however attempts to obtain this nitrile by reaction of the same bromide with sodium cyanide in acetone or in dimethyl sulfoxide²⁴ were unsuccessful. In the latter solvent, after addition of water 4,4'-diphenylbenzophenone (27% yield) was isolated in addition to bis(*p*-biphenyl)carbinol. The carbinol doubtlessly arose from hydrolysis of the bromide while the ketone possibly arose from O-alkylation of the solvent, followed by base-catalyzed elimination. Attempts to hydrolyze bis(*p*-biphenyl)ethanenitrile with dilute potassium hydroxide²⁵ in diethylene glycol at 80° resulted in essentially quantitative recovery of starting nitrile, while at 160° a 94% yield of bis(*p*-biphenyl)methane arose, doubtlessly by decarboxylation of the desired acid. At 120° bis(*p*-biphenyl)ethanoic acid was obtained in some 60% yield. Methyl bis(*p*-biphenyl)ethanoate was alkylated with 3-(bromomethyl)biphenyl in moderate yield by a procedure similar to that of Hauser;²⁶ saponification of the product gave the desired 3-*m*-biphenyl-2,2-bis(*p*-biphenyl)propanoic acid-1-C¹⁴ in an over-all yield of some 15% from bromobis(*p*-biphenyl)methane.

2-*m*-Biphenyl-2,3-bis(*p*-biphenyl)propanoic acid-1-C¹⁴ was synthesized according to the method of Scheme III. While all of the products from the reactions shown in Scheme III are new compounds, the reactions are quite similar to those which have been discussed earlier (Schemes I and II).

Reaction of 2-Chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane with Lithium. The reaction of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane with lithium in tetrahydrofuran at -65° followed by carbonation gave a carboxylic acid which was found to be identical with the sample of 3-*m*-biphenyl-3,3-bis(*p*-biphenyl)propanoic acid (mp 226.4–228.1°) whose synthesis is reported above. Thus this reaction with

Scheme III



lithium gave the expected organolithium compound and provides confirmation of the structure of the starting chloride.

In contrast reaction of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane with lithium in tetrahydrofuran at 0° gave according to Gilman's double-titration technique²⁷ a 45% yield of organolithium compound and, after carbonation, a 30% yield of crude acid of mp 208.0–209.5°. This acid was essentially identical with the sample of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid-1-C¹⁴ (mp 209.0–210.0°) prepared by Scheme III. According to an isotope-dilution analysis with this radioactive acid, 98.1 ± 0.5% of the crude acid was 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid. From this result it is obvious that a *p*-biphenyl group has undergone a 1,2 shift during the reaction of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane with lithium at 0° some time prior to carbonation.

In order to provide more information concerning the nature of this rearrangement, the reaction of the chloride was repeated as before with lithium at -65°. After the usual 3-hr stirring period at this temperature, titration indicated a 39% yield of organolithium compound. The solution was then allowed to warm to 0° and stirred at this temperature for 4 hr before carbonation. The crude acid was obtained in 38% yield and according to isotope-dilution analysis contained 98.6 ± 0.4% of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid. This result together with the first reaction at -65° implies that reaction of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane with lithium in tetrahydrofuran at -65° yields 2-*m*-biphenyl-2,2-bis(*p*-biphenyl)ethylolithium and that upon increase of temperature to 0° this organolithium compound rearranges to 1-*m*-biphenyl-1,2-bis(*p*-biphenyl)ethylolithium. Attempts to analyze the crude reaction product for 3-*m*-biphenyl-2,2-bis(*p*-biphenyl)propanoic acid (the product expected for migration of the *m*-biphenyl group) were unsuccessful; the 98.6 ± 0.4% yield of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid corresponds to the minimum amount of *p*-biphenyl migration in the product acid since the remainder of the crude product may have been an impurity (solvent, stopcock grease, etc.).

(27) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

(23) P. Gagnon, *Ann. Chim. (Paris)*, [10] **12**, 299 (1929).

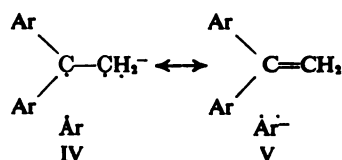
(24) Cf. A. C. Cope and A. S. Mehta, *J. Am. Chem. Soc.*, **86**, 5626 (1964).

(25) Cf. F. S. Prout, *et al.*, in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 95.

(26) W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

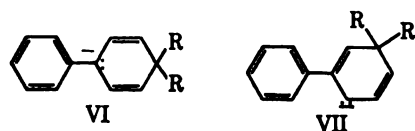
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present demonstration that in the rearrangement *n*-biphenyl-2,2-bis(*p*-biphenyl)ethylolithium the phenyl group migrates, after statistical correction unequal numbers of biphenyl groups, more than times more readily than the *m*-biphenyl group. This provides strong evidence against rearrangement proceeding by elimination of a biphenyl anion and re-union of this anion to the resulting 1,1-bis(biphenyl)ethene according to any of the detailed paths that have been previously discussed. This argument is based on the basis that a *m*-biphenyl anion should be eliminated more readily than a *p*-biphenyl anion if it agrees with the relative ease of formation^{9,10} of *p*-biphenyl anions during base-catalyzed hydrogen exchange upon biphenyl are pertinent and if, as stated, a 1,1-bis(*p*-biphenyl)ethene moiety is somewhat more stable than a 1-*m*-biphenyl-*p*-biphenyl moiety in the transition state for the elimination. With less certainty, the present migratory aptitudes rule out migration by way of a biphenyl radical, 1,1-bis(biphenyl)ethene radical anion. This conclusion is based on the probable argument that the 1,1-bis(biphenyl)ethene radical anion is somewhat more stable (thanks to greater electron delocalization) and is therefore more readily formed than 1-*m*-biphenyl-*p*-biphenylethene radical anion and also that *m*-biphenyl radical is likely more readily formed than *p*-biphenyl radical because of greater contribution of the polar structure V in the transition state for cleavage. Structure V should be more stable when the



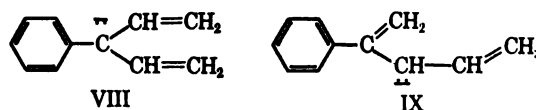
being cleaved is *m*-biphenyl rather than *p*-biphenyl because of the greater stability of a *m*-biphenyl anion than *p*-biphenyl anion, which is implied by the greater ease of formation of the former. For rearrangement proceeding by way of cleavage into a biphenyl radical and 1,1-bis(biphenyl)ethene radical anion, we would, therefore, anticipate that *m*-biphenyl would cleave and hence appear to migrate more readily than *p*-biphenyl radical, a result contrary to the observed migratory aptitudes.

The observed migratory aptitudes are in good agreement with rearrangement proceeding by way of a cyclic transition state or intermediate such as II or III. The energies of II and III which are of significant energetic importance are contained in structures VI and VII,



actively, which are illustrated for simplicity by the canonical structures. In the simple Hückel molecular orbital approximation, the energies of structures VI and VII are the same as those of structures VIII and IX, respectively. Calculations²⁹

A. Streitwieser, Jr., and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Vol. I, Pergamon Press Inc., New York, 1965, pp 92 and 94.



show that VIII is more stable than IX by 0.97 $|\beta|$ unit. While $|\beta|$ must be regarded as an empirical parameter, a value of 35 kcal/mole has been found²⁹ for attachment of a proton upon a benzenoid ring to give a cationic σ complex. If this value of $|\beta|$ is assumed in the present case, the equilibrium ratio of VI to VII (or of II to III after statistical correction for unequal numbers of migrating groups) is calculated to be 525; if $|\beta|$ is 20 kcal/mole, the calculated ratio is 36. These calculations suffice to show that transition states or intermediates II and III differ sufficiently in energy to account for the observed highly preferential migration of *p*-biphenyl over *m*-biphenyl.

While we believe that the present migratory aptitudes are best accommodated by rearrangement occurring in a carbanion by way of II or III, it might be noted that preferential migration of *p*-biphenyl over *m*-biphenyl would also be expected if the rearrangement occurred in the corresponding free radical through transition states or intermediates differing from II or III by one less electron each. Previously it has been argued that the greater migratory aptitude of benzyl over phenyl in rearrangement of 2,2,3-triphenylpropyllithium provides evidence for rearrangement occurring in a carbanion rather than a free radical.⁷ While this general argument still appears correct, the conclusion is restricted to migration of benzyl and is not applicable to migration of phenyl in 2,2,2-triphenylethyllithium since migration of benzyl occurs by an intermolecular process while migration of phenyl occurs by an intramolecular process.^{3,5} It has also been argued that rearrangement of phenyl in 2,2-diphenylpropyllithium occurs in a carbanion rather than a free radical, because *inter alia* rearrangement of 2-*p*-tolyl-2-phenylpropyllithium occurs with preferential migration of phenyl over *p*-tolyl;⁸ in this argument it was assumed on general grounds that *p*-tolyl would migrate more readily than phenyl for rearrangement of a free radical. More recently, however, it has been demonstrated that phenyl migrates more readily than *p*-tolyl in rearrangement of free radicals.³⁰ While for 1,2 shifts of phenyl and other aryl groups occurring during rearrangements of organolithium compounds, the evidence in favor of rearrangement occurring in a carbanion rather than a free radical is not as strong as once supposed; the general evidence^{8,31} can still be most simply accommodated on the view that these are rearrangements of carbanions.

Finally it is of interest to note that intramolecular rearrangements of carbanions or organometallic compounds have been observed for 1,2 shifts of vinyl³² and carbonyl³³ as well as aryl. These reactions,

(29) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1962, p 342.

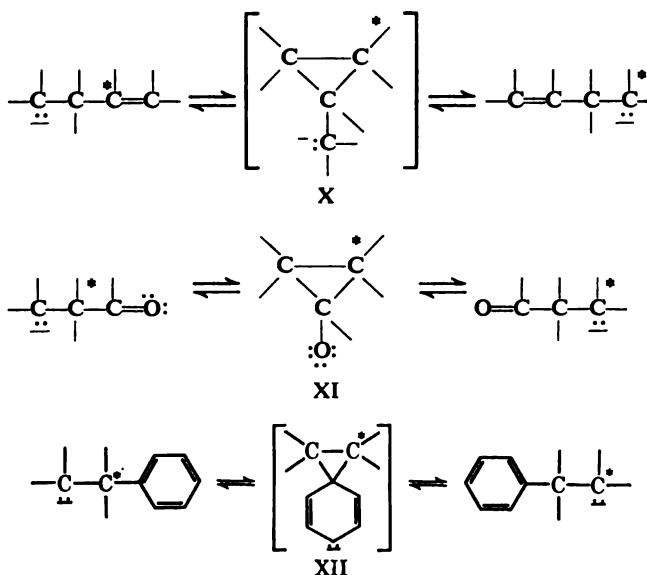
(30) C. Rüchardt and R. Hecht, *Tetrahedron Letters*, 961 (1962).

(31) E. Grovenstein, Jr., and L. P. Williams, Jr., *J. Am. Chem. Soc.*, **83**, 412 (1961).

(32) D. J. Patel, C. L. Hamilton, and J. D. Roberts, *ibid.*, **87**, 5144 (1965); P. T. Lansbury, V. A. Pattison, W. A. Clement, and J. Sidder, *ibid.*, **86**, 2247 (1964); M. L. Silver, P. R. Shafer, J. E. Norlander, C. Rüchardt, and J. D. Roberts, *ibid.*, **82**, 2646 (1960).

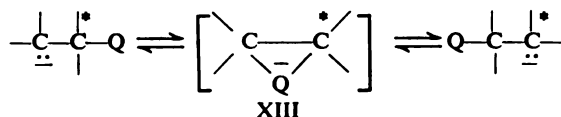
(33) A. Nickon, J. L. Lambert, R. O. Williams, and N. H. Werstiuk, *ibid.*, **88**, 3544 (1966); A. Nickon, J. L. Lambert, and J. E. Oliver, *ibid.*, **88**, 2787 (1966); A. Nickon and J. L. Lambert, *ibid.*, **88**, 1905 (1966); J. P. Freeman and J. H. Plonka, *ibid.*, **88**, 3662 (1966).

stripped of complicating details such as the role of the metallic cation and solvent, can be represented in the simplified form



The remarkable similarity of these three rearrangements does not appear to have received adequate emphasis. While it is not known whether the species (X and XII) shown in brackets are transition states or reaction intermediates, at least cyclopropylcarbinyllithium and magnesium derivatives are stable under certain experimental conditions.³²

Vinyl, carbonyl, and aryl groups have in common an unsaturated character which permits these groups to accept additional electrons during the course of rearrangement as illustrated by the fairly classical structures of the proposed intermediates (X, XI, XII). It seems reasonable also that groups which are "unsaturated" because of the presence of vacant d or p orbitals on the atom Q to which the carbanionic center becomes attached (see XIII) should have high migratory aptitudes



in carbanion rearrangements.³⁴ A pertinent example in the field of nitrogen chemistry is provided by the recent report of facile base-catalyzed 1,2 shift of the trimethylsilyl group in various hydrazines;³⁵ here a vacant 3d orbital of silicon is likely utilized during rearrangement. These considerations imply that the area of carbanion rearrangements is more general than usually supposed and that additional research in this area is desirable. Thus carbanion rearrangements involving a 1,2 shift of an acetylenic group (e.g., $\text{C}\equiv\text{CPh}$) appear likely. Also numerous possibilities involving hetero atoms (Zn, B, Al, Si, Ge, Sn, P) centrally located in the group Q appear promising. In some of these the intermediate XIII may be isolable; in others polymerization, elimination, or other side reactions may occur in place of rearrangement.

(34) A similar conclusion has been arrived at independently and communicated to us recently by Professor Robert West.

(35) R. West, M. Ishikawa, and R. E. Bailey, *J. Am. Chem. Soc.*, **88**, 4648 (1966); R. E. Bailey and R. West, *ibid.*, **86**, 5369 (1964).

Experimental Section³⁶

m-Biphenylbis(p-biphenyl)carbinol. Into a 1000-ml Morton flask equipped with a high-speed stirrer³⁷ and dropping funnel, 42.0 g (0.180 mole) of 3-bromobiphenyl was added slowly onto 3.33 g (0.480 g-atom) of finely cut lithium and 0.1 ml of methyl iodide in 550 ml of tetrahydrofuran (freshly distilled from NaAlH_4) at 5° under an atmosphere of dry nitrogen. After addition of about one-third of the bromide, the reaction temperature was lowered to -25°, and the remainder of the bromide was added. After addition of the bromide was completed, the deep purple solution was stirred for 1 hr at -25°. Gilman titration³⁸ indicated the formation of 105 mmoles (58% yield) of 3-lithiotiphenyl. The solution was siphoned through a glass-wool filter (to remove unreacted lithium) under a nitrogen atmosphere into a 3-l. Morton flask. A solution of 30.1 g (0.090 mole) of 4,4'-diphenylbenzophenone³⁹ in 1500 ml of dry tetrahydrofuran was added at a flask temperature of 5°, over a period of 1 hr, and the resulting green solution was stirred vigorously at room temperature for 1 hr. The reaction mixture was acidified with 400 ml of 5% hydrochloric acid and the tetrahydrofuran removed on a rotating evaporator. The remaining aqueous suspension of solid was extracted with ether. A quantity of off-white solid (7.8 g), which was insoluble in both aqueous and ether phases, was isolated by filtration and dried *in vacuo*. The ether extract upon evaporation to dryness yielded an orange solid residue which was washed with cyclohexane to remove biphenyl. The total weight of crude white and orange product was 20.6 g (mp 201–229°) of a mixture of the desired carbinol and unreacted ketone. Repeated recrystallizations from benzene removed most of the ketone and gave 11.0 g (0.022 mole or 25% yield based on starting ketone) of white powder of mp 227–231°. A 2.00-g sample of this powder was subjected to vacuum sublimation at 230° (0.02 mm), and the sublimate was recrystallized four times from benzene to give 0.83 g of compound, mp 231–233°. This product upon admixture with 4,4'-diphenylbenzophenone (mp 235–237°) had mp 203–222°; moreover the infrared spectrum of the product was substantially different from that of the ketone (O–H absorption at 2.75 μ and absence of carbonyl absorption at 6.1 μ).

Anal. Calcd for $\text{C}_{27}\text{H}_{20}\text{O}$: C, 90.95; H, 5.78. Found: C, 90.93, 90.90; H, 5.79, 5.88.

Reaction of a portion of the carbinol with acetyl chloride⁴⁴ gave, after recrystallization of the product from benzene, a white solid, mp 128–133° dec. A portion of the sample in ethanol failed to give a precipitate when treated with acidified silver nitrate (triphenylmethyl chloride under these conditions gave an instantaneous white precipitate) and the sample also gave a negative sodium fusion test for halogen. The infrared spectrum of the product showed strong absorption at 7.9 μ (C–O stretching frequency), and the nmr spectrum showed aromatic but no aliphatic hydrogens. The product is likely bis[m-biphenylbis(p-biphenyl)methyl] ether.

Bis(p-biphenyl)methane. To a solution of 4,4'-diphenylbenzophenone (75.0 g, 0.224 mole) in 2000 ml of triethylene glycol containing 38 g of potassium hydroxide at 120° was added 44.7 g (0.90 mole) of hydrazine hydrate, and the mixture was heated at gentle reflux (175°) for 3 hr. Excess hydrazine-water was then allowed to distil from the reaction mixture until a flask temperature of 210° was attained and the mixture was maintained at this temperature for 26 hr. The mixture was cooled to room temperature, diluted with an equal volume of water, and filtered. The precipitate was washed well with water and this white solid after drying amounted to 69.8 g (97% yield) of product of mp 157–161°. One recrystallization from absolute ethanol (the product was placed in the cup of a Soxhlet extraction apparatus and extracted with ethanol in order to avoid use of a large quantity of solvent) gave 63.0 g of white crystalline product of mp 162–163° [lit.³⁹ bis(p-biphenyl)methane

(36) Melting points were taken on a Mel-Temp apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates A-60 instrument. Infrared spectra were determined on a Perkin-Elmer Infracord Model 137 spectrophotometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Bernhardt Microanalytical Laboratory, Mülheim, West Germany. The technique of combustion and counting of radioactive compounds was the same as that described earlier [E. Grovenstein, Jr., S. Chandra, C. E. Collum, and W. E. Davis, Jr., *J. Am. Chem. Soc.*, **88**, 1275 (1966)].

(37) A. A. Morton and L. M. Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).

(38) C. Calzolari and C. Furlani, *Ann. Triest. Cura Univ. Trieste, Sez. 2*, 22–23, 63 (1953); *Chem. Abstr.*, **49**, 938g (1955).

(39) J. Weiler, *Chem. Ber.*, **7**, 1188 (1874).

2^o). The average yield of crude product from five similarations was 96%.

bis(*p*-biphenyl)methane. A solution of 11.0 g (0.0343 mole) *p*-biphenyl)methane, 6.71 g (0.0377 mole) of *N*-bromosuccinide, and 0.05 g of dibenzoyl peroxide in 300 ml of carbon lorida was heated at reflux 76 hr. Three additional 0.05-g is of dibenzoyl peroxide were added periodically to the n mixture. The solution was allowed to cool to room temere and succinimide was removed by filtration. The filtrate aporated to dryness on a rotating evaporator and the lightid residue, after a recrystallization from benzene-petroleum gave 10.5 g (0.0264 mole, 77% yield) of off-white crystals, 38–141°. After further recrystallization from benzene-um ether the product had mp 142–144° [lit.⁴⁰ bromobis-venyl)methane mp 143°]. The average yield of six such ations was 73%.

1,2-Tetrakis(*p*-biphenyl)ethane. A. Preparation with 3-*p*-biphenyl. From the reaction of 9.3 g (0.040 mole) of 3-*p*-biphenyl with 0.61 g (0.088 g-atom) of lithium in the usual n apparatus, a solution of 24 mmoles (60% yield by Gilman n⁴¹) of 3-lithiobiphenyl in 300 ml of tetrahydrofuran was ed at –20°. A solution of 8.0 g (0.020 mole) of bromobis-venyl)methane in 50 ml of tetrahydrofuran was added to the lithium compound at –20° over a period of 20 min. The ng mixture was stirred for 10 min and then forced onto solid dioxide. To the carbonated mixture was added 200 ml of ydrochloric acid, and the mixture was extracted with five l portions of ether. A quantity of solid, which remained ded in the ether layers, was isolated by filtration and dried : 3.96 g of product, mp 260–270°. An additional 0.67 g of me product [a total of 74% yield of crude 1,1,2,2-tetrakis(*p*-ylyl)ethane] was isolated from the ether extract together with ; of 3-phenylcarboxylic acid and 2.6 g of biphenyl. A xortion of the hydrocarbon, mp 260–270°, was heated at 260° nm) to remove 0.05 g of volatile impurity. The residue after xcrystallizations from chloroform and two recrystallizations toluene amounted to 0.83 g of white crystals, mp 275–279° l,1,2,2-tetrakis(*p*-biphenyl)ethane mp 276–279°].

l. Calcd for C₂₄H₂₀: C, 94.00; H, 6.00. Found: C, 93.87; H, 6.17, 5.97.

B. Preparation with *m*-Biphenylmagnesium Bromide. A n of *m*-biphenylmagnesium bromide was prepared by dropddition of 13.3 g (0.057 mole) of 3-bromobiphenyl in 50 ml of ydrofuran to 2.53 g (0.104 g-atom) of magnesium turnings ided in 500 ml of tetrahydrofuran at reflux temperature in ual Morton apparatus. After 4 hr of vigorous stirring, the re was cooled to 25° and a solution of 11.4 g (28.6 mmoles) of bis(*p*-biphenyl)methane in 100 ml of tetrahydrofuran ided dropwise over a period of 20 min and stirring was con- for another 20 min before addition of 100 ml of 5% hydro- c acid. The organic layer was separated, the aqueous layer tracted with ether, and the ether extract was combined with ganic layer. Evaporation to dryness gave a gummy solid when washed with chloroform gave 6.2 g of white powder, 69–277°. Concentration of the chloroform solution and on of ethanol gave upon chilling 2.0 g of solid which when l at 245° (0.02 mm) gave 0.38 g of sublimate, mp 192–207°. residue upon recrystallization from toluene afforded 1.3 g of ct, mp 270–276°. The total yield of high-melting product herefore 7.5 g (83% yield). After recrystallization from e the product had mp 274–278°; the infrared absorption um of this product was identical with that of the previous e of 1,1,2,2-tetrakis(*p*-biphenyl)ethane prepared from 3-*p*-biphenyl. The sublimate after recrystallization from chloro- ethanol had mp 205–208° and is likely *m*-biphenylbis(*p*-ylyl)methane. It was thought possible that the large excess gnesium used in this reaction might have been responsible for rmation of the coupling product of bromobis(*p*-biphenyl)- ne. Hence the reaction was repeated but the solution of enyl)magnesium bromide was filtered through a glass- plug in order to remove unreacted magnesium metal before on of bromobis(*p*-biphenyl)methane; however, an 84% of crude 1,1,2,2-tetrakis(*p*-biphenyl)ethane, mp 271–277°, btained.

biphenylbis(*p*-biphenyl)methane. The Grignard reagent romobiphenyl was prepared in 500 ml of ethyl ether by reac- f 18.6 g (0.080 mole) of 3-bromobiphenyl with 2.04 g (0.084

g-atom) of magnesium turnings at the boiling point of ether with stirring in the usual Morton apparatus for 6 hr. To the solution of *m*-biphenylmagnesium bromide in refluxing ether was added over a 30-min period a slurry of 16.0 g (0.040 mole) of bromobis- (*p*-biphenyl)methane in 200 ml of ether, and the mixture was stirred for 30 min before decomposition with 100 ml of 5% hydro- chloric acid. A white solid (12.1 g), insoluble in both aqueous and ether phases, was isolated by filtration and had mp 203–227°. The ether phase was condensed to about 150 ml and yielded 2.46 g of white solid, mp 201–229°. The two fractions, after a loss of 4.0 g of the first fraction during an attempt at recrystallization from toluene, were combined and sublimed at a bath temperature of 210–230° (0.03 mm). The sublimate amounted to 8.3 g (44% yield) of product, mp 202–210°. Another vacuum sublimation and two recrystallizations from chloroform-ethanol gave 7.5 g of white solid, mp 205–211°. A chloroform solution of this solid was extracted with several portions of 94% sulfuric acid. The chloro- form solution after addition of ethanol and cooling deposited 5.9 g of white solid, mp 211–213°. Vacuum sublimation gave 4.9 g of a white powder, mp 212–213.5°.

Anal. Calcd for C₂₇H₂₂: C, 94.03; H, 5.97; mol wt, 472. Found: C, 93.71, 93.87; H, 6.18, 6.02; mol wt, 508.

A more convenient synthesis of *m*-biphenylbis(*p*-biphenyl)- methane utilized benzene to dissolve the bromobis(*p*-biphenyl)- methane. From the reaction of 11.65 g (0.050 mole) of 3-bromo- biphenyl with 1.22 g (0.050 g-atom) of magnesium turnings, a solu- tion of 0.040 mole (80% yield) of *m*-biphenylmagnesium bromide in 250 ml of ethyl ether was prepared. (The quantitative analysis⁴¹ of the Grignard reagent was carried out by hydrolyzing an aliquot with water, acidifying with dilute sulfuric acid, adjusting the pH to 10 with an ammonium hydroxide-ammonium chloride buffer, and titrating for magnesium ion with a solution of the disodium salt of ethylenediaminetetraacetic acid to an end point marked with Eriochrome Black T. For confirmation a portion of the original acidified hydrolysate was titrated potentiometrically for bromide ion with standardized silver nitrate solution.) A solution of 14.0 g (0.035 mole) of bromobis(*p*-biphenyl)methane in 100 ml of dry benzene was added to the stirred solution of Grignard reagent at room temperature over a period of 30 min, and the resulting mixture was heated at reflux for 1 hr. The reaction mixture was decom- posed by addition of 150 ml of 5% hydrochloric acid. A quantity of solid, insoluble in both aqueous and organic phases, was removed by filtration and after drying weighed 14.3 g, mp 193–229°. This material was subjected to vacuum sublimation (0.05 mm); the fraction collected at a bath temperature of 225–240° weighed 11.9 g (72% yield) and had mp 203–208°. The brown residue from the sublimation weighed 2.05 g (18% yield of crude product) and after recrystallization from toluene had mp 272–277°; this material is identified as 1,1,2,2-tetrakis(*p*-biphenyl)ethane and had the same infrared absorption spectrum as the previous more highly purified sample. The ether-benzene phase was evaporated to dryness and the residue extracted with 200 ml of cyclohexane; the undissolved solid consisted of 1.3 g (11% yield) of a substance of mp 147–150°, which was identified as bis(*p*-biphenyl)methanol on the basis of the identity of its infrared absorption spectrum with that of an authentic sample. The 11.9 g of hydrocarbon after another vacuum sublimation and two recrystallizations from chloroform-ethanol gave 8.1 g of white crystals, mp 208–211°. Two further such crystallizations and a final vacuum sublimation gave 5.9 g of product, mp 212–214°, as obtained earlier for *m*- biphenylbis(*p*-biphenyl)ethane.

2-Chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane. Potas- sium amide was prepared in a 500-ml Morton flask equipped with a Morton stainless steel, high-speed stirrer and a Dry Ice-acetone condenser, from the reaction of 3.91 g (0.100 g-atom) of potassium with 200 ml of anhydrous ammonia containing a small crystal of ferric nitrate. After the blue color of the solution of potassium metal had changed to gray-brown a slurry of 4.72 g (0.010 mole) of *m*-biphenylbis(*p*-biphenyl)methane in 100 ml of dry ether was added and the resulting mixture stirred vigorously at reflux for 8 hr. The deep purple-blue solution was siphoned under an atmos- phere of dry nitrogen into a flask containing 30 ml of freshly dis- tilled methylene chloride at –30°. The blue color disappeared after the mixture was stirred for 15 min. Unreacted potassium amide was destroyed by addition of 5.35 g (0.100 mole) of solid ammonium chloride; then 200 ml of water and 250 ml of methylene chloride was added. The organic phase was separated, dried over

W. Schlenk, J. Renning, and G. Racky, *Chem. Ber.*, 44, 1178

(41) We are indebted to Dr. E. C. Ashby for this procedure.

anhydrous magnesium sulfate, and evaporated to dryness on a rotating evaporator. The light tan solid residue was recrystallized from methyl ethyl ketone to give 4.61 g of nearly white powder, mp 219–223° (88.5% yield). This material after five recrystallizations from methyl ethyl ketone gave 3.3 g of white product, mp 223.2–224.3°.

Anal. Calcd for $C_{28}H_{22}Cl$: C, 87.59; H, 5.61; Cl, 6.80. Found: C, 87.41, 87.35; H, 5.81, 5.67; Cl, 7.10, 6.97.

In a similar preparation an 84% yield of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane, mp 218–222°, was obtained.

3-*m*-Biphenyl-3,3-bis(*p*-biphenyl)propanoic Acid. In an unsuccessful experiment modeled after the procedure of Hellerman,²² 2.44 g (5.0 mmoles) of *m*-biphenylbis(*p*-biphenyl)carbinol was ground up in a mortar and pestle with 2.6 g (25 mmoles) of malonic acid and then the mixture was heated at a bath temperature of 225° under a nitrogen atmosphere under conditions such that volatile products could distill from the reaction mixture. Additional 2.6-g portions of malonic acid were added at three 3-hr intervals, and after 12 hr of heating the reaction mixture was ground with an excess of potassium hydroxide and then thoroughly stirred with 500 ml of hot water. Undistilled solid (2.27 g, mp 225–233°) was isolated and identified as unreacted carbinol by its infrared spectrum; acidification of the filtrate failed to yield detectable carboxylic acid. An experiment in which *m*-biphenylbis(*p*-biphenyl)carbinol was heated at reflux with a molecular equivalent of acetic anhydride and 25% excess of malonic acid for 3 hr and then, after removal of acetic anhydride (*in vacuo*), heating was continued at reflux for 6 hr with 1 molar equiv of propionic anhydride, gave an 86% recovery of unreacted carbinol and a dark resin which yielded none of the desired carboxylic acid upon attempted crystallization. In a successful experiment, to an intimate mixture of *m*-biphenylbis(*p*-biphenyl)carbinol (1.00 g, 2.05 mmoles) and malonic acid (2.13 g, 20.5 mmoles) was added 0.35 g (2.2 mmoles) of *n*-butyric anhydride, and the mixture was heated rapidly in an oil bath at 200° until gas evolution had ceased (15 min). After work-up as in the first experiment, 0.73 g of unreacted carbinol was recovered and 0.198 g (16.7% yield) of acid, mp 223–227°. After three recrystallizations from ethanol white crystals, mp 226–228.1°, were obtained.

Anal. Calcd for $C_{38}H_{30}O_2$: C, 88.27; H, 5.70. Found: C, 88.13, 88.01; H, 5.69, 5.60.

Bis(*p*-biphenyl)ethanenitrile-1-C¹⁴. In a preliminary experiment a solution of 0.98 g (0.020 mole) of sodium cyanide and 4.0 g (0.010 mole) of bromobis(*p*-biphenyl)methane in 300 ml of dimethyl sulfoxide (Baker Analyzed Reagent) was warmed at about 60° with stirring for 36 hr while protected from atmospheric moisture by a drying tube filled with anhydrous $CaSO_4$. The solution was diluted with 800 ml of water and the solid which separated was isolated by filtration. Recrystallization of the solid from ethanol gave 0.90 g (27% yield) of a product, mp 234–236°, which was identified as 4,4'-diphenylbenzophenone according to infrared spectral comparisons. From the mother liquors was isolated 2.4 g (72% yield) of a compound, mp 145–150°, which was primarily bis(*p*-biphenyl)carbinol according to its infrared spectrum.

In another experiment 0.98 g (0.020 mole) of sodium cyanide and 4.0 g (0.010 mole) of bromobis(*p*-biphenyl)methane in 250 ml of acetone (freshly distilled from P_2O_5) was heated at reflux with stirring for 72 hr with protection from atmospheric moisture. After dilution with water, only impure bis(*p*-biphenyl)carbinol (2.6 g, 77% yield) was recovered.

In a successful experiment cuprous cyanide-C¹⁴ was prepared from sodium cyanide-C¹⁴ (from Tracerlab, Inc.; activity of 9.8 μ curies/mole) according to the procedure²³ for nonradioactive compounds. Freshly dried cuprous cyanide (0.737 g, 8.25 m-equiv) was mixed with 2.98 g (7.48 mmoles) of bromobis(*p*-biphenyl)methane and the mixture heated at 160° under an atmosphere of dry nitrogen for 12 hr. The organic product was extracted from the cooled melt with acetone, the acetone extract evaporated to dryness, and the residue subjected to vacuum sublimation (0.05 mm). The fraction collected at a bath temperature of 150–160° weighed 0.73 g (29% yield) and had mp 146–149°; this was identified as impure bis(*p*-biphenyl)carbinol by its infrared spectrum. The fraction collected at 175–200° weighed 1.83 g (71% yield) and had mp 182–186°. A recrystallization of this material from ethanol gave 1.62 g of white crystals, mp 184–186°. In three such prepara-

tions the average yield of crude bis(*p*-biphenyl)ethanenitrile was 63%. The analytical sample after another recrystallization from ethanol and another vacuum sublimation had mp 185.8–187.2°.

Anal. Calcd for $C_{26}H_{18}N$: C, 90.40; H, 5.54; N, 4.05. Found: C, 90.42, 90.37; H, 5.74, 5.74; N, 3.75, 3.78.

Methyl Bis(*p*-biphenyl)ethanoate-1-C¹⁴. In a preliminary experiment bis(*p*-biphenyl)ethanenitrile (0.89 g, 2.6 mmoles) was heated with 125 ml of 0.082 *N* KOH in diethylene glycol at 80° for 10 hr; however, upon cooling to room temperature and dilution with water, the starting nitrile was precipitated (99% recovery). When this experiment was identically repeated except that the temperature was 160° for 8 hr, dilution with water gave 0.77 g (94% yield) of a compound, mp 159–161°, which was identified as bis(*p*-biphenyl)methane by mixture melting point and infrared spectral comparisons. The following procedure was the most successful of a number of others tried for hydrolysis of the nitrile to the corresponding carboxylic acid. A solution of 32 g (0.50 mole) of potassium hydroxide in 100 ml of water was added to a solution of 2.00 g (5.80 mmoles) of bis(*p*-biphenyl)ethanenitrile in 400 ml of diethylene glycol and the resulting solution heated at 120 ± 10° for 48 hr. The solution was cooled to room temperature, diluted with 1.0 l. of water, and filtered to give 0.75 g of precipitate. Vacuum sublimation of this material at a bath temperature of 155–185° (0.05 mm) gave 0.170 g (9.1% yield) of bis(*p*-biphenyl)methane (mp 160–162°) and at 170–190° 0.45 g (22% recovery) of bis(*p*-biphenyl)ethanenitrile. Acidification of the alkaline filtrate with concentrated hydrochloric acid and filtration gave 1.29 g (61% yield) of acid, mp 201–206°. Two recrystallizations from 95% ethanol gave 0.99 g of white crystals, mp 206.5–207.5° [lit.²⁴ bis(*p*-biphenyl)ethanoic acid mp 208°]. Repetition of this hydrolysis with bis(*p*-biphenyl)ethanenitrile-1-C¹⁴ gave 60% yield of bis(*p*-biphenyl)ethanoic acid-1-C¹⁴. Reaction of an ethereal solution of 0.82 g (2.25 mmoles) of bis(*p*-biphenyl)ethanoic acid-1-C¹⁴ with an excess of diazomethane in ether at 0° gave, after evaporation of the ether and recrystallization of the residue from methanol, 0.76 g (89% yield) of methyl ester, mp 125–127°. After two further recrystallizations from methanol the product had mp 126.3–127.8°.

Anal. Calcd for $C_{27}H_{22}O_2$: C, 85.69; H, 5.86. Found: C, 86.00, 85.76; H, 5.67, 5.73.

3-(Bromoethyl)biphenyl. A solution of 75.0 g (0.446 mole) of 3-methylbiphenyl (Aldrich Chemical Co.), 87.2 g (0.490 mole) of *N*-bromosuccinimide, and 0.2 g of dibenzoyl peroxide in 400 ml of carbon tetrachloride was heated at reflux. After 3 hr, an additional 0.2 g of dibenzoyl peroxide was added, and then the mixture was heated at reflux for an additional 22 hr. Insoluble succinimide was removed by filtration, solvent was removed on a rotating evaporator, and the residue distilled *in vacuo*. The fraction boiling at 165–180° (1.5 mm) weighed 82.3 g (75% yield) and solidified upon standing. This orange solid, after three recrystallizations from petroleum ether, gave off-white crystals, mp 56.5–58.0°.

Anal. Calcd for $C_{12}H_{11}Br$: C, 63.18; H, 4.48; Br, 32.34. Found: C, 63.13; 63.33; H, 4.49, 4.55; Br, 32.48, 32.60.

3-*m*-Biphenyl-2,2-bis(*p*-biphenyl)propanoic Acid-1-C¹⁴. In a 500-ml Morton flask equipped with a stainless-steel Morton high-speed stirrer and Dry Ice-acetone condenser was condensed 200 ml of anhydrous ammonia. Under an atmosphere of dry nitrogen, 0.340 g (8.7 mg-atoms) of potassium and a small crystal of ferric nitrate was added, and the solution stirred for 1 hr. To the resulting solution of potassium amide was added 2.08 g (5.5 mmoles) of methyl bis(*p*-biphenyl)ethanoate-1-C¹⁴ in 50 ml of anhydrous ether, and the solution stirred for 2 hr. A solution of 1.43 g (5.8 mmoles) of 3-(bromomethyl)biphenyl in 50 ml of anhydrous ether was added over a period of 30 min and the resulting solution stirred for 30 min at reflux. Ammonium chloride (1.0 g) was added, and the ammonia was allowed to evaporate from the mixture. After 100 ml of water was added, the ether phase was separated and allowed to evaporate to dryness. The yellow solid residue was heated at reflux for 15 hr with 250 ml of 15% aqueous potassium hydroxide. A small amount of undissolved, brown solid was removed by filtration and the filtrate acidified with hydrochloric acid. The white solid (2.17 g) which separated from the solution was isolated by filtration and had mp 182–200°. This material was subjected to partial vacuum sublimation at a bath temperature of 200–220° (0.04 mm). The sublimate, after recrystallization from aqueous ethanol, weighed 0.238 g (12% yield) and had mp 205–207°. This substance was identified as bis(*p*-biphenyl)ethanoic

(42) J. V. Supniewski and P. L. Salzberg, "Organic Syntheses," Coll. Vol. I, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p 46.

(43) E. Shilow and S. Burmistrov, *Chem. Ber.*, **68**, 582 (1935).

infrared spectral comparisons. The residue from the sublimation, after two recrystallizations from absolute ethanol, gave 44% yield of white solid, mp 202–204.5°. After two more recrystallizations from ethanol the melting point was 203.5–204.5°.

Calcd for $C_{23}H_{18}O_2$: C, 88.27; H, 5.70. Found: C, 88.34; H, 5.60, 5.68.

3-biphenylcarboxylic Acid. A solution of *m*-biphenylmagnesium bromide in 250 ml of ether was prepared by the reaction of 23.3 g (0.1 mole) of 3-bromobiphenyl (K and K Laboratories, Inc.) with 15 g (0.105 g-atom) of magnesium turnings. The Grignard reagent was siphoned onto a large excess of solid carbon dioxide or the usual work-up 10.6 g (53% yield) of acid, mp 160–162° was obtained. After two recrystallizations from ethanol 8.7 g of white crystals was obtained, mp 162–163° (lit.⁴⁴ mp 160°).

Diphenylbenzophenone. This ketone was synthesized by a procedure like that used for 4,4'-diphenylbenzophenone.³⁸ Reagents: 18.0 g (0.091 mole) of 3-biphenylcarboxylic acid and 150 ml of thionyl chloride at reflux temperature for 2 hr; 10 ml of *p*-phenylbenzoyl chloride, to which, after removal of excess thionyl chloride by distillation, was added 250 ml of carbon disulfide and 10 g of anhydrous aluminum chloride, and 28.1 g (0.182 mole) of *p*-phenyl. After the initial vigorous reaction had subsided the mixture was heated at reflux with stirring for 3 hr. The black tar-like product, after standing overnight, was isolated by filtration, washed with carbon disulfide (to remove unreacted biphenyl), and then washed with ice-cold concentrated hydrochloric acid. The residue was separated by filtration and washed well with water and 5% ethanol. The crude product (26.9 g, mp 131–136°) was recrystallized from benzene-petroleum ether (amounted to 66% yield) of white crystals, mp 138–141°. Two recrystallizations from ethanol gave 15.5 g of crystals of mp 142–144°. An analytical sample after two further recrystallizations from ethanol and sublimation [at a bath temperature of 150° (0.02 mm)] gave mp 143.8–145.0°.

Calcd for $C_{23}H_{18}O$: C, 89.79; H, 5.43. Found: C, 89.71; H, 5.43.

3-biphenyl-*p*-biphenylmethane. A solution of 14.2 g (0.0425 mole) of 3,4'-diphenylbenzophenone, 8.5 g (0.17 mole) of hydrazine hydrate, and 8.4 g (0.128 mole) of potassium hydroxide pellets in 600 ml of diethylene glycol was heated at 175° for 2 hr. The excess hydrazine was allowed to distil from the reaction mixture, where the temperature was raised to 205° and maintained at that temperature for 36 hr. The solution was cooled to room temperature, diluted with 1500 ml of water, and extracted with six 500-ml portions of ether. The ether extract yielded 13.0 g (95% yield) of white solid, mp 92–96°. After two recrystallizations from ethanol and a distillation in a sublimation apparatus [bath temperature 150° (0.03 mm)], 9.2 g of hydrocarbon, mp 99.3–100.4°, was obtained.

Calcd for $C_{23}H_{20}$: C, 93.71; H, 6.29. Found: C, 93.55; H, 6.43, 6.31.

3-biphenyl-*p*-biphenylmethane. A solution of 9.10 g (0.0425 mole) of *m*-biphenyl-*p*-biphenylmethane, 5.35 g (31.3 mmol) of *N*-bromosuccinimide, and 0.1 g of dibenzoyl peroxide in 100 ml of carbon tetrachloride was heated at reflux for 48 hr. An additional 0.05 g of dibenzoyl peroxide was added after the first 24 hr of reaction. Insoluble succinimide, formed in the reaction, was removed by filtration and the filtrate evaporated to dryness on a rotary evaporator. The residue upon recrystallization from cyclohexane gave 3.2 g of yellow powder, mp 142–144°; recrystallization of this product gave 2.7 g of nearly white solid, mp 145°, which was identified as 3,4'-diphenylbenzophenone by its infrared spectrum. Evaporation of the mother liquor from the cyclohexane crystallization gave 6.2 g of nearly white powder, mp 94–100°; three recrystallizations of this material from cyclohexane gave 4.9 g of white product, mp 102–103.5°. A portion of this product upon two further recrystallizations from cyclohexane had mp 103.4–104.7°; since the infrared spectrum of this substance showed appreciable contamination with 3,4'-diphenylbenzophenone, the crude bromide was not submitted for analysis but was employed for synthesis of the following acid.

3-biphenyl-*p*-biphenylethanoic Acid-1-C¹⁴. A mixture of 4.14 g (0.021 mole) of crude bromo-*m*-biphenyl-*p*-biphenylmethane (mp 102–103.5°) and 1.02 g (11.4 mequiv) of cuprous cyanide (radioactivity was 9.8 μ curies/mmequiv) was heated at 160° for 2 hr under an atmosphere of dry nitrogen. The organic phase was extracted from the cooled melt with chloroform, the

chloroform extract evaporated to dryness, and the residue distilled in an apparatus for vacuum sublimation at a bath temperature of 150–195° (0.03 mm). The product amounted to 3.27 g, mp 135–148°. Recrystallization from ethanol gave 3.0 g of white solid of mp 135–148°, whose infrared spectrum indicated that it was a mixture of *m*-biphenyl-*p*-biphenylethanoic acid and 3,4'-diphenylbenzophenone. This mixture was dissolved in 200 ml of diethylene glycol and a solution of 16 g (0.25 mole) of potassium hydroxide pellets in 50 ml of water was added and the solution heated at 110–120° for 24 hr. The solution was diluted with 300 ml of water and a precipitate (1.26 g) was isolated by filtration of the cool solution. This precipitate, mp 137–141°, was identified as somewhat impure 3,4'-diphenylbenzophenone according to its infrared spectrum. Acidification of the filtrate with hydrochloric acid gave 1.66 g (4.6 mmoles) of acid, mp 168–173°. Two recrystallizations from aqueous ethanol gave 1.31 g of white crystals, mp 172–174°.

Anal. Calcd for $C_{23}H_{18}O_2$: C, 85.69; H, 5.53. Found: C, 85.88, 85.94; H, 5.63, 5.63.

Methyl *m*-Biphenyl-*p*-biphenylethanoate-1-C¹⁴. An ethereal solution of *m*-biphenyl-*p*-biphenylethanoic acid-1-C¹⁴ (1.03 g, 2.83 mmoles) was treated at 0° with excess diazomethane. The solution was evaporated to dryness and the residue crystallized from methanol to give 0.98 g (2.59 mmoles, 91% yield) of ester, mp 87–90°. The analytical sample after two further recrystallizations from methanol had mp 89.5–90.5°.

Anal. Calcd for $C_{27}H_{22}O_2$: C, 85.69; H, 5.86. Found: C, 85.71, 85.87; H, 5.78, 5.85.

2-*m*-Biphenyl-2,3-bis(*p*-biphenyl)propanoic Acid-1-C¹⁴. 4-Methylbiphenyl was synthesized from *p*-toluidine by the procedure of Gomberg and Pernert⁴⁵ and converted to 4-(bromomethyl)biphenyl, mp 85–87°, by the method of Zervas and Dilaris¹⁸ (but with traces of dibenzoyl peroxide used as catalyst). In a 500-ml Morton flask equipped with a stainless steel Morton high-speed stirrer and a Dry Ice-acetone condenser, 200 ml of anhydrous ammonia was condensed. Potassium (0.415 g, 10.6 mg-atoms) and then a small crystal of ferric nitrate were added and the solution was stirred for 1 hr (under an atmosphere of dry nitrogen throughout this and the following reactions in liquid ammonia solution). A solution of 0.950 g (2.51 mmoles) of methyl *m*-biphenyl-*p*-biphenylethanoate-1-C¹⁴ in 75 ml of anhydrous ether was added and the resulting solution stirred for 2 hr. A solution of 0.945 g (3.8 mmoles) of 4-(bromomethyl)biphenyl in 25 ml of anhydrous ether was then added over a period of 10 min and the solution stirred for 30 min. Unreacted potassium amide was destroyed by adding 0.54 g (10 mmoles) of solid ammonium chloride, and the ammonia was allowed to evaporate from the mixture. Dilute hydrochloric acid was added, the ether phase was separated, and the aqueous layer extracted once with ether. Evaporation of the combined ether phases yielded a solid residue which was heated at reflux for 24 hr with 250 ml of 15% aqueous potassium hydroxide. A quantity of dark brown, undissolved solid was removed by filtration and the filtrate acidified with hydrochloric acid. The white solid (0.545 g, 41% yield) was isolated by filtration and had mp 205–209.5°. After four recrystallizations from ethanol, this material yielded 0.28 g of white crystals, mp 209.0–210.0°.

Anal. Calcd for $C_{30}H_{22}O_2$: C, 88.27; H, 5.70. Found: C, 88.22, 88.39; H, 5.60, 5.58.

Reaction of 2-Chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane with Lithium. A. Reaction at –65°. To a 500-ml Morton flask (previously flame dried under a stream of dry nitrogen) equipped with a high-speed stirrer³⁷ and dropping funnel was added 150 ml of tetrahydrofuran (freshly distilled from NaAlH₄), 0.153 g (22.1 mg-atoms) of lithium, about 2% of a solution of 3.00 g (5.75 mmoles) of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane in 100 ml of dry tetrahydrofuran, and 0.05 ml of methyl iodide. The reactants were kept under an atmosphere of dry nitrogen throughout all of the following reactions with lithium. The solution was stirred vigorously at 0 \pm 5° until a faint purple color appeared (2 hr); the reaction temperature was then lowered to –65 \pm 5° and the remainder of the chloride added over a period of 30 min. The solution was stirred at –65° for 3 hr; Gilman double titration³⁷ of four 5-ml aliquots of this solution indicated that the yield of organolithium compound was 50 \pm 10%. The deep purple solution was forced onto a large excess of solid carbon dioxide. To the carbonated mixture, after sublimation of unreacted carbon dioxide, was added 200 ml of 10% sulfuric acid. The acidified mixture was extracted with ether and the organic phase was evaporated to dryness.

(45) M. Gomberg and J. C. Pernert, *J. Am. Chem. Soc.*, **48**, 1372 (1926).

The solid residue was stirred vigorously (3 hr) with 500 ml of 2% aqueous potassium hydroxide. Undissolved solid (2.1 g, mp 190–225°) was separated by filtration. Acidification of the filtrate brought about the precipitation of 0.722 g (24% yield) of solid, mp 225–228°. This acid after three recrystallizations from ethanol amounted to 0.489 g of white crystals, mp 226.5–228°. This acid gave no depression of melting point when mixed with the sample of 3-*m*-biphenyl-3,3-bis(*p*-biphenyl)propanoic acid synthesized above from *m*-biphenylbis(*p*-biphenyl)carbinol. Moreover, the infrared spectra of the acid and the synthetic sample were identical.

B. Reaction at 0°. This reaction was run in the same apparatus and by the same general technique as that for the reaction at –65°. To 0.133 g (19.2 mg-atoms) of lithium and 200 ml of tetrahydrofuran was added 0.05 ml of methyl iodide and about 10% of a solution of 2.50 g (4.80 mmoles) of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane in 50 ml of tetrahydrofuran. The solution was stirred vigorously at 0 ± 5° until a purple color appeared (1 hr). Then the remainder of the chloride was added over a period of 30 min at 0° and the solution stirred at this temperature for 6 hr before carbonation. The color of the solution just before carbonation was blue black; Gilman's double titration²⁷ indicated the presence of 45% yield of organolithium compound. After the usual work-up, 1.88 g of neutral product (mp 109–177°) and 0.995 g (39% yield) of crude acid, mp 208.0–209.5°, were obtained. This acid showed no melting point depression when mixed with a sample of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid synthesized previously according to Scheme III. Mixtures (about 50:50) of the acid with 3-*m*-biphenyl-3,3-bis(*p*-biphenyl)propanoic acid and with 3-*m*-biphenyl-2,2-bis(*p*-biphenyl)propanoic acid (synthesized according to Scheme II) had mp 201–219° and 180–202°, respectively. The infrared spectrum of the acid (in carbon disulfide) was identical with the infrared spectrum of the independently synthesized sample of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid; however, the infrared spectrum of 3-*m*-biphenyl-2,2-bis(*p*-biphenyl)propanoic acid was almost identical with these spectra except that the absorptions at 13.4 and 14.4 μ were broader.

The remaining crude acid (0.9861 g, mp 208.0–209.5°) was diluted with 0.1386 g of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid-1-C¹⁴ (mp 209.0–210.0°, specific activity 9.793 ± 0.002 μ curies/mmmole from Scheme III). The mixture was recrystallized to constant specific activity. After four recrystallizations from ethanol and one from benzene, the acid had mp 209.0–210.0° and specific activity 1.227 ± 0.005 μ curies/mmmole. From these data, it follows that 98.1 ± 0.5% of the crude acid was 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid.

C. Reaction at –65° and Rearrangement at 0°. Reaction between 0.106 g (15.3 mg-atoms) of lithium and 2.00 g (3.84 mmoles) of 2-chloro-1-*m*-biphenyl-1,1-bis(*p*-biphenyl)ethane in 250 ml of tetrahydrofuran at –65 ± 5° was run as in the first run at –65°. After the 3-hr stirring period at this low temperature, Gilman's double titration²⁷ indicated a 39% yield of organolithium compound. The solution was then allowed to warm to 0 ± 5° and stirred at this temperature for 4 hr before carbonation. After the usual work-up 1.33 g of neutral product (mp 79–132°) and 0.781 g (38% yield) of acid, mp 205–208°, were isolated. This acid gave no depression of melting point and had an infrared spectrum identical with that of a sample of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid (synthesized by Scheme III), while this acid on admixture with the synthetic samples of 3-*m*-biphenyl-3,3-bis(*p*-biphenyl)propanoic acid and with 3-*m*-biphenyl-2,2-bis(*p*-biphenyl)propanoic acid gave mixtures which melted with considerable depression of melting point. The crude acid (0.7802 g), mp 205–208°, was mixed with 0.1400 g of 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid-1-C¹⁴ (activity of 9.793 ± 0.002 μ curies/mmmole, mp 209.0–210.0°) and the mixture recrystallized to constant radioactivity. After four recrystallizations from ethanol and two recrystallizations from benzene, the acid had mp 209.2–210.1° and activity of 1.508 ± 0.005 μ curies/mmmole. From these data it can be calculated that 98.6 ± 0.4% of the crude acid was 2-*m*-biphenyl-2,3-bis(*p*-biphenyl)propanoic acid.

In an attempt to analyze the crude carboxylic acid from this run and the preceding run at 0° for any 3-*m*-biphenyl-2,2-bis(*p*-biphenyl)propanoic acid, the combined mother liquors from recrystallization of the crude acid from these two runs were evaporated to dryness to give 0.053 g of acid, mp 207–208.5°. To this acid was added 0.50 g of pure 3-*m*-biphenyl-2,2-bis(*p*-biphenyl)propanoic acid-1-C¹⁴. After one recrystallization from benzene, crystals, mp 175–196°, were obtained; the melting point of this material was not altered after two more recrystallizations from benzene. Benzene was removed from the mother liquors and the residue combined with the recrystallized material. After four recrystallizations from ethanol, crystals, mp 180–197°, were obtained. Since only impure acid was obtained by any of the procedures tried, isotope-dilution analysis for 3-*m*-biphenyl-2,2-bis(*p*-biphenyl)propanoic acid was abandoned.

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Singlet and Triplet Nitrenes. I. Carbethoxynitrene Generated by α Elimination

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Abstract: Carbethoxynitrene was generated by α elimination and the stereospecificity of its addition to *cis*- and *trans*-4-methylpentene-2 was investigated. The addition is the less stereospecific the lower the olefin concentration. The data fit quantitatively a scheme in which all the nitrene is generated in the singlet state, and then decays to triplet in competition with addition to the olefin. Both singlet and triplet add, the former stereospecifically, the latter completely nonstereospecifically. Triplet carbethoxynitrene can be trapped by α -methylstyrene, with which it reacts at least 85 times faster than with *cis*-4-methylpentene-2. Decay of the singlet nitrene to triplet is about one-thirtieth as fast as addition to the *cis* olefin. The structure of an α -methylstyrene dimer is revised.

nitrenes³ have long been discussed as intermediates in organic chemistry,^{4,5} and the subject has been extended.⁶⁻⁸ For a species $R-\ddot{N}:$, singlet and triplet are possible. The singlet with two paired sets of electrons on the nitrogen, or the triplet with one and two electrons of parallel spins, might *a priori* be the ground state of a given nitrene. However, a nitrene need not be generated in its ground state, and it may well react before it reaches the ground state. Beyond ascertaining the nature of the ground state, one has to determine the electronic state of the nitrene in a given chemical reaction before one can give a detailed mechanism for it.

Electron spin resonance studies have shown that the singlet is the ground state for a number of nitrenes,⁹⁻¹² including carbethoxynitrene.¹³ The ultraviolet spectroscopic triplet nitrenes have also been reported.¹⁴ Less information is available for the electronic state of nitrenes at the moment of their chemical reaction. Attempts have been made to correlate chemical reactivity with electronic multiplicity—radical character ascribed to the triplet species—but such correlations are not unequivocal.

In an attempt to determine the electronic state of carbethoxynitrene at the moment of reaction, we have investigated the stereochemistry of the nitrene's addition

to *cis*- and *trans*-4-methylpentene-2. This is an extension into the nitrene field of a method developed by Skell¹⁵ for carbenes. This method, although it caused much controversy,¹⁶ works very well with carbenes. Skell proposed that addition of singlet species to an olefin should produce the three-membered ring adduct in one single step, thus in a stereospecific fashion. A triplet species, however, should first form an open-chain triplet diradical. This is supposed to establish conformational equilibrium, by rotation around the former double bond, much faster than close to the three-membered ring. Skell assumed that the delay in ring closure is due to the necessity of inversion of one of the spins of the triplet diradical. An alternative explanation by Hoffmann¹⁷ does not alter the stereochemical consequences. Written for a nitrene, Skell's scheme is shown in Figure 1.

In the following, we want to show that Skell's scheme explains our data not only qualitatively, but quantitatively as well. Strictly speaking, what we observe is a "stereospecifically adding carbethoxynitrene" and a "nonstereospecifically adding carbethoxynitrene." Our final conclusion is that these can be identified with the singlet and triplet species, respectively. To make the discussion less awkward, we shall call them singlet and triplet from the beginning.

After completion of the work described here, Scheiner¹⁸ presented data which independently support the validity of Skell's scheme, applied to aziridine formation. Scheiner obtained diradical intermediates, of the type shown in Figure 1, not by addition of a nitrene to an olefin, but by direct and by sensitized photodecomposition of triazolines. Direct photolysis gave aziridines stereospecifically, perhaps *via* a singlet diradical, perhaps by a concerted process. Photosensitized decomposition gave aziridines nonstereospecifically, presumably *via* triplet diradical intermediates.

Results and Discussion

Carbethoxynitrene, $EtO-CO-N$, was generated by

(15) P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **78**, 4496 (1956); R. C. Woodworth and P. S. Skell, *ibid.*, **81**, 3383 (1959).

(16) Cf. P. P. Gaspar and G. S. Hammond in "Carbene Chemistry," W. Kirmse, Ed., Academic Press Inc., New York, N. Y., 1964, p. 259 ff.

(17) R. Hoffmann, *Trans. N. Y. Acad. Sci.*, [2] **28**, 75 (1966).

(18) P. Scheiner, *J. Am. Chem. Soc.*, **88**, 4759 (1966).

ational Institutes of Health Predoctoral Fellow, 1965-1966.
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The name "nitrene" for species $R-N$ is most often used, but is controversial. The objection that systematic nomenclature requires ending -ene for unsaturated compounds can perhaps be met by giving the last "e," and calling the species "nitren." This would be due to the change of "urethane" to "urethan," for the same reason.

1. Tiemann, *Ber.*, **24**, 4162 (1891).

2. Stieglitz, *Am. Chem. J.*, **18**, 751 (1896).

3. Kirmse, *Angew. Chem.*, **71**, 537 (1959).

4. Horner, *ibid.*, **75**, 707 (1963).

5. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).

6. Smolinsky, E. Wasserman, and W. A. Yager, *J. Am. Chem. Soc.*, **84**, 3220 (1962).

7. G. Smolinsky, L. C. Snyder, and E. Wasserman, *Rev. Mod. Phys.*, **35**, 576 (1963).

8. E. Wasserman, G. Smolinsky, and W. A. Yager, *J. Am. Chem. Soc.*, **86**, 3166 (1964).

9. R. M. Moriarty, M. Rahman, and G. J. King, *ibid.*, **88**, 842 (1966).

10. E. Wasserman, private communication.

11. A. Reiser and V. Frazer, *Nature*, **208**, 682 (1965); A. Reiser, H. G. B. Bowes, *Tetrahedron Letters*, 2635 (1966).

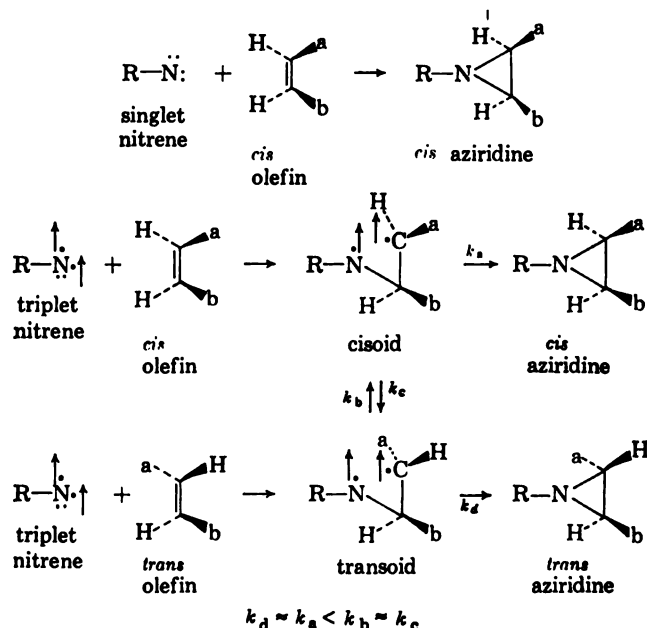
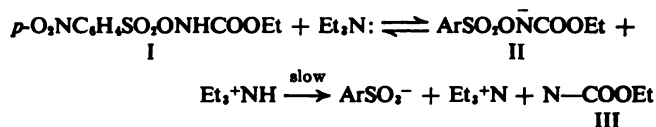


Figure 1.

photolysis¹⁹ and thermolysis^{19,20} of ethyl azidoformate and by base-induced, α -elimination of arylsulfonate ion from *N*-(*p*-nitrobenzenesulfonyloxy) urethan.^{21,22} Especially the latter reaction is expected to give initially the singlet carbethoxynitrene, since nonconservation of electron spin seems unlikely in a room-temperature ionic reaction.



Owing to the insolubility of the nitrene precursor I, the α -elimination method cannot be used in pure hydrocarbons, and a solvent, usually dichloromethane, was employed. Dichloromethane is quite inert toward the nitrene, as shown by the observation²³ that a 35% yield of aziridine was obtained from carbethoxynitrene in a 0.2 mole % solution of cyclohexene in dichloromethane. *cis*- and *trans*-4-methylpentene-2 were employed as the olefins, mostly because they are liquids and are commercially available. As communicated earlier,²⁴ the degree of stereospecificity of the aziridine formation is strongly dependent on the olefin concentration. Even in pure olefin, the addition is not fully stereospecific. While our work was in progress, Hafner reported²⁵ that the photolysis of methyl azidoformate in *cis*- and *trans*-2-butene gave 87% *cis*-plus 13% *trans*-aziridines in the former case, and 8% *cis* and 92% *trans* in the latter. During the progress of our work, studies of the dependence of stereospecificity of addition on substrate concentration have been carried out on fluorenylidene,²⁶ dicyanocarbene,²⁷ and cyanonitrene.²⁸

(19) W. Lwowski and T. W. Mattingly, Jr., *Tetrahedron Letters*, 277 (1962); W. Lwowski and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **87**, 1947 (1965).

(20) R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964).

(21) W. Lwowski, T. J. Maricich, and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **85**, 1200 (1963).

(22) W. Lwowski and T. J. Maricich, *ibid.*, **87**, 3630 (1965).

(23) W. Lwowski and F. P. Woerner, *ibid.*, **87**, 5491 (1965).

(24) W. Lwowski and J. S. McConaghy, Jr., *ibid.*, **87**, 5490 (1965).

(25) K. Hafner, W. Kaiser, and R. Puttner, *Tetrahedron Letters*, 3953 (1964).

The imperfect stereospecificity cannot be attributed to secondary reactions. The stability of the star olefins and the products under the reaction conditions was established both by independent experiments by taking samples during early and late stages of individual runs, and comparing the ratios of *cis* and *trans* products. Both olefins and the products were stored under the conditions employed.

Making carbethoxynitrene by α elimination in chloromethane solutions of *cis*- and *trans*-4-methylpentene-2 gave, as the main products, mixtures of *cis* and *trans*-1-carbethoxy-2-isopropyl-3-methylaziridine

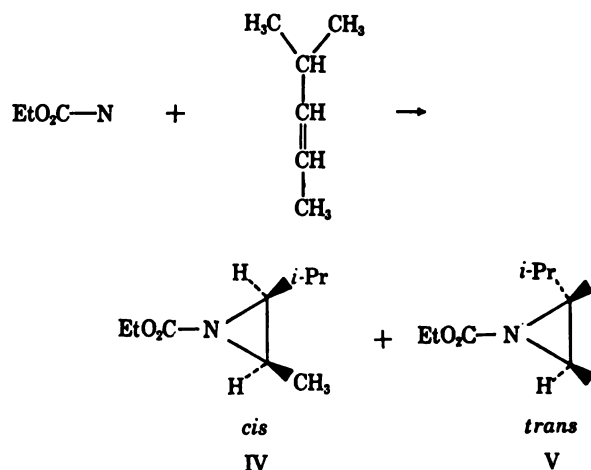


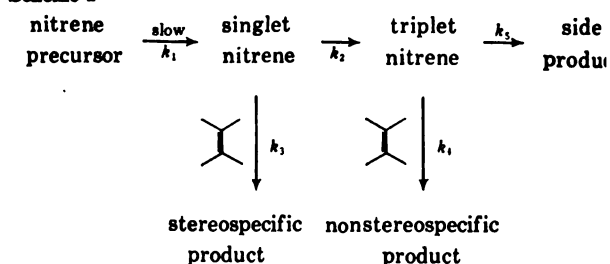
Table I gives yields and compositions of the aziridine mixtures obtained at olefin concentrations between

Table I. Addition of Carbethoxynitrene to *cis*- and *trans*-4-Methylpentene-2, α -Elimination Route, Dichloromethane Solutions

Mole % olefin	Yield of aziridines	From <i>cis</i> olefin, % Fraction of <i>trans</i> product	From <i>trans</i> olefin, % Fraction of <i>cis</i> product
33	57	7.8	2.6
10	50	17.5	
5		26	8.0
3.3	38	34	
2.5		37.5	
1.5	24	43	12.3

and 1.5 mole %. It is clear that the data of Table I are in qualitative agreement with Scheme I.

Scheme I



(26) M. Jones and K. R. Rettig, *J. Am. Chem. Soc.*, **87**, 4013, (1965).

(27) E. Ciganek, *ibid.*, **88**, 1979 (1966).

(28) A. G. Anastassiou, *ibid.*, **88**, 2322 (1966).

proposed Scheme I holds true, the fraction of specific reaction should depend only on the time that elapses from the formation of a nitrone molecule to its consumption. The nitrone should produce only one geometric isomer of aziridine from each (*cis* or *trans*) olefin; the specific triplet reaction should produce the stereoisomers from either olefin. The fraction of triplet reaction can be calculated from our experimental data if one assumes that the nonstereospecific reaction is total, i.e., that the composition of the mixture produced by the triplet depends solely on the position of the equilibrium of the two conformers of the open-chain diradical intermediate of Figure 1, on the nature (*cis* or *trans*) of the starting olefin. In the following discussion, we will show that, on the basis of the above assumption, and on Scheme I, the experimental data can indeed be correlated.

In a given experiment, a fraction of the nitrone is produced by the triplet, and will produce (nonstereospecifically) a fraction of the total aziridines obtained. This fraction is different for each substrate concentration (*Y*).

X. The aziridine produced by the triplet is a mixture of *trans* and *cis* isomers; the ratio of the fractions of *trans* and *cis* aziridines should be constant (see preceding paragraph) and is called *X*. The fraction of *trans*-aziridine in this mixture is *X*. The values of *X* for each experiment and of *Y* are to be determined from the experimental data: the fractions of *trans*-aziridine in the mixture from *cis* olefin, called *A* (and dependent on olefin concentration), and the fractions of *cis*-aziridine in the mixture from *trans* olefin, called *B* (and dependent on olefin concentration) which we will use. *A* and *B* will always be smaller than *X*, since some of the nonstereospecific reaction will produce the same aziridine isomer that is produced specifically by the singlet nitrone. With *Y* being the fraction of triplet nitrone, we have

$$A = XY \quad (1)$$

(experiments starting with the *cis* olefin)

$$B = X(1 - Y) \quad (2)$$

(experiments starting with *trans* olefin, the fraction of *cis*-aziridine in the "nonstereospecific mixture" being $1 - Y$)

Eq 1 and 2 gives

$$A + B = X \quad (3)$$

Substituting (3) into (1) gives

$$Y = A/(A + B) \quad (4)$$

A is supposed to be constant, $A/(A + B)$ and *Y* are also supposed to be constant. *A* is obtained from investigation of reactions with *cis* olefin, and *B* from the *trans* olefin. To select values of (concentration-dependent) *A* and *B* a series of *A/B* values and to check for their concentration independence, it is not enough to compare *A* and *B* values obtained at the same concentrations of *cis* and *trans* olefins, respectively. One has to account the different reactivities of the two olefins toward the nitrenes. In our reaction Scheme I the competition is set up between k_2 and $k_3[\text{olefin}]$. For olefins of different reactivity, the latter

term contains different k_3 values, and it becomes necessary to know the ratio of $k_{3,trans}:k_{3,cis}$. This ratio was determined by direct competition, using a mixture of 10 mole % *cis*, 20 mole % *trans*-4-methylpentene-2, and 70 mole % dichloromethane. The ratio of reactivities at these particular olefin concentrations was found to be *trans*:*cis* = 0.7. Since the singlet:triplet ratio of carbethoxynitrenes is supposed to change with olefin concentration, one might anticipate that the reactivity ratio would also depend on olefin concentration. Fortunately, there is little or no such dependence. The values for *A* and *B* were plotted vs. olefin concentration, and *A* at a given concentration was compared with the *B* at 1/0.7 of that concentration. The values for *A/B* so obtained vary from 3.7 to 4.15 for concentrations from 33 to 1.5 mole %, and no clear trend is observed. Thus, the ratios of reactivities of *cis* and *trans* olefins seem to be nearly the same for the reactions with singlet and triplet carbethoxynitrone. The average of these reactivity-corrected *A/B* values is 3.9; thus *Y* is found to be 0.80 and the fraction of *trans* open-chain diradical intermediate in our case is 80%. *X*, the fraction of triplet reaction, then is calculated as $A/0.8$ or $X = 1.25A$. *X* equals 1.25 times the fraction of *trans*-aziridine in the aziridine mixture produced from *cis* olefin. It may be mentioned here that the average value for *A/B* obtained from experiments with photolytically generated nitrone (100 and 1.5 mole % olefin) is 3.87. The relation $X = 1.25A$ is sufficiently accurate for our further use, since a 10% error in the ratio *A/B* would lead only to a 3% error in the factor 1.25.

If we use Scheme I, neglect side reactions of the triplet (k_4), and call the aziridine from singlet nitrone *S*, the aziridine mixture from the triplet nitrone *T*, the singlet nitrone *N*, the triplet nitrone 3N , and assume that nitrone production is the slow reaction step, then

$$d[T]/dt = k_4[^3N][\text{olefin}]$$

$$d[S]/dt = k_3[N][\text{olefin}]$$

$$(d[T]/dt)/(d[S]/dt) = k_4[^3N]/k_3[N]$$

and with $d[^3N]/dt = 0$

$$d[^3N]/dt = k_2[N] - k_4[^3N][\text{olefin}] = 0$$

$$[^3N]/[N] = k_2/k_4[\text{olefin}]$$

and

$$(d[T]/dt)/(d[S]/dt) = k_4k_2/k_3k_4[\text{olefin}] = k_2/k_3[\text{olefin}]$$

with the olefin concentration constant throughout the run

$$[T]/[S] = k_2/k_3[\text{olefin}]$$

Consequently, a plot of $[T]/[S]$ vs. $1/[\text{olefin}]$ should give a straight line with the slope k_2/k_3 . Table II gives the data used to construct Figure 2.

The curve in Figure 2 follows the predicted straight line only down to about 3 mole % olefin. In our computation, k_4 was neglected; that is, the assumption was made that all triplet nitrone produced is quantitatively converted to aziridines. At low olefin concentrations, this seems not nearly to be true, and the scheme has to be refined. It is not necessary to take into account side

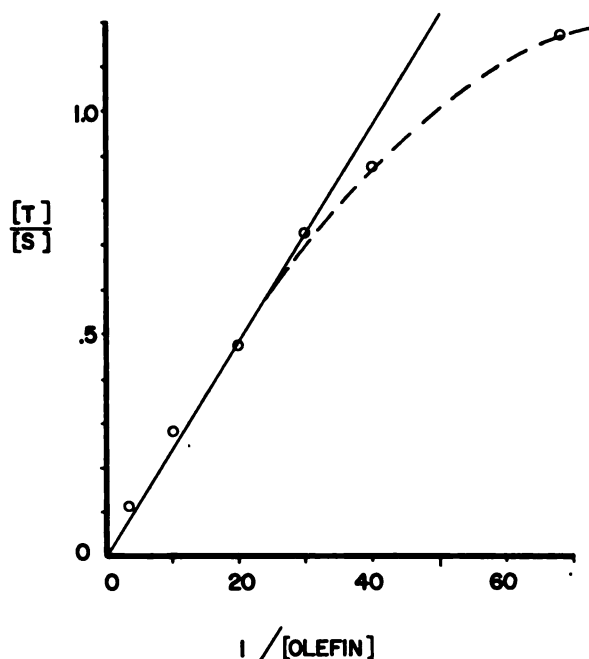
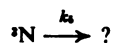


Figure 2.

reactions of the singlet nitrene, since the steady-state assumption $d[N]/dt = 0$ was not needed in the calculations made above. However, the assumption $d[{}^3N]/dt = 0$ was made, and side reactions of the triplet nitrene have to be considered. Adding the reaction



is indeed all that is required to obtain a straight line in Figure 2. The reaction or reactions described by k_5 could be those of the triplet nitrene with solvent. Re-

Table II. Addition of Carboethoxynitrene to *cis*-4-Methylpentene-2, α -Elimination Route, Dichloromethane Solution, Reduced Data

$[\text{Olefin}]^{-1}$	A	$[T]$	$[S]$	$[T]/[S]$
3	0.078	0.098	0.90	0.11
10	0.175	0.22	0.78	0.28
20	0.26	0.325	0.675	0.48
30	0.34	0.425	0.575	0.74
40	0.375	0.47	0.53	0.89
67	0.43	0.54	0.46	1.18

arrangement or dissociation of the triplet nitrene, as well as return to the singlet state, could also be contained in k_5 . With the new reaction, we have

$$d[{}^3N]/dt = k_2[N] - k_4[{}^3N][\text{olefin}] - k_5[{}^3N] = 0$$

In the same way as above, this yields

$$[T]/[S] = k_2/\{k_3([\text{olefin}] + k_5/k_4)\}$$

Thus, a plot of $[T]/[S]$ vs. $1/([\text{olefin}] + k_5/k_4)$ should now give a straight line. To find k_5/k_4 , the logarithms of all our $[T]/[S]$ values were plotted against $\log 1/([\text{olefin}] + x)$ and various values tried. With $x = 0.01$ to 0.025 , straight lines could be drawn that passed through the error boxes of all points. The best fit seems to be given by $k_5/k_4 = 0.015$. Figure 3 shows plots with k_5/k_4 taken as 0.01 , 0.015 , and 0.025 . The slopes of the lines in Figure 3 correspond to k_2/k_3 , the ratio of the (first-

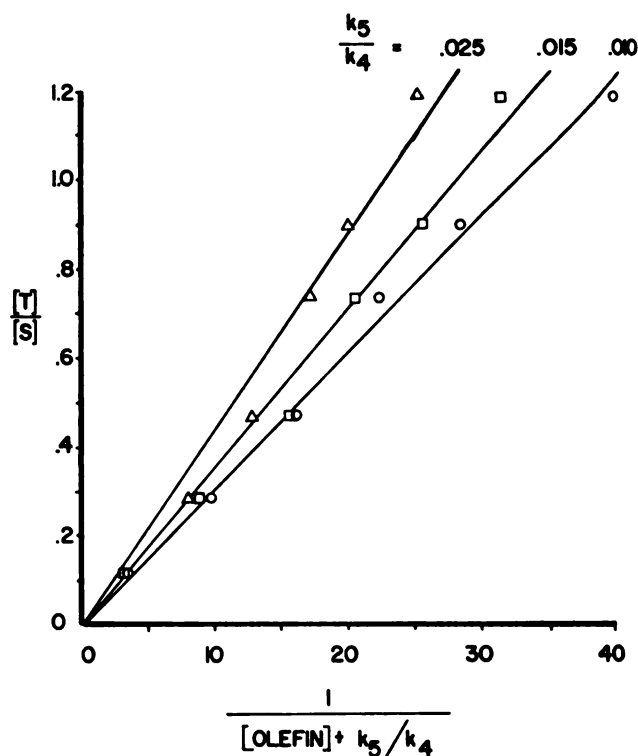


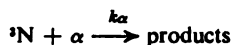
Figure 3.

order) rate constant of singlet-triplet conversion and the (second-order) rate constant for the singlet addition to *cis*-4-methylpentene-2. If k_3/k_4 is taken to be 0.015 ± 0.005 , the k_2/k_3 is equal to 0.036 ± 0.004 . Thus it appears that the addition of the singlet nitrene is about 30 times as fast as the decay to triplet.

The quantitative compatibility of the observed data with a scheme based on singlet-triplet conversion competing with the addition of singlet to olefin is encouraging, but does not itself prove the validity of the scheme. To provide independent evidence, attempts were made to trap the triplet nitrene selectively.

Trapping of Triplet Carboethoxynitrene. The reactions reported above were done in degassed solutions under nitrogen. Changing to solutions saturated with oxygen resulted in slightly more stereospecific addition (at 3.3 mole % olefin concentration), but the change was not large enough to be convincing. Since the first intermediate in the addition of the triplet nitrene to an olefin is supposed to be a diradical, we tried next an addend which would give a highly stabilized diradical, hoping that this stabilization might be reflected in the transition state enough to lead to very fast addition. Our choice was α -methylstyrene, which we did not expect to be particularly reactive toward the singlet nitrene. Indeed, addition of 3.3 mole % of β -methylstyrene to an otherwise unchanged run with 3.3 mole % *cis*-4-methylpentene-2 in dichloromethane gave a 16% yield of *cis*-1-carbethoxy-2-isopropyl-3-methylaziridine, and only a trace of the *trans* isomer. Without the α -methylstyrene, the reaction gave a 25% yield of the *cis*- and a 13% yield of the *trans*-aziridine. A similar experiment, using 1.5 mole % each of α -methylstyrene and *cis*-4-methylpentene-2, gave an aziridine mixture containing at the most 2.1% of the *trans* compound. Thus, the α -methylstyrene reduced the yield of the *cis*

by a factor of 1.6, but the yield of *trans* product is a factor of greater than 30 (at 3.3 mole % concentration). The simplest explanation is that the triplet is removed because its reaction rate with α -methylstyrene is much greater than that of the singlet. Hence I is extended by the reaction

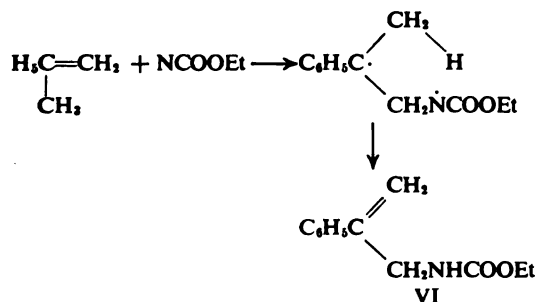


α stands for α -methylstyrene, then a treatment analogous to the one used above gives

$$[T]/[S] = k_2 / \{k_3([\text{olefin}] + k_5/k_4) + k_6[\alpha]/k_4\}$$

values except $k_6[\alpha]/k_4$ are known, and k_6/k_4 is estimated to be 86 (using $A = 0.021$ and $[T]/[S] =$

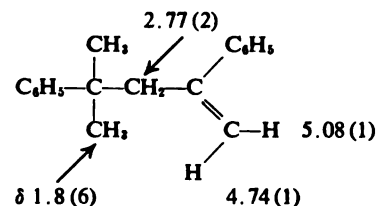
It appears that α -methylstyrene is 86 times more reactive toward triplet carbethoxynitrene than is ethylpentene-2. Since the 2.1% *trans*-aziridine product mixture is the maximum value, the rate for the α -methylstyrene might be greater. Our results agree very well with Skell's contention that the triplet state in the triplet addition has much radical character. The nature of the product from α -methylstyrene and carbethoxynitrene supports this further. The aziridine corresponding to nitrene addition to the α -methylstyrene could not be found. The main product is a 1:1 adduct, 3-carbethoxyamino-2-phenylpentene-1 (VI). Its structure was established by its infrared spectra, elemental analysis, and independent synthesis. Presumably, VI is formed not by insertion into the methyl group, but *via* a di-intermediate.



possibility that VI is a decomposition product of the dimer formed from α -methylstyrene was not rigorously tested, but it was shown that VI is present in the reaction mixture before the gas chromatographic separation.

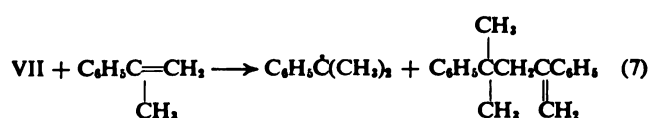
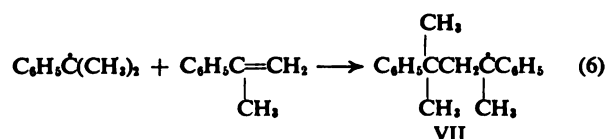
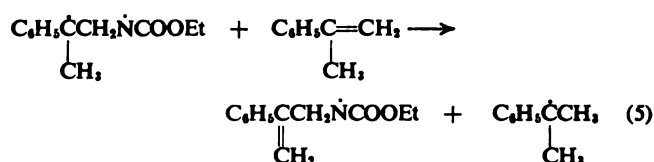
Unsaturated Dimer of α -Methylstyrene. Vpc analysis of the product mixture from α -methylstyrene and carbethoxynitrene (produced by α elimination) showed a further major product, which was found to be present as well as in the absence of *cis*-4-methylpentene-2 in the reaction mixture. The new product was found to be identical with the "liquid dimer" or "undimer" of α -methylstyrene. This dimer had been characterized by Bergmann²⁹ and later by Hukki,³⁰ and had been assigned the structure of 2,4-diphenyl-4-methylpentene-2 on the basis of ozonization studies.²⁹ He observed 2,4-ditoyl-4-methylpentene-1 among the products of the (analogous) acid-induced dimerization of dimethylstyrene, and proposed that the corresponding terminal olefin also might be present in the product from acid-induced dimerization of α -methyl-

styrene, and that Bergmann might have overlooked it. We prepared the α -methylstyrene dimer by Hukki's method, and found it to have vpc retention time, infrared, and nmr spectra identical with the product from the reaction of our nitrene with α -methylstyrene in dichloromethane. The vpc analysis shows that little or no isomeric olefin is present, and the nmr spectrum shows two nonequivalent vinyl protons. This, and the rest of the spectral data, establish the structure of the liquid, unsaturated α -methylstyrene dimer as 2,4-diphenyl-4-methylpentene-1.



A broad multiplet representing the ten aromatic protons is centered around $\delta 7.1$.

As shown by a control experiment, the strongest acid present in our system, triethylammonium ion, does not convert α -methylstyrene to the dimer. In our case, it is probably formed by a radical chain mechanism, such as

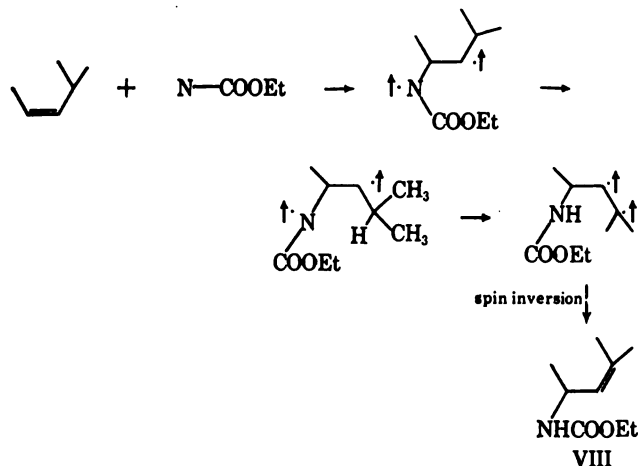


Side Reactions of Carbethoxynitrene. In the preceding discussion, only aziridines were considered as products from nitrene and the 4-methylpentene-2. The experience gathered with other olefins^{19,22} leads one to expect other products as well: all the possible insertion products, especially the allylic ones. A crude estimation, based on the data from cyclohexene experiments, shows that only the insertion product into the tertiary C-H bond at C-4 is expected to be formed in a quantity greater than 1% of the quantity of the aziridines. However, the 4-carbethoxyamino-4-methylpentene-2 might be formed in a quantity as much as 12% of that of the aziridines. While C-H insertion seems to be a property of the singlet only,²³ and thus should not influence the stereospecificity (see above), it was at first surprising that no tertiary allylic insertion product could be found. Inspection of models, however, shows that the tertiary allylic hydrogen in *cis*-4-methylpentene-2 is very shielded by three methyl groups, and attack on the C-4-H bond would be very difficult sterically. In the *trans* olefin, the steric hinderance of such an attack is also severe.

While C-H insertion seems to make a negligible contribution, a more serious interference could be caused

²⁹ Bergmann, H. Taubadel, and H. Weiss, *Ber.*, **64B**, 1493 (1931).
³⁰ Hukki, *Acta Chem. Scand.*, **3**, 279 (1949).

by reactions of the triplet nitrene with olefin other than aziridine formation. Especially formation of 4-carbethoxyamino-2-methylpentene-2 (VIII) was anticipated.



Compound VIII was synthesized and a reaction mixture that contained a high proportion of triplet products (from a run with 1.5 mole % olefin concentration) was analyzed for VIII. A trace of a product with vpc retention time identical with that of VIII was found, but its quantity was too small to attempt identification by infrared spectrum. The peak area corresponded to its being formed in a yield no greater than 2.4% of the aziridine yield, or no greater than 4.5% of the yield of the part of the aziridines formed from the triplet nitrene. Consequently this side reaction does not seriously affect our conclusions.

Conclusion

The results discussed above show that the α -elimination route produces carbethoxynitrene that adds fully stereospecifically to the methylpentenes (extrapolation to infinite olefin concentration), but changes to a nitrene that adds nonstereospecifically. Since the mode of generation makes it very likely that the singlet nitrene is produced, and since the ground state has been proved to be the triplet,¹³ we think it reasonable to identify the two species with the singlet and the triplet states. Our results with α -methylstyrene support the contention that the intermediate produced in the nonstereospecific process is a diradical.

Experimental Section

General. Infrared spectra were obtained with a Perkin-Elmer Model 421 spectrometer. Unless specified otherwise, carbon tetrachloride was the solvent used for the infrared as well as the proton magnetic resonance spectra. Tetramethylsilane was used as an internal standard for the latter, and the chemical shifts are reported as δ values (ppm downfield from the TMS signal). Ultraviolet spectra were taken on a Cary Model 14 spectrometer, mass spectra on a Model 21-103 Consolidated Electrodynamics Corp. instrument.³¹ Microanalyses are by Galbraith Laboratories. Melting points were taken on a Fisher-Jones block, and are uncorrected, as are the boiling points. Vapor phase chromatography was done with a Varian Aerograph Model A-90-P unit and helium was used as the carrier gas. The columns employed were: column A: 6 ft \times 0.25 in. stainless steel; 20% GE-SF-96 silicone oil on 60-80 mesh Firebrick; column B: 15 ft \times 0.25 in. aluminum; 5% cyanosili-

cone XF 1150 on 45-60 mesh Chromosorb W; column C: 15 ft \times 0.25 in. aluminum; 20% Carbowax 20M on 45-60 mesh Chromosorb W; and column F: 11 ft \times 0.25 in. stainless steel; 25% silver nitrate in glycerol on 60-80 mesh Chromosorb P.

Quantitative vpc analyses were carried out by making four injections per determination, tracing the peaks on unlined filing cards, cutting them out, and weighing. The error was taken to be twice the standard deviation found. Relative errors were less than 2% where the ratio of compared peak areas was less than 10:1. To obtain absolute yields, the peaks from aliquots of reaction mixtures were compared with peaks from the injections of known volumes of standard solutions of the product in question. Unless stated otherwise, all reactions were run under nitrogen, and the solvents were deoxygenated before use. *cis*- and *trans*-4-methylpentene-2 were Phillips "pure grade," 99+ % pure. The olefins were distilled before use and gave a negative peroxide test. Each sample of olefin was first analyzed by gas chromatography on column F. If a measurable amount of the other isomer was found, it was corrected for, but such corrections never were larger than 1%. Triethylamine (Matheson Coleman and Bell) was distilled from barium oxide. Dichloromethane (Fisher Certified Reagent) was used without further purification.

Preparation of Authentic *cis*- and *trans*-1-Carbethoxy-2-isopropyl-3-methylaziridines (IV and V). The aziridines were prepared by a slight modification of Hassner's method.³²

a. N-Carbethoxy-2-amino-3-iodo-4-methylpentanes. Iodine (25.4 g, 0.1 mole) was added in one portion to a stirred, cooled mixture of 20 g (0.133 mole) of freshly prepared, dry, silver cyanate, 8.4 g (0.1 mole) of *cis*- or *trans*-4-methylpentene-2, and 200 ml of anhydrous ether. After 2 hr of stirring in an ice-salt bath and 1 hr at room temperature, the filtered solution was concentrated to half its original volume, 200 ml of absolute ethanol was added, and the solution heated to reflux for 2 hr. Solvent was distilled to reduce the volume by half, and the solution was poured into 150 ml of water, containing a little sodium sulfite. The aqueous layer was washed once with ether, and the combined organic layers were washed five times with water. The combined aqueous extracts were once extracted with ether, and this ether extract was washed five times with water. The washed ether extract was combined with the other organic phase, washed once with saturated sodium chloride solution, and dried over sodium sulfate. Evaporating the ether left the products as yellow oils. The crude yield from the *cis* olefin was 23.3 g (78%), from the *trans* olefin 20.8 g (70%). Both iodo urethans show the ester carbonyl band at 1720 cm^{-1} ; the NH band of the compound from *cis* olefin is at 3435, that from the *trans* olefin is at 3440 cm^{-1} . The nmr spectra of the products from *cis* and *trans* olefin are different in that the isopropyl CH_3 signals form two doublets at δ 1.01 and 1.07 in the product from *trans* olefin, while they are not separated (at δ 1.00) in the product from *cis* olefin. The other nmr signal positions are common to both products: CH_3 at C-1 at δ 1.12, ethoxy CH_3 at 1.12, isopropyl CH at 1.3-1.8, N-C-H at 3.3-3.7, I-C-H at 3.8-4.1, ethoxy CH_2 at 4.04, and N-H at 5.25. The products crystallized on standing in the refrigerator, but were usually used as oils without further purification.

b. 1-Carbethoxy-2-isopropyl-3-methylaziridines (VI and V). A solution of the appropriate N-carbethoxy-2-amino-3-iodo-4-methylpentane (15 g, 0.05 mole) in 15 ml of *t*-butyl alcohol was added in one portion to a rapidly stirred solution of 15 g (0.134 mole) of potassium *t*-butoxide (MSA Research Corp.) in 200 ml of *t*-butyl alcohol. After 10 min of stirring at room temperature, the mixture was poured into a solution of 15 g of ammonium chloride in 400 ml of water. The solution was extracted twice with 200-ml portions of ether, and the ether phase was washed with water and sodium chloride solution and dried. After removal of ether and *t*-butyl alcohol, the product was distilled over a short Vigreux column. The *cis*-aziridine had bp 63-66° (3 mm); the *trans* boiled at 67-70° (3 mm). The yields were 3.38 g (40%) for the *cis*, and 4.42 g (51%) for the *trans* isomer. Vpc analysis on column B showed the products not to be contaminated by the other isomers. Infrared and nmr spectra confirm the structures of IV and V. The signals from the methyl groups are split not only by the H on the adjacent carbon, but also due to the asymmetry on ring carbon 2 ($J = 12$ cps for the *cis*, $J = 4$ cps for the *trans*-aziridine). Similar effects have been observed,³³ and it has been suggested that restricted rotation

(32) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 3640 (1964); **30**, 1748 (1965).

(33) A. T. Bottini, R. L. VanEtten, and A. J. Davidson, *J. Am. Chem. Soc.*, **87**, 755 (1965).

(31) We wish to thank Mr. David Friedland for his generous and competent help with the mass spectra.

most of the effect,³⁴ but the spectrum of our *cis*-aziridine appreciably different at 150° and at room temperature. The spectra showed correct integrals, and the chemical shifts assigned as shown in Table III.

I

Group	<i>cis</i> , δ	<i>trans</i> , δ
propyl CH ₂	0.94, 1.13	0.95, 1.02
ng CH ₂	1.21	1.21
oxy CH ₂	1.22	1.22
propyl C-H	1.3-1.7	1.3-1.6
ng protons	1.7-2.6	1.7-2.4
oxy CH ₂	4.04	4.04
e carbonyl frequencies of both isomers were at 1720 cm ⁻¹		
	Anal., %	
	C	H N
lcd for C ₁₂ H ₁₇ NO ₂	63.13	10.01 8.18
und <i>cis</i>	62.72	10.18 8.20
<i>trans</i>	63.18	10.13 8.47

Induced Decomposition of N-(*p*-Nitrobenzenesulfonyl)urea in Solutions of 4-Methylpentene-2 and Dichloromethane. A rapidly stirred solution of 0.252 g (0.00087 mole) of I in 30 ml of appropriate dichloromethane-olefin mixture was added dropwise over 8 min 0.10 g (0.0010 mole) of triethylamine in 10 ml of the chloromethane-olefin mixture. The temperature was maintained between 35 and 40°. After 3 hr, the volume was reduced to 10 ml, and 50 ml of ether was added to precipitate the triethylammonium *p*-nitrobenzenesulfonate, which was usually obtained in 80% yield. The solvent was removed from the filtrate, and the residue was analyzed by vpc. Urethane, IV, and V, were identified by their retention times and their infrared spectra, IV and V also by their mass spectra. No single column was found to separate all the components. Column A separated urethane and diethyl hydrazodiformate from the aziridines IV and V; column B separated the aziridines from each other, but not V from diethyl hydrazodiformate; column C separated all components but a decomposition product (possibly from the aziridines) appeared together with IV. The standard procedure used was to separate the aziridines from the decomposition product on column A (120°), collect them, and analyze them on column B (112°) to determine their ratio. A synthetic mixture of IV and V was analyzed on column B directly, and after passing it through column A, the fraction of IV was found to be 45.1%, respectively, showing that passage over column A did not affect the ratio of IV:V. Aziridine mixtures containing equal quantities of urethane were analyzed both directly on column A and after passage over column A. The results confirmed the utility of the method. Analysis of recovered olefin on column F showed that less than 1% had isomerized. To determine the influence of the ratio of nitrene precursor to olefin, the experiment using 1.5 mole % olefin concentration was repeated, but at 400 ml of the dichloromethane-olefin mixtures. Results are shown in Table IV.

V. Reactions of I, Base, and Olefin in Dichloromethane Solutions

% n	Yields from <i>cis</i> olefin, %		From <i>cis</i> olefin, % V in IV + V	From <i>trans</i> olefin, % IV in IV + V
	Aziridines	Diethyl hydrazo- diformate		
57	1.5		7.8	2.6
50	5	6-7	17.5	
			26	8.0
3	38	3	34	
5			37.5	
5	24	4-8	43	12.3
		In 400-ml Solution		
5	43	1.5	45.5	
10-ml Solution and with Fivefold Excess of Triethylamine		5.7		
5	35		43	

G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1964), and references therein.

Competition of *cis*- and *trans*-4-Methylpentene-2 for the Nitrene. Decomposition of I as above in solvent consisting of 10 mole % of *cis* and 20 mole % of *trans* olefin, and 70 mole % of dichloromethane, and work-up as above, gave IV and V in the ratio 1:1.73. The relative reactivity was calculated assuming that the nitrene would react with the *cis* olefin with the same stereospecificity as in a solution containing 10 mole % *cis* olefin, 90 mole % dichloromethane [V:(IV + V) = 0.175], and with the *trans* olefin as if in a solution of 20 mole % *trans* olefin and 80 mole % dichloromethane [IV:(IV + V) = 0.04]. Under these assumptions, the reactivity of the *trans* olefin is calculated to be 0.70 times that of the *cis* olefin.

Preparation of 3-Carboethoxamino-2-phenylpropene-1. a. Bromination of α -methylstyrene³⁵ gave a mixture of about 75% 3-bromo-2-phenylpropene-1 and 25% 1-bromo-2-phenylpropene-1 in 52% yield. This mixture, a powerful lachrymator, was used in the next step.

b. To prepare 3-N-phthalimido-2-phenylpropene-1, 5.07 g (0.0257 mole) of the bromophenylpropene mixture was treated with 4.7 g (0.0254 mole) of potassium phthalimide in 20 ml of dimethylformamide at 40°, then 55° for 2 hr. Diluting with chloroform, washing with water and sodium hydroxide solution, drying, and concentrating *in vacuo* gave crystals. Recrystallization from cyclohexane gave product (3.94 g, 58% yield), mp 123-124°.

c. To prepare 3-amino-2-phenylpropene-1, 3.4 g (0.013 mole) of the phthalimido compound was heated to reflux for 1 hr in 30 ml of methanol containing 1.2 ml (0.02 mole) of 85% hydrazine hydrate. After addition of 20 ml of water, just enough hydrochloric acid was added to make the solution acidic. After filtration, the solution was concentrated, 15 ml of 6 N sodium hydroxide solution was added, and the mixture extracted four times with 30-ml portions of ether. From the dried ether extract, 1.03 g (60% yield) of 3-amino-2-phenylpropene-1 was isolated by distillation, bp 95-98° (17 mm). Tiffeneau reported bp 90-92° (14 mm).³⁶

d. **3-Carboethoxamino-2-phenylpropene-1.** A solution of 0.85 g (0.0064 mole) of the amine and 0.65 g (0.0064 mole) of triethylamine in 15 ml of ether was treated in an ice bath with 0.70 g (0.0064 mole) of ethyl chloroformate. Filtration and removal of the ether gave a product, bp 123-125° (2 mm), a pale yellow solid, mp 39.5-41.5°, yield 0.82 g (63%). The infrared spectrum showed N-H at 3457 (sharp) and 3360 (broad); olefinic and aromatic C-H at 3090, 3060, and 3030; carbonyl at 1720; C=C at 1628; aromatic ring at 1600 (weak) and 1500 cm⁻¹. The nmr spectrum showed the ethoxy CH₃ at δ 1.22 (t), ethoxy CH₂ at 4.04 (q), CH₂ at 4.15 (d), olefinic C-H's at 5.20 and 5.34, N-H at 5.3-5.8, and the aromatic CH's at 7.34.

Anal. Calcd for C₁₂H₁₅NO₂: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.27; H, 7.44; N, 7.01.

The α -methylstyrene dimer, 2,4-diphenyl-4-methylpentene-1, was prepared after Hukki.³⁰ Its infrared spectrum showed olefinic and aromatic C-H's at 3087, 3060, 3025; C=C at 1623; aromatic ring at 1600 and 1490 cm⁻¹. The nmr spectrum showed the methyl signal at δ 1.18 (s, 6.0); CH₂ at 2.77 (s, 2.1); olefinic C-H at 4.74 (broad, 1.0) and 5.08 (broad, 0.95); aromatic CH centered around 7.1 (multiplet, area 9.5).

Reaction of Carboethoxynitrene with α -Methylstyrene. A solution of 0.254 g (0.00088 mole) of I in a mixture of 35 ml of dichloromethane and 2.5 ml of α -methylstyrene (3.5 mole % in α -methylstyrene) was decomposed and worked up as described above. Vpc analysis on column A (210°) gave two major peaks, identified as 3-carboethoxamino-2-phenylpropene-1 and 2,4-diphenyl-4-methylpentene-1, respectively, by comparison of their vpc retention times and infrared and nmr spectra with those of the authentic compounds.

To determine whether the 3-carboethoxamino-2-phenylpropene-1 was formed during the vpc analysis from some other original reaction product, the original reaction mixture was analyzed by thin layer chromatography, using five solvent systems (cyclohexane:dichloromethane:ethyl acetate, 2:2:1; benzene-ether, 1:1; benzene-ether, 95:5; benzene; and dichloromethane). On silica gel (Merck), in all cases a spot was found that had run as far as a spot of the authentic compound.

Reaction of Carboethoxynitrene with *cis*-4-Methylpentene and α -Methylstyrene in Dichloromethane. The same procedure as described above for solutions not containing α -methylstyrene was employed. The analysis procedure could be employed unchanged,

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since products formed from the α -methylstyrene did not overlap with the aziridines IV and V.

Preparation of 4-Carboethoxamino-2-methylpentene-2 (VIII). A solution of 1.5 g (0.005 mole) of the N-carboethoxy-2-amino-3-iodo-4-methylpentane (from *trans*-4-methylpentene-2) and 2.5 g (0.025 mole) of triethylamine in 50 ml of absolute ethanol was stirred at room temperature for 3 hr, poured into water, and extracted with ether. From the washed ether solution, a residue was obtained that yielded VIII by gas chromatography on column B (145°). It was identified by its infrared, nmr, and mass spectra. The infrared spectrum showed N-H at 3450 (sharp) and 3350 (broad), carbonyl at 1715 cm^{-1} . The nmr spectrum showed the ethoxy CH_3 at δ 1.22 (t), ethoxy CH_2 at 4.10 (q); CH_3 at 1.17 (d), CH_2 groups at C-2 1.72 and 1.74; N-C-H at 4.0-4.7 (m); olefinic C-H and N-H at 4.7-5.2 (m); all with the proper integrals. The parent peak in the mass spectrum was, as expected, at m/e 171; ratio $(M + 1)/M$

10.4% (calcd for $\text{C}_9\text{H}_{17}\text{NO}_2$: 10.6%); base peak at m/e 156, corresponding to the loss of a methyl to give $\text{EtOOC-NH-CH-CH}=\text{C}(\text{CH}_3)_2$ for this latter peak, the ratio of $(M + 1)/M$ was found as 8.5% (calcd for $\text{C}_8\text{H}_{15}\text{NO}_2$: 9.3%).

Analysis for 4-Carboethoxamino-2-methylpentene-2 (VIII). A reaction mixture from a run with 1.5% olefin concentration (*cis*-olefin) was analyzed for VIII on column B. A trace of material with the retention time of VIII was noted; its peak area was 2.4% of that of the combined aziridines, IV + V.

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Disproportionation of Organic Polysulfides

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Abstract: The thermal decomposition of dimethyl tetrasulfide and trisulfide at 80° has been followed by the use of nmr spectroscopy. In the first case, dimethyl tri-, tetra-, penta-, and hexasulfides were found in the early stages of the decomposition. In the second case, decomposition was much slower and dimethyl di-, tri-, and tetrasulfides were initially present. Addition of a stable free radical to dimethyl tetrasulfide was found to inhibit the formation of tri- and higher polysulfides. A mechanism for the decomposition of dimethyl tetrasulfide is suggested.

The facile thermal decomposition of organic tetra- and trisulfides has been known for many years. For example, Twiss recorded that diethyl tetrasulfide gives diethyl trisulfide and free sulfur on distillation *in vacuo*;¹ Jones and Reid reported that the same tetrasulfide decomposes to diethyl disulfide and sulfur at 140-150°;² Bloomfield found that dicyclohexyl tetrasulfide gives a material of reduced sulfur content and dicyclohexyl hexasulfide when heated at 140-150°;³ Fuson, *et al.*, found that bis(2-chloroethyl) trisulfide gives a mixture of bis(2-chloroethyl) disulfide, higher sulfides, and sulfur on heating at 145-160°;⁴ and Guryanova, *et al.*, showed that when ditolyl trisulfide, in which the central sulfur atom is radioactive, is heated with diethyl trisulfide the latter becomes radioactive through exchange of the central sulfur atoms.⁵ Recently we have illustrated the instability of the tetrasulfide linkage in a more quantitative manner with the finding that the dissociation energy of the tetrasulfide linkage in dimethyl tetrasulfide is only about 36 kcal/mole.⁶

Although the lability of the polysulfide linkage has been recognized, systematic studies of the thermal decomposition of organic polysulfides have been hindered by lack of suitable means of analysis. Because the products of decomposition are themselves thermally

unstable, quantitative data based on classical methods of separation are not only difficult to obtain but are also suspect. Recently Grant and Van Wazer have reported that various dimethyl and di-*t*-butyl polysulfides can be distinguished by nmr spectroscopy.⁷ Using an analogous procedure we have followed the thermal decomposition of dimethyl tetrasulfide and trisulfide at 80°. Investigations into the mechanism of decomposition were also carried out.

Experimental Section

Reagents. Dimethyl tetrasulfide was prepared as previously reported by us.⁶ Dimethyl trisulfide was prepared by an analogous procedure using sulfur dichloride (Matheson Coleman and Bell) distilled immediately before use, bp 57-58°. The trisulfide had bp 56-57° (13 mm) (lit. 59° (12 mm)),⁸ 54-55° (11 mm),⁹ 58-59° (15 mm)¹⁰; n_D^{20} 1.5973 (lit.¹⁰ 1.5972). The yield was 87%.

Anal. Calcd for $\text{C}_2\text{H}_6\text{S}_3$: C, 18.95; H, 4.78; S, 76.24. Found: C, 18.99; H, 4.75; S, 76.30.

β -(Phenyl nitrogen oxide)- β -methylpentan- δ -one oxime (hereafter called Banfield's free radical) was prepared by the method of Banfield and Tüdös.^{11,12} Azobisisobutyronitrile (Du Pont) was used as received.

Procedure. The polysulfide under investigation (0.6 ml) and a small sealed capillary tube containing tetramethylsilane were placed in a precision-bore Pyrex nmr tube to which a standard taper joint had been attached. The tube was then degassed and sealed off under a slight pressure of nitrogen following the method previously

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described by us.⁶ The tube was heated at 80° in a bath completely protected from light. It was removed at intervals, quenched in liquid nitrogen, and allowed to attain room temperature. The nmr spectrum was taken and the tube returned to the bath.

In the other systems investigated the following materials were used: (a) dimethyl tetrasulfide (1.12 g), Banfield's free radical (0.100 g), carbon tetrachloride (0.8 ml); (b) dimethyl trisulfide (0.668 g), dimethyl tetrasulfide (0.014 g); (c) dimethyl trisulfide (0.75 ml), azobisisobutyronitrile (0.107 g); (d) dimethyl trisulfide (0.25 ml), benzene (0.5 ml); and (e) dimethyl trisulfide (0.25 ml), nitrobenzene (0.5 ml). In each case 0.6 ml of solution was placed in an nmr tube and treated as above.

Nmr Analysis. Grant and Van Wazer⁷ found that the position of the methyl resonance in a dimethyl polysulfide was progressively shifted to lower fields as the number of sulfur atoms in the polysulfide increased. In mixtures of polysulfides and in the presence of solvents the positions of the peaks, relative to tetramethylsilane, were variable, depending on the composition of the system. However, the positions of the peaks, relative to each other, were practically constant over a range of systems.

In the present work the peaks obtained from the various reaction mixtures were assigned as due to dimethyl di-, tri-, and tetrasulfides by comparison with positions and separation of the peaks obtained from authentic samples and mixtures thereof. The assignment of peaks to higher sulfides was made on the assumption that the extent of deshielding is a smooth monotonous function of the number of sulfur atoms in the polysulfide.

The difference in chemical shift of polysulfides differing by one sulfur atom was averaged over a selection of spectra obtained. The values obtained are shown in Table I; for comparison values computed from the data of Grant and Van Wazer are also given.

Table I. Differences in Chemical Shifts of Dimethyl Polysulfides

$\Delta S_{1,2}^a$	$\Delta S_{1,3}^a$	$\Delta S_{1,4}^a$	$\Delta S_{2,3}^a$	
9.1	5.7	1.7	1.2	This work
8.8	5.6	1.0	1.9	Ref 7

^a $\Delta S_{m,n}$ is equal to the chemical shift of the methyl protons in $\text{Me}_m\text{S}_n\text{Me}$ minus the chemical shift of the methyl protons in MeS_nMe in cps.

The nmr spectra were taken on a Varian A-60 high-resolution spectrometer using a sweep width of 50 cps and a sweep time of 250 sec. Peak areas were determined by machine integration. For each spectrum the area of each peak assigned to a particular polysulfide was expressed as a percentage of the total area due to all the polysulfides present. Since all dimethyl polysulfide molecules contain the same number of hydrogen atoms, this percentage area is equal to the number of molecules of the particular polysulfide present expressed as a percentage of the total number of polysulfide molecules present, *i.e.*, to the molar percentage.

Results

The percentage molar distributions of dimethyl polysulfides in the systems investigated at various time intervals are shown in Tables II–VIII. The quantities given are probably accurate to about ± 2 . (Several duplicate nmr measurements were made in each case.) In no spectrum obtained was there evidence of monosulfide, and hydrocarbons were not formed since the sum of the peak areas remained constant relative to the peak area given by the tetramethylsilane standard. The constancy of the $\text{CH}_3:\text{S}$ mole ratio in each system investigated shows that in no case is free sulfur formed in detectable quantity.

Discussion

In an earlier publication⁶ we suggested that the primary mode of decomposition of dimethyl tetrasulfide was symmetrical homolytic cleavage of the tetrasulfide linkage. Our present findings are in accord with this suggestion.

Table II. Decomposition of Dimethyl Tetrasulfide at 80°; Percentage Molar Composition of Product

Time, hr	Me_2S_2	Me_2S_3	Me_2S_4	Me_2S_5	Me_2S_6
0	0	3	97	0	0
0.5	0	8	80	10	2
1.0	0	13	72	11	4
2.5	0	20	60	16	4
5.2	0	31	49	13	7
20.1	0	47	30	15	8
43.7	0	49	27	15	9
138.0	Trace	48	26	14	10
393.5	1	49	25	14	11
1828.8	6	46	24	13	11

Table III. Decomposition of Dimethyl Trisulfide at 80°; Percentage Molar Composition of Product

Time, hr	Me_2S_2	Me_2S_3	Me_2S_4	Me_2S_5	Me_2S_6
0	0	100	0	0	0
5.2	1	98	1	0	0
20.1	3	94	3	0	0
64.6	5	89	6	0	0
237.2	13	73	12	2	0
552.3	21	62	14	3	Trace
767.2	21	61	16	2	Trace
1368.6	23	60	14	3	Trace

Table IV. Decomposition of Dimethyl Tetrasulfide at 80° in the Presence of Banfield's Free Radical; Percentage Molar Distribution of Dimethyl Polysulfides in Product

Time, hr	Me_2S_3	Me_2S_4	Me_2S_5	Me_2S_6
0 ^a	3	97	0	0
1.0	3	97	0	0
2.75	10	82	8	0
5.5	20	62	15	3
18.75	44	36	15	2

^a The nmr spectrum was taken before the addition of Banfield's free radical since it was not possible to obtain the spectrum in the presence of the initial concentration of free radical.

Table V. Decomposition of Dimethyl Trisulfide at 80° in the Presence of Added Dimethyl Tetrasulfide; Percentage Molar Composition of Product^a

Time, hr	Me_2S_2	Me_2S_3	Me_2S_4
0	0	98	2
1.0	0	98	2
2.5	0	98	2
7.5	Trace	98	2
18.0	1	97	2
41.5	3	95	2

^a No Me_2S_5 or Me_2S_6 were found.

Table VI. Decomposition of Dimethyl Trisulfide at 80° in the Presence of Azobisisobutyronitrile; Percentage Molar Distribution of Dimethyl Polysulfides in Product^a

Time, hr	Me_2S_2	Me_2S_3	Me_2S_4
0	0	100	0
4.0	Trace	97	3

^a No Me_2S_5 or Me_2S_6 were found.

Table VII. Decomposition of Dimethyl Trisulfide at 80° in Benzene; Percentage Molar Distribution of Dimethyl Polysulfides in Product^a

Time, hr	Me ₂ S ₂	Me ₂ S ₃	Me ₂ S ₄
0	0	100	0
24.9	Trace	100	Trace
139.9	2	96	2
638.2	4	90	6
1137.0	5	89	6

^a No Me₂S₅ or Me₂S₆ were found.**Table VIII.** Decomposition of Dimethyl Trisulfide at 80° in Nitrobenzene; Percentage Molar Distribution of Dimethyl Polysulfides in Product^a

Time, hr	Me ₂ S ₂	Me ₂ S ₃	Me ₂ S ₄
0	0	100	0
24.9	Trace	100	Trace
139.9	1	98	1
638.2	3	94	3
1137.0	4	92	4

^a No Me₂S₅ or Me₂S₆ were found.

The absence of dimethyl disulfide in the early stages of the decomposition of dimethyl tetrasulfide indicates that only symmetrical cleavage of the tetrasulfide linkage occurs. Unsymmetrical cleavage would give rise to MeS· and MeS₃· radicals. The MeS· radical would be expected to give rise to dimethyl disulfide by coupling or by reaction with a polysulfide molecule. In the decomposition of dimethyl trisulfide, where only unsymmetrical cleavage can occur, dimethyl disulfide is a primary decomposition product.

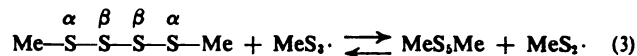
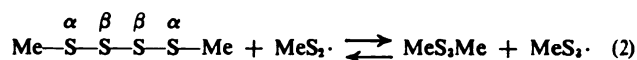
It has been suggested that MeS_x· radicals, where $x > 1$, can be stabilized by a resonance interaction with the adjacent S atoms.^{13,14} The estimated dissociation energy of the S-S bond in polymeric S is about 33 kcal/mole,¹⁵ not very different from the value of the dissociation energy of dimethyl tetrasulfide. This indicates that if such stabilization exists, only two or three sulfur atoms are effective in the delocalization. If more were involved, one would expect a substantially larger difference in the dissociation energy of these two materials.

A crude estimate of the magnitude of the stabilization can be made as follows. The dissociation energy of dimethyl disulfide is known to be about 70 kcal/mole.¹⁶ The difference between this value and the 36 kcal/mole found for the dissociation energy of dimethyl tetrasulfide may be attributed to the stabilization each of the fragments from dimethyl tetrasulfide derives from delocalization. This stabilization is thus (70-36)/2 or about 17 kcal/mole. From the arguments given above we would expect that the amount of stabilization available to a fragment such as MeS₃· would not be greater than about 20 kcal/mole. Thus symmetrical cleavage of the tetrasulfide linkage would give two stabilized fragments with roughly 34 kcal/mole of "delocalization" energy. Unsymmetrical cleavage would give an MeS· fragment, which cannot be stabilized, and an

MeS₃· fragment, which is stabilized to the extent of *ca.* 20 kcal/mole or less. Thus unsymmetrical cleavage would result in the loss of about 14 kcal/mole in stabilization energy in the products and should be very unfavorable.

Table IV shows that the decomposition of dimethyl tetrasulfide is completely suppressed by addition of a free-radical scavenger. From the rate constant for cleavage of the tetrasulfide linkage reported earlier⁴ it was possible to compute how long it would take for the scavenger to be consumed. Under our conditions about 47 min should have been required. Most of the scavenger was consumed after 45 min. This could be ascertained by the appearance of a resolvable nmr spectrum at the end of this period. (No resolvable spectrum could be obtained in the presence of the initial amount of free-radical scavenger, owing to the presence of the unpaired electron.) This offers convincing proof that radicals are involved in this decomposition; otherwise it is difficult to envisage a way of removing the unpaired spin. Dimerization of the free-radical scavenger may be ruled out by the observation that no decomposition occurs during the first hour in the presence of the scavenger whereas about 25% of the initial amount of dimethyl tetrasulfide is decomposed in a similar period in the absence of the scavenger. After the free-radical scavenger has been consumed, the decomposition proceeds in virtually identical fashion with that observed in the absence of inhibitor.

We wish to suggest the following mechanism for the decomposition of dimethyl tetrasulfide



It may be noted that α attack by MeS₃· radicals on dimethyl tetrasulfide results in no new products. The same is true of β attack by MeS₂· radicals on dimethyl tetrasulfide. The higher polysulfides can undergo cleavage at these temperatures and give rise to the same type of reactions as described above for dimethyl tetrasulfide. We also believe that reactions such as



are very unfavorable under our reaction conditions since the MeS· radical would almost certainly give rise to dimethyl disulfide (which was not observed until after long periods of heating).

The greater thermal stability of the trisulfide linkage as compared to the tetrasulfide linkage is apparent from the slower rate of decomposition of dimethyl trisulfide. If this decomposition involves homolytic cleavage, this observation is to be expected from our previous remarks concerning stabilization of the fragments.

An attempt was made to react dimethyl trisulfide with Banfeld's free radical in a manner analogous to that used with the tetrasulfide. However, the slow rate of decomposition and the thermal instability of the free-radical scavenger combined to yield inconclusive results.

(13) G. Gee, *Sci. Progr.* (London), **43**, 193 (1955).(14) G. Gee, F. Fairbrother, and G. T. Merrall, *J. Polymer Sci.*, **16**, 459 (1955).(15) D. M. Gardner and G. K. Fraenkel, *J. Am. Chem. Soc.*, **78**, 3279 (1956).(16) H. Mackle, *Tetrahedron*, **19**, 1159 (1963).

dition of a small amount (2% molar) of dimethyl disulfide to the trisulfide did not accelerate the rate of decomposition of the latter. This indicates that a free-radical chain reaction does not occur at any appreciable



A similar conclusion follows from consideration of the effect of azobisisobutyronitrile on the decomposition of dimethyl trisulfide. The initial rate of formation of dimethyl tetrasulfide is slightly accelerated, as the rate of production of disulfide is unaffected. It is almost certain that the role of the azobisisobutyronitrile is to generate isobutyronitrile radicals which subsequently attack the trisulfide. The following reactions are possible.



Reaction 8 may be excluded since the formation of $\text{Me}_2(\text{MeS}_2)\text{CCN}$ radicals would almost certainly result in the formation of dimethyl disulfide. For the same reason, $\text{MeS}_2\cdot$ radicals produced cannot participate in reaction 7 but must undergo recombination to give dimethyl tetrasulfide.

These last two experiments show that the decomposition of dimethyl trisulfide does not occur by a free-radical chain reaction initiated by the fragments of homolytic dissociation. A nonchain radical mechanism is possible and the similarity in the rates of decomposition in the solvents benzene and nitrobenzene is in accordance with this mechanism. However, we feel that our evidence is not sufficient to allow a firm conclusion to be made at the present time.

Preliminary studies in our laboratories have indicated that polysulfenyl radicals, $\text{RS}_x\cdot$, where $x > 1$, have substantially different reactivity than sulfenyl radicals, $\text{RS}\cdot$.¹⁷ In the past workers have found that non-Markovnikov addition of sulfenyl radicals to olefins is suppressed in the presence of sulfur and polysulfides.^{2,3} Such results have been explained in terms of an ionic addition caused by the presence of sulfur. While such explanations are quite reasonable, we suggest that they be viewed with due caution until the reactions of polysulfenyl radicals are more completely understood.

Acknowledgments. The authors gratefully wish to acknowledge support from the Army Research Office (Durham) and to the Sulfur Institute, Washington, D. C.

(17) S. Chubachi, Ph.D. Thesis, Princeton University, 1966.

The Vacuum Ultraviolet Photochemistry of *o*-Xylene

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Abstract: The vapor-phase photolysis of *o*-xylene has been investigated using light of 1600–2100 Å. With the exception of a small amount of benzocyclobutene which is formed by vacuum ultraviolet photolysis, the same products are formed as those produced by irradiation with 2537-Å light (toluene, *m*-xylene, *p*-xylene, and *o*-ethyltoluene). This coincidence of products suggests that both photolyses may proceed through a common set of reactive intermediates. Fluorescence measurements, as well as the effect of added inert gases on the reaction, indicate that the first excited singlet and lowest lying triplet states are not suitable choices for such common intermediates. The intermediacy of highly vibrationally excited ground electronic states seems to be most consistent with the available facts. The mechanism of formation of benzocyclobutene has been investigated by deuterium labeling, and found to proceed by the loss of a single hydrogen (or deuterium) atom from each methyl group, rather than loss of molecular hydrogen from one methyl group. The construction of lamps which emit 10^{16} to 10^{17} quanta/sec in the vacuum ultraviolet is described.

The interest in the photochemical reactions of simple, noncondensed, aromatic hydrocarbons has recently heightened by the reports of Wilzbach and Kaplan of rearrangements to the nonbenzenoid "isomers" on irradiation at the 2537-Å mercury line. In the case where the benzene ring is heavily substituted with *tert*-butyl groups (e.g., 1,2,4-tri-*t*-butylbenzene) these isomers are isolable;¹ with smaller groups the intermediacy of the isomers is inferred from the isomerization of model compounds.² These reactions occur with low quantum efficiencies, typically about 0.01.

K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.*, **87**, 4004 (1965).

(a) L. Kaplan, K. E. Wilzbach, W. G. Brown, and S. S. Yang, *J. Am. Chem. Soc.*, **87**, 675 (1965); (b) K. E. Wilzbach and L. Kaplan, *ibid.*, **86**, 2307 (1964).

Irradiation with light of wavelengths of less than 2000 Å is expected to bring about reactions much more efficiently. This expectation is based on a report³ that no fluorescence was observed when simple aromatics (benzene, toluene, *p*-xylene, and mesitylene) were irradiated in the vapor phase at wavelengths corresponding to their second and third absorption bands, approximately 1600–2100 Å. It is reasonable that the failure to observe light emission may result from an efficient predissociation path available to the excited molecule.

Since only fragmentary reports of the vacuum ultraviolet photochemistry of aromatics were available, an

(3) C. L. Braun, S. Kato, and S. Lipsky, *J. Chem. Phys.*, **39**, 1645 (1963).

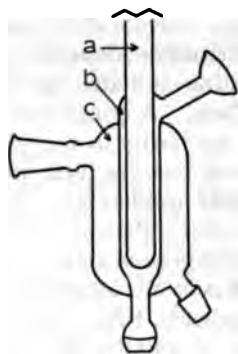


Figure 1. Vacuum ultraviolet discharge lamp: a, discharge tube; b, cooling jacket; c, photolysis cell.

investigation of the photolysis of very simple members of this compound class has been initiated in this laboratory. This paper is a report of the results observed from a single compound, *o*-xylene, and of the construction of light sources suitable for such an investigation.

Results

Vacuum Ultraviolet Light Sources. The most obvious practical reason for the neglect of studies of vacuum ultraviolet photochemistry has been the difficulty of the construction of sources of suitable intensity and stability. The production of very pure fused silica (Suprasil or Spectrosil) has been of great assistance in the solution of such problems. Lamps constructed of this material transmit light down to about 1600 Å and do not appear to degrade with use (as does lithium fluoride). Also, such lamps are relatively sturdy, and the organic polymers that are frequently deposited during photolyses are easily removed from them.

Two lamp designs were used in the present investigation; both were constructed of Suprasil where vacuum ultraviolet light transmission was required, and of ordinary fused silica elsewhere. Both lamps consisted of a discharge tube surrounded by a toroidal cell. One lamp was filled with xenon at a pressure of 190 torr as suggested by Wilkinson and Tanaka,⁴ and powered by a 2450-mc microwave generator. The discharge was contained in a Suprasil tube, part of which was surrounded by a quartz jacket which formed the photolysis cell; the unjacketed portion of the tube was inserted into a slotted wave-guide termination of the generator. The output of the lamp was inspected with a vacuum monochromator, and it agreed well with the published data.⁴ The principal ultraviolet output is a continuum which rises steeply from the Suprasil cutoff at 1600 Å to a maximum at 1760 Å and tails off to 2200 Å. No other radiation is observed until a few weak bands begin at about 3000 Å. The output of the lamp was about 6×10^{15} quanta/sec as measured by oxygen actinometry. The inner wall of the cell compartment was heated by the discharge to about 300°.

The second lamp design interposed a cooling jacket between the discharge and the photolysis cell (see Figure 1). The cell temperature was controlled by electrically heating the outer jacket and forcing nitrogen from a liquid nitrogen boiler through the inner cooling jacket. This lamp was filled with oxygen at 0.3–0.6 torr, and was powered in the same manner as the xenon

(4) P. G. Wilkinson and Y. Tanaka, *J. Opt. Soc. Am.*, **45**, 344 (1955).

lamp. The principal light output was a series of sharp lines beginning at 1600 Å⁵ and falling off to 2200 Å, with no further radiation at increasing wavelengths until a few weak and widely spaced lines appeared at 2800 Å. Approximately 95% of the ultraviolet light output below 2800 Å is between 1600 and 2000 Å. Intensity by oxygen actinometry was 10^{16} to 10^{17} quanta/sec, depending on the power input to the lamp. Temperatures in the cell could be varied from below 0 to 280°. The oxygen discharge appears to offer significant advantages over the xenon discharge in intensity, reproducibility, and cost. Since no particular care was used to purify the oxygen it is probable that impurities are present in the discharge, and there is some evidence that they are necessary to maintain the discharge.⁶

Photolysis with Vacuum Ultraviolet Radiation. The products obtained in the vacuum ultraviolet vapor-phase photolysis of *o*-xylene are listed in Table I. These products were formed in approximately the same ratios by both the xenon and oxygen lamps described above; the reported distributions are for photolysis with the oxygen lamp. The conversions in all photolyses were kept to less than 1% (and more usually <0.3%) to ensure that effectively all of the radiation was absorbed by the reactant. Thus direct photolytic destruction of products was prevented. Further reactions of products, photosensitized by *o*-xylene molecules, is of course not eliminated by this precaution.

Table I. Products of the Vapor-Phase Photolysis of *o*-Xylene^a

	Vacuum ultraviolet, ^d		2537 Å		<i>e</i>
	Static	Flow	250°	40°	
Benzene	2	<i>b</i>	<i>b</i>	<i>b</i>	0.6
Toluene	30	6	6	16	15.6
Ethylbenzene	3	<i>b</i>	<i>b</i>	<i>b</i>	0.5
<i>m</i> -Xylene	39	88	82	64	68.4
<i>p</i> -Xylene	5	5	10	7	6.2
Benzocyclobutene	5	2	<i>c</i>	<i>c</i>	<i>c</i>
<i>o</i> -Ethyltoluene	15	<i>b</i>	2	10	7.3
<i>m</i> -Ethyltoluene	1	<i>b</i>	<i>b</i>	2	1.4

^a The data are in mole %, normalized to 100% for the products reported. ^b Product present in minor amounts, less than 1 mole %. ^c Product could not be detected, <0.01 mole %. ^d The reported percentages are averages of analyses of three photolyses; the agreement was usually to $\pm 1\%$ or better between the individual photolyses. ^e Calculated from data reported by Wilzbach and Kaplan.^{1b}

Photolyses were carried out in both static and flow systems. The pressure of reactant in the photolysis cell in the static system was controlled by thermostating a reservoir of liquid *o*-xylene connected to the cell at 25°. The equilibrium vapor pressure is sufficiently high at this temperature to ensure that more than 99% of the incident light was absorbed by the sample.⁷

(5) The Suprasil cutoff at 1600 Å prevents photoionization of *o*-xylene, which does not set in until wavelengths of less than 1500 Å are reached.

(6) Lamps worked best with oxygen flowing past the discharge tube during the operation. Sealed lamps frequently failed after several hours use, and one acceptable explanation is that "impurities" necessary for breakdown were destroyed during the first hours of operation.

(7) Calculated from the absorption spectra published by J. R. Platt and H. B. Klevens, *Chem. Rev.*, **41**, 301 (1947).

ie flow photolyses the *o*-xylene sample was carried in the cell in a helium stream at a total pressure of 1 atm. The concentration of *o*-xylene in the cell was monitored by a thermal conductivity cell. The products and unreacted *o*-xylene were trapped from the stream in a trap cooled with liquid nitrogen. The same products were formed in both systems, but the ratios were changed appreciably and the quantum yield of product formation (Φ , defined as quantum yield of reaction for C_6 to C_9 compounds) was lower in the flow system ($\Phi = 0.10$) than in the static system ($\Phi = 0.15$).

At relatively large increases of the temperatures of the lamp (from 150 to 240°) for photolyses in the flow system, there was caused little change in product composition, but there was an increase in quantum yield: $\Phi = 0.02$ at 150° and $\Phi = 0.1$ at 240°. This increase in Φ is at least partially and perhaps completely due to the diminished deposition of polymer on the lamp jacket at the higher temperature.

A spectral analysis of the noncondensable gas (K) present after a static photolysis indicated that benzene was present along with smaller amounts of toluene. Polymer formation was visible only when the trap was cooled (to about 150° or lower) or when large amounts of material were passed through the lamp flow system. The visible polymer at low lamp temperatures probably resulted from further photolysis of "oligomeric" products which condensed on the "cold" jacket. Some dimeric products are formed in much smaller amounts than the volatile products. The principal dimeric product has been identified by mass spectrometry as *o,o'*-dimethylbibenzyl; other compounds of similar molecular weight are present but have not been identified.

Polymer is certainly formed in photolyses at higher temperatures, because a slight decrease in light output from the lamp (about 10%) is observed by oxygen actinometry following a photolysis.⁸ Some ring fragmentation products, C_6 and less, were also formed in small amounts (less than 1 mole %), but could not be reproducibly measured and are not included in the reported quantum yields.

Photolysis at 2537 Å. The photochemistry of *o*-xylene at 2537 Å has been reported by Wilzbach and his co-workers.^{1,2b} Their results and those obtained under different conditions (static system, 7 torr *o*-xylene pressure, 10°, low-pressure mercury lamp) in this study are in excellent agreement. When the experiment was repeated using a sample heated to 250° the product composition changed only slightly.

Pyrolysis. To ensure that the products formed in the photolysis at 250° were not merely pyrolytic products, simple pyrolysis experiments were carried out. *o*-Xylene was passed through a quartz tube at 250° in a helium stream, no observable reaction occurred. At 300° a very small conversion was observed to products expected from free-radical reactions: benzene, toluene, *o*-ethyltoluene, and *o,o'*-dimethylbibenzyl. Benzocyclobutene or *m*- or *p*-xylene was not formed.

Quantum yields for polymer formation were not determined because a photolysis to 1% conversion on samples of 50 mg did not give sufficient material for even approximate gravimetric determination. Photolysis to much higher conversions or on larger quantities of *o*-xylene gave polymer coatings on the lamp windows which made the determinations inaccurate.

Discussion

The most striking feature of the results reported in Table I is the close correspondence between the products formed by irradiation at 2537 Å and with vacuum ultraviolet radiation. Except for the benzocyclobutene which is formed only in the vacuum ultraviolet photolysis, all of the appreciable products (greater than 1 mole %) formed at 2537 Å are also formed by the vacuum ultraviolet. It is possible that this similarity is merely coincidental and that excitation at these different energies leads to the same products by different paths; no data are in hand which exclude this possibility. However, an entirely reasonable alternative is that both photolytic systems lead to a common set of reactive intermediates which proceed to the stable products. Of the two hypotheses, the second is best supported by the product studies, and leads to interesting speculation as to the possible identities of such intermediates.

A summary of the facts which are relevant to such a speculation is presented below. These facts have been gathered from the results of the closely related photolysis of benzene,⁹ and from fluorescence studies in the vacuum ultraviolet³ as well as from the data reported in this study.

1. Fluorescence measurements³ with benzene, toluene, and *p*-xylene (vapor phase) clearly indicate that excitation in the first allowed absorption band ($\lambda < 2000$ Å) does not lead to light emission. It has been concluded from this study that neither the first excited singlet state (S_1) or the lowest triplet state can be formed by such irradiation. Similar studies have not been done for *o*-xylene, but the spectral assignments,⁷ absorption intensities,⁷ and photochemistry¹⁰ are so similar for *o*- and *p*-xylene that the assumption that S_1 and the lowest triplet are not formed by vacuum ultraviolet photolysis is a satisfactory one.

2. The addition of inert gases or an increase in reactant pressure decreases the observed quantum yield of benzene disappearance at 1849 Å¹¹ and a similar effect of inert gas is observed on the 2537-Å isomerization of *m*-xylene.^{2b} Helium (1 atm) lowered the Φ from *o*-xylene by 40%.

3. When oxygen is added to photolysis samples, it is found to be only slightly more effective in lowering conversions than are other foreign gases. Thus oxygen was only three times as effective in quenching *m*-xylene isomerization as was nitrogen (both at 100 torr, *m*-xylene at 5–7 torr).^{2b} Oxygen (2 torr) had no effect on the disappearance of benzene (1 torr) with 1849-Å irradiation.¹¹

4. Pyrolysis of *o*-xylene at 550° led to a few of the photolysis products in very low conversions, but the major product, *m*-xylene, was not formed.

5. Product ratios from both 2537 Å and the vacuum ultraviolet photolysis of *o*-xylene were changed by changes in temperature and by addition of inert gases.

(9) There is every reason to believe from spectral assignments⁷ that the same excited states are being examined in each case. Photoproducts are very different in the two cases because the principal reactions which occur with the xylenes are either reiterative (isomerization) or impossible (loss of methyl or benzylic hydrogen) with benzene. As a result no photoproducts form from benzene with 2537-Å radiation in the vapor phase [J. N. Pitts, Jr., J. K. Foote, and J. K. S. Wan, *Photochem. Photobiol.*, **4**, 323 (1965)], and the principal reaction with vacuum ultraviolet irradiation is the formation of fulvene [H. R. Ward, J. S. Wishnok, and P. D. Sherman, Jr., *J. Am. Chem. Soc.*, **89**, 162 (1967)].

(10) H. R. Ward, unpublished data.

(11) K. Shindo and S. Lipsky, *J. Chem. Phys.*, **45**, 2292 (1966).

The excited state which *prima facie* is expected to be common between excitation at 2537 Å and by the vacuum ultraviolet is the S_1 state, since intersystem crossing from higher singlets to the first excited singlet is usually thought to be very efficient.¹²

The S_1 state seems unlikely as a common reactive intermediate in this case for several reasons. First, fluorescence studies³ (1) strongly suggest that this state cannot be formed by vacuum ultraviolet irradiation. Second, inert gas gives almost no quenching of benzene fluorescence¹³ (when pressures in the range of these experiments are considered), but does quench *m*-xylene isomerization.^{2b} Finally, oxygen has no effect on benzene disappearance at 1849 Å (3) even though it is known to quench the S_1 state.¹¹ The presence of any triplet state in the reaction scheme also can be eliminated by the small effect of added oxygen.¹⁴

A higher singlet, S_n , can hardly be reached by 2537-Å excitation, but can be eliminated as an intermediate leading directly to products even from vacuum ultraviolet photolysis, because its lifetime is so short (10^{-12} sec) that no effect of added inert gas would be expected³ (collision times under these conditions are about 10^{-9} to 10^{-10} sec). The most reasonable remaining alternatives for common reactive intermediates are various highly vibrationally excited ground electronic states (S_0^*). Thus a molecule excited to an S_n state might undergo rapid internal conversion to such a S_0^* state; conversion from S_1 to S_0^* must compete with fluorescence. The higher quantum yield for product formation with the vacuum ultraviolet than with 2537 Å is consonant with such a system.

The effect of oxygen in decreasing the quantum yield of isomerization of *m*-xylene may be due to quenching of S_1 before internal conversion occurs. Added inert gases would be expected to decrease Φ of product formation by collisional deactivation. This postulate is also consistent with the observations listed in 1. Similar arguments have been used by Shindo and Lipsky¹¹ to propose an excited ground state in benzene photolysis.

The sensitivity of product ratios to changes in temperature and added foreign gases indicates that the products do not proceed directly from any single excited state. A single intermediate which could lead to such a variety of products would be very difficult to visualize in any case. It is not possible from the available data to say anything about which vibrational states might be involved, but a close inspection of the product ratios reported in Table I leads to some interesting suggestions. Thus at constant temperature, introduction of 1 atm of helium (in the vacuum ultraviolet system) causes a decrease in Φ which is almost entirely in products involving bond cleavage and bond formation (called, for convenience, decomposition products). Isomerization proceeds almost unhindered. This is consistent with a model in which highly vibrationally excited molecules lead to isomeriza-

tion in a time comparable to collisional times and other vibrational states (probably lower lying than those leading to isomerization) lead less rapidly to decomposition. Although energy surfaces are so complex as to be almost abstract for molecules as complicated as *o*-xylene, this situation is approximated by a surface leading to isomerization which crosses the ground-state surface at a high vibrational level, and a surface which crosses at a lower level leading to decomposition products. Reactions which lead to isomerization probably give the initially formed isomer at a high vibrational level. An increase in sample or foreign gas pressure should operate to stabilize the isomer and prevent its further decomposition. This expected effect is also compatible with the observed results.

Such a model is also consistent with the effect of temperature on product distribution in 2537-Å radiation. Internal conversion from the S_1 level would probably enter the ground-state manifold at a level lower than that for S_n crossing. Raising the sample temperature would give a greater number of molecules the vibrational energy necessary to isomerize. Such a model predicts that hot-tube pyrolysis should lead mostly to decomposition, since the vibrational levels are populated from the bottom in a Boltzmann fashion and excited molecules would be "siphoned" off onto the decomposition route before gaining enough energy to isomerize. The conceptual model is of course highly oversimplified. It is probably more reasonable to postulate that each decomposition product results from different levels of vibrational excitation. Also, if the simple model were to be strictly applied, it would predict a larger relative percentage of isomerization in vacuum ultraviolet photolysis than is actually observed.

Wilzbach and Kaplan found no evidence of *p*-xylene at low photolytic conversions of *o*-xylene vapor.^{2a} In vacuum ultraviolet photolysis, *p*-xylene is present even at conversions of 0.05%, and in a relatively constant ratio with *m*-xylene, so that it is most unlikely that *p*-xylene forms from a further isomerization of *m*-xylene. The suggestion of Wilzbach and Kaplan that isomerization proceeds through intermediates of benzvalene (I) and prismane types (II) has considerable



experimental support. A benzvalene intermediate formed from *o*-xylene can lead only to *m*-xylene (or back to *o*-xylene), all three isomers can be formed from the dimethylprismanes. (No stable dimethylbenzvalene or dimethylprismane has yet been detected in this system.) The suggestion of Bryce-Smith and Longuet-Higgins¹⁵ that the first excited singlet state in benzene should lead to benzvalene, and the lowest triplet to prismane appears to be inapplicable to *o*-xylene at least (*vide supra*). The exact method by which isomerization occurs has not been established for the xylenes, nor has the excited state leading to isomerization been identified. Hopefully these problems will yield to experiments presently in progress.

Mechanism of Benzocyclobutene Formation. The only isolated product that is unique to the vacuum

(12) N. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 64.

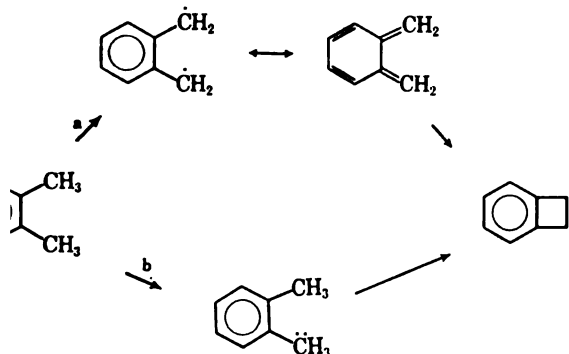
(13) H. Ishikawa and W. A. Noyes, Jr., *J. Chem. Phys.*, **37**, 583 (1962); G. B. Kistiakowsky and C. S. Parmenter, *ibid.*, **42**, 2942 (1965).

(14) Oxygen is reported to bring about the radiationless quenching of both excited singlets and triplets on virtually every collision (J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, p 599).

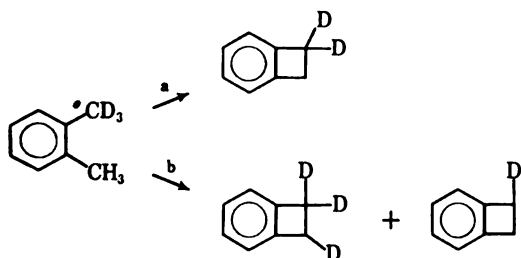
(15) D. Bryce-Smith and H. C. Longuet-Higgins, *Chem. Commun.*, 593 (1966).

violet photolysis of *o*-xylene (as compared to 2537 Å benzocyclobutene. This product must also come from some vibrationally excited and relatively lived intermediate because its yield is decreased with a decrease in temperature and by an increase in gas pressure.

To effect the formation of benzocyclobutene, two hydrogen atoms must be lost from the *o*-xylene molecule, most probably from the methyl groups. Two routes can be envisioned for this loss.



Two routes can be supported by analogy to known chemical reactions. Cleavage of C-H bonds to form benzylic radicals (as in a) has been demonstrated by Porter and Wright.¹⁶ Loss of molecular hydrogen from a single carbon atom (as in b) is the preferred mechanism of decomposition of ethane with 1470-Å photons.¹⁷ The proof that benzocyclobutene is preferentially formed by path a was obtained by the photolysis of α,α,α -trideuterio-*o*-xylene. The isotopic content of the benzocyclobutene product was determined



by mass spectroscopy at low ionizing voltage. The chromatograph direct coupled to a mass spectrometer showed that 90% of the benzocyclobutene contained two deuterium atoms, and only 4% d_3 and 4% d_1 . This particular analysis provides a convincing demonstration of the power of this analytical combination.

The photolysis was run on a 35-mg sample of deuterated material, and the product contained 3 μ g of benzocyclobutene. This amount of material would have been sufficient to obtain over 100 satisfactory analyses of product distribution (from the chromatograph trace) and isotopic composition (from the mass spectrometer output).

Experimental Section

Ultraviolet Lamps. Xenon Lamps. Research grade (at 190 torr) was sealed in a Suprasil tube, 12 mm o.d. \times 9 cm of the length was enclosed in a 20-mm o.d. quartz jacket which was fitted with ground joints at the top and bottom.

The lamp was powered by inserting the unjacketed stub of the Suprasil envelope into the slotted wave guide of a PGM-100 Raytheon microwave power generator (2450 mc, 150-800 w). The lamp was cooled during operation by air blasts from several directions.

Oxygen Lamps. The lower 8-cm portion of a 12 mm o.d. \times 16 cm Suprasil tube (0.5-mm wall) was jacketed by a 18 mm o.d. Suprasil tube carrying ground joints at the bottom and near the top ring seal. This jacket was used for cooling the lamp. The cooling jacket was in turn enclosed by a 40-mm o.d. quartz jacket, also fitted with top and bottom joints, which comprised the photolysis cell (see Figure 1). The discharge tube of this lamp was not sealed, but operated with oxygen flowing past the top of the discharge tube through a T joint. The pressure was held at 0.3-0.6 torr (as measured by a thermocouple gauge) by an adjustment of a needle valve on an oxygen cylinder leading to the T joint and a needle valve leading away from the T joint to a mechanical pump. The lamp was powered in the same manner as the xenon lamp. The light output was inspected by a Robin, 0.5-m vacuum monochromator through the top joint of the photolysis cell.

Actinometry. Oxygen actinometry was used to measure the output of both lamps. Oxygen was passed through the photolysis cell at 100-160 cc/min and bubbled through a dispersion tube into a 0.1 M solution of potassium iodide buffered with sodium acetate and acetic acid. The I_2^- concentration was determined spectroscopically at 350 m μ . Duplicate determinations usually agreed to $\pm 5\%$.

Photolysis Technique. Static System. The *o*-xylene sample (Phillips Petroleum Research grade) was placed in a small flask on the bottom joint of the cell of the oxygen lamp, frozen at 77°, the jacket was evacuated to 0.005 torr, and the sample was degassed by a freeze-thaw cycle. The cell was isolated by a stopcock and the sample flask thermostated at 25°. After allowing sufficient time for equilibrium to be reached, the lamp was started, and cooling nitrogen was passed through the cooling jacket. The extent of cooling was determined by the voltage on a heater in a liquid nitrogen boiler. After the photolysis, the sample was condensed in the flask and removed for analysis.

Flow Systems. The *o*-xylene sample was injected into a glass container installed in the place of a column in the oven of an Auto-prep gas chromatograph. The effluent stream from the thermal conductivity cell was conducted to the photolysis cell through a heated line. The temperature of the *o*-xylene was controlled by the oven thermostat, the helium flow was held constant by the chromatograph flow controller, and the *o*-xylene concentration was precisely monitored by the chromatograph detector. For sample sizes of 0.1 ml at temperatures of 40 to 50° the technique gave a nearly constant *o*-xylene concentration for greater than 90% of the photolysis time. Samples were trapped at liquid nitrogen temperature for analysis.

Photolysis at 2537 Å. Ten germicidal lamps (GE G25-T8) were arranged in a 26-cm diameter circle with a stainless steel reflector surrounding the lamps. The photolysis cell was a fused quartz tube, 2.54 cm o.d. \times 54 cm, fitted with a sample holder and a stopcock. The sample of *o*-xylene (0.01 ml) was frozen in the sample holder, the cell was evacuated to less than 0.005 torr and isolated with the stopcock, and the sample was allowed to warm to room temperature. The cell was suspended along the vertical axis of the circle of lamps during the photolysis. For photolysis at 250°, the cell was loosely wrapped with fine resistance wire. Temperatures inside the tube were measured by a thermocouple. Heating by this method showed a variation of $\pm 10^\circ$ along the tube; the reported temperature is an average.

Pyrolysis. A quartz tube 1.8 cm o.d. \times 14 cm was wrapped with resistance wire for use as a pyrolysis tube. The *o*-xylene sample was passed through the tube in a helium stream, as described for the vacuum ultraviolet photolysis flow system.

Analysis. All analyses were done by flame-ionization gas chromatography, occasionally in conjunction with mass spectroscopy. The most useful columns were 5% DEGA-5% Bentone-34 on 100-120 mesh Chromosorb W, 1/8 in. o.d. \times 20 ft, operated at about 70°. A support-coated Carbowax 1540 capillary column, 0.02 in. i.d. \times 50 ft, was useful in separating benzocyclobutene from the ethyltoluenes. Analysis for dimeric hydrocarbons was done on Silicone SE-30, Silicone QF-1, and DEGA-Bentone-34 columns at higher temperatures (100-140°). Quantitative determinations were averages of triplicate analyses, and areas were measured by planimeter or disk integrator and corrected for sensitivity to the flame detector to give the mole fraction. Identification was by comparison of retention times with known compounds on at least two (and

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usually three) columns, and by comparing the fragmentation pattern in the mass spectrum. In the gas chromatograph-mass spectrometer combination, a Varian Aerograph, Model 204-2, was connected by a low volume heated line, fed through an effluent stream splitter, to the helium concentrator of a Perkin-Elmer-Hitachi RMU 6-D.

Synthesis of α,α,α -Trideuterio-*o*-xylene. A solution of 2.65 g (0.0175 mole) of methyl *o*-toluate and 0.6 g of lithium aluminum deuteride (Metal Hydrides) in 10 ml of ethyl ether was stirred at reflux for 12 hr. Work-up with aqueous acid gave 2.14 g (0.0172 mole) of a white solid, mp 31–33° (lit.¹⁸ *o*-methylbenzyl alcohol mp 34°). The crude dideuterio alcohol (1 g) was added to 20 ml of cold, freshly distilled thionyl chloride, and the solution was slowly warmed to the boiling point and refluxed until gas evolution ceased. Excess thionyl chloride was removed on a rotary evaporator, and small portions of pentane were added and removed under vacuum to flush out the remaining traces of thionyl chloride. The resulting clear oil was dissolved in 20 ml of dry tetrahydrofuran and stirred

at reflux under nitrogen with 0.26 g of lithium aluminum deuteride. The reaction mixture was acidified, and the product *o*-xylene was extracted into a known volume of pentane. Comparison of the gas chromatogram of this solution with a standard mixture indicated that 0.76 g of the deuterated *o*-xylene was present (theory, 0.88 g). The *o*-xylene was isolated by preparative gas chromatography to ensure purity of the sample. Analysis by mass spectroscopy at reduced ionization voltage showed the *o*-xylene to be 98% d_4 and 2% d_5 , with no detectable amounts of d_1 or d_6 .

Acknowledgments. The support of this research by the National Science Foundation (GP-3496) is gratefully acknowledged. The mass spectrometer used in this investigation was purchased under a National Science Foundation Research Instrument Grant. Mr. John S. Wishnok and Mr. Charles I. Barta participated in the development of the oxygen lamp and in measuring its spectral output.

(18) "Handbook of Chemistry and Physics," 32nd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1950, p 806.

Photochemistry of Sodium 9-Anthroate in Aqueous Solution¹

Anne W. Bradshaw and O. L. Chapman

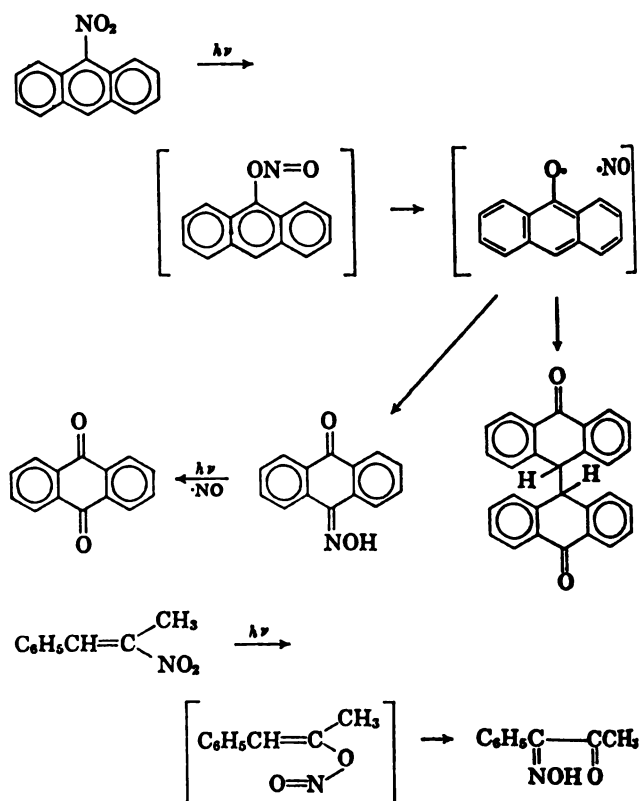
Contribution from the Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50010. Received November 5, 1966

Abstract: The photochemistry of sodium 9-anthroate in aqueous solution has been investigated. Earlier reports that irradiation of sodium 9-anthroate in the presence of air gives photodimer and anthraquinone have been confirmed, and carbon monoxide, 10,10'-bianthrone, and anthracene have also been isolated. In degassed solutions sodium 9-anthroate gives anthrol anion and carbon monoxide. Air oxidation of the anthrol anion is responsible for formation of anthraquinone and 10,10'-bianthrone. The photochemical isomerization of sodium 9-anthroate to anthrol anion is considered to be analogous to the photoisomerization of 9-nitroanthracene.

Recent investigations of vinyl^{2,3} and aryl^{2,4} nitro compounds have uncovered photochemical rearrangements in which the nitro group isomerizes to a nitrite ester which then gives rise to products.

Irradiation ($\lambda < 410 \text{ m}\mu$) of 9-nitroanthracene gives, for example, 10,10'-bianthrone as the major product and lesser amounts of anthraquinone and anthraquinone monooxime,^{2,5} while β -methyl- β -nitrostyrene gives 1-phenyl-1-oximino-2-propanone.^{2,3}

As one aspect of our investigation of these rearrangements, we have considered whether the carboxylate anion which is isoelectronic with the nitro group might show related rearrangements. Both the nitro group and the carboxylate group are capable of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. Sodium 9-anthroate was selected for initial study because of its relationship to 9-nitroanthracene. Weigert and Ludwig have reported⁶ that irradiation of aqueous solutions of sodium 9-anthroate which were open to air gave a precipitate (anthraquinone)



(1) Photochemical Transformations, part XVIII. Portions of this report were abstracted from the M.S. thesis of A. W. Bradshaw, Iowa State University of Science and Technology, 1966.

(2) O. L. Chapman, A. A. Griswold, E. Hoganson, G. Lenz, and J. Reasoner, *Pure Appl. Chem.*, **9**, 585 (1964).

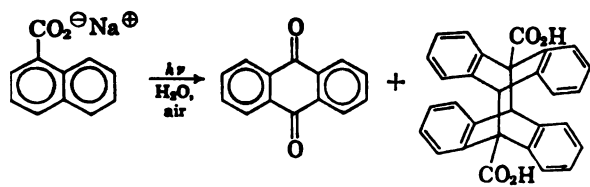
(3) O. L. Chapman, P. G. Cleveland, and E. D. Hoganson, *Chem. Commun.*, 101 (1966).

(4) O. L. Chapman, D. C. Heckert, J. W. Reasoner, and S. P. Thacker, *J. Am. Chem. Soc.*, **88**, 5550 (1966).

(5) F. D. Greene, *Bull. Soc. Chim. France*, 1356 (1960).

(6) F. Weigert and L. Ludwig, *Ber.*, **47**, 898 (1914).

upon acidification the photodimer. Subsequent studies⁷ have shown that the photodimer has the head-



to structure. Dufrasse and Mathieu have shown that irradiation of disodium anthracene-9,10-dicarboxylate in solutions exposed to air also gives anthraquinone.⁸ It has been assumed generally that the formation of anthraquinone in these irradiations involved a 10-epidioxide in each case.

Its

The results of our initial irradiations of sodium 9-anthroate are given in Table I. The formation of

I. Irradiation of Sodium 9-Anthroate

Conditions	% pure compound isolated				
	Starting material	Dimer of 9-anthroic acid	Anthraquinone	Anthracene	10,10'-Bianthrone
1-hr irradiation in water in a Pyrex vessel open to the atmosphere; concn, 0.040 M	58	25	3
1-hr irradiation in water in a Pyrex vessel with nitrogen flush; concn, 0.040 M	33	39	4
3-hr irradiation in water in a Pyrex vessel with nitrogen flush; concn, 0.0045 M	42	31	9	4	2
5-hr irradiation in water in a Pyrex vessel using λ 290-360 m μ and nitrogen flush, concn, 0.0033 M	54	11	11	3	7

anthracene dimer and anthraquinone was confirmed, and 10,10'-bianthrone and anthracene were observed as products. Flushing the solution with purified nitrogen⁹ during the irradiation (which should remove most all oxygen from the solution) had little effect on product composition. A change in concentration of sodium 9-anthroate from 0.040 to 0.0045 M reduced the yield of dimer slightly but did not affect the yields of other products significantly. Use of light of wave-

D. E. Applequist, T. L. Brown, J. P. Keiman, and S. T. Young, *J. Am. Chem. Soc.*, **81**, 5050 (1959).

C. Dufrasse and J. Mathieu, *Bull. Soc. Chim. France*, **14**, 307, 1959.

Rigorous degassing by freeze-thaw cycles was not practical for this scale work. Nitrogen flushing during the irradiation should be solutions almost oxygen free. In rigorously degassed solutions oxidation occurred during work-up, and this is presumed to be the case for solutions flushed with nitrogen.

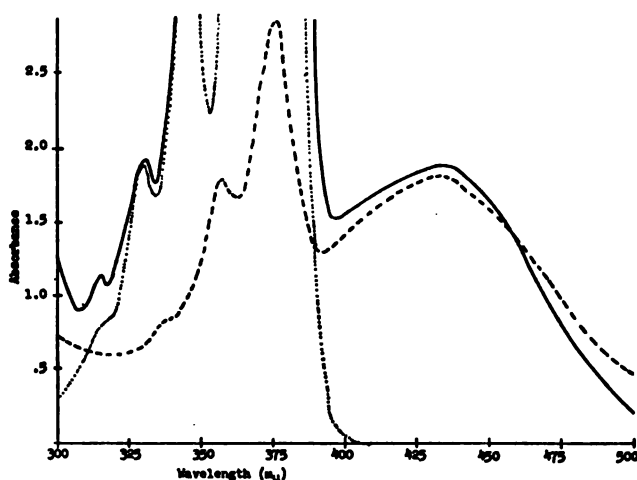


Figure 1. Ultraviolet spectra of anthrol anion, ---; sodium 9-anthroate, . . . ; and the aqueous solution of sodium 9-anthroate after irradiation and before exposure to atmospheric oxygen, —.

length 290-360 m μ gave substantially lower yields of photodimer than were obtained when the full output of lamp above 290 m μ was used.¹⁰ Irradiation of carefully degassed aqueous solutions of sodium 9-anthroate in sealed ampoules permitted isolation and characterization of carbon monoxide. Monitoring the irradiation of the degassed solutions in sealed ampoules by ultraviolet absorption spectroscopy revealed the presence of an intermediate with an absorption maximum at about 453 m μ . This absorption is characteristic of 9-anthrol anion (Figure 1).

Irradiation (290-360 m μ) of the disodium salt of the photodimer in degassed solution in a sealed tube gave sodium 9-anthroate and the anthrol anion. The formation of dimer is thus photochemically reversible when light is absorbed by the dimer. Formation of anthrol anion presumably is a secondary process based on sodium 9-anthroate which has a greater molar extinction coefficient in this region than the dimer.

Discussion

The photochemical conversions of sodium 9-anthroate are summarized in Chart I. Formation of the photodimer is reversible, and this reversibility is presumably responsible for the wavelength dependence of dimer yield. Decarboxylation of sodium 9-anthroate is mildly surprising, but other photochemical decarboxylations are known.¹¹ In any event, decarboxylation is a minor process. The most interesting reaction is the photochemical conversion of 9-anthroate anion to anthrol anion. The anthrol anion is known to react rapidly with oxygen giving both anthraquinone and 10,10'-bianthrone.¹² In the absence of oxygen only anthrol anion is formed, but when oxygen is admitted during work-up it is oxidized to the observed products. The nature of the excitation (n, π^* or π, π^*) in sodium 9-anthroate and the multiplicity of the reactive state are not known.

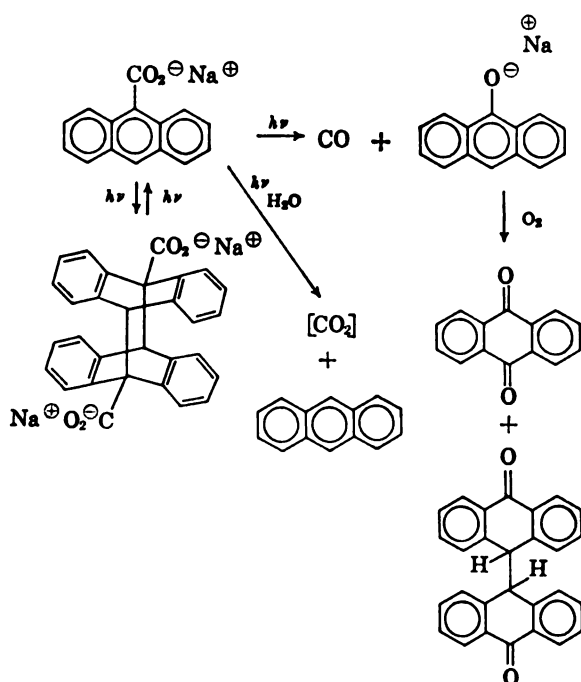
The formation of the anthrol anion can be described in much the same fashion as the nitro to nitrite rearrangements. It is assumed for the sake of discussion

(10) This wavelength dependence is analogous to that reported by Greene for 9-nitroanthracene.⁴

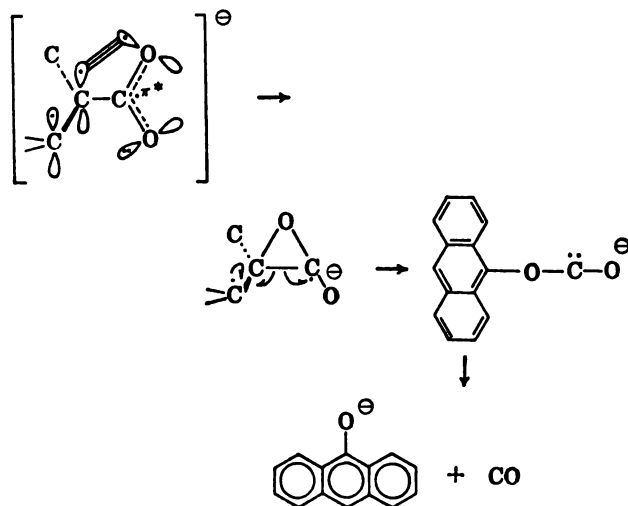
(11) J. D. Margcrum, *J. Am. Chem. Soc.*, **87**, 3772 (1965).

(12) H. L. J. Backstrom and H. A. Beatty, *J. Phys. Chem.*, **35**, 2530 (1931).

Chart I



that the excitation responsible for this reaction is localized in the carboxylate group and is n, π^* . The plane of the carboxylate group will be nearly at right angles to the plane of the aromatic rings because of the *peri* hydrogens.



The out-of-plane carboxylate group has the half-vacant nonbonding orbital properly aligned for interaction with the π system of the aromatic rings.¹³ The anthrol anion formed by loss of carbon monoxide is stable (in the absence of oxygen), in contrast to the 9-anthryloxy radical which is formed when nitric oxide is lost from the corresponding nitrite.

Experimental Section

Irradiation of Sodium 9-Anthroate Open to the Atmosphere. A water solution of sodium 9-anthroate was made by dissolving 9-anthroic acid (4.0 g, 0.018 mole) in water (450 ml) to which sodium hydroxide (18.0 ml of 1.00 M, 0.018 mole) had been added.

(13) The description of the excited state given above is very crude. Actually, the two nonbonding p atomic orbitals combine to give symmetric (n_s) and antisymmetric (n_a) combinations. The p atomic orbital representation is used for convenience.

The solution (0.040 M, pH 9.5) was filtered into a 500-ml capacity Pyrex immersion well. The solution, open to the atmosphere, was irradiated for 5 hr with a Hanovia Type A, medium-pressure, mercury arc lamp. The solution was filtered. The solid (56 mg, 1.4% of the sample weight, mp 234–237°) was dissolved in hot benzene and chromatographed on 40 g of silica gel giving anthraquinone (0.04 g, 1.1%, mp 255–262°). The filtrate from the irradiation was continuously extracted with ether giving anthraquinone (0.07 g, 1.8% yield). The total yield of anthraquinone was 2.9%.

The water solution was acidified with 1.5 ml of concentrated hydrochloric acid and continuously extracted with ether. White crystals formed in the yellow ether solution. Filtration yielded the photodimer of 9-anthroic acid (0.99 g, 25% yield, mp 216–220°, infrared 5.88 μ).

Anal. Calcd for $C_{20}H_{10}O_4$: C, 81.07; H, 4.54. Found: C, 80.98; H, 4.63.

The acid dimer was converted to the methyl ester (mp 222–223°, lit.⁷ 226–227°) by addition of the acid chloride to methanol. The mass spectrum of the methyl ester showed m/e 472 (0.5% of base) for the parent ion and m/e 236 (93.5% of base) for symmetrical cleavage of the dimer.

Evaporation of the ether solution gave crude 9-anthroic acid (2.3 g, 58%) which was identified by infrared comparison.

Irradiation of Sodium 9-Anthroate with a Nitrogen Flush. A water solution of sodium 9-anthroate was made from 9-anthroic acid (4.0 g, 0.018 mole) and sodium hydroxide (18 ml of 1.00 M, 0.018 mole) and enough water to make a total volume of 450 ml. The solution (0.040 M, pH 9) was filtered into a 500-ml capacity Pyrex well. Nitrogen was passed through the solution for 1 hr. The yellow solution was irradiated for 5 hr with a Hanovia Type A, medium-pressure, mercury arc lamp with a continuous flow of purified nitrogen. The solution was filtered. The solid (120 mg, 3.0% of the sample weight) was chromatographed on 50 g of silica gel giving anthraquinone (0.10 g, 2.7%, mp 232–238°, identified by infrared comparison with an authentic sample). The mass spectrum of the product showed m/e 208 for the parent ion, m/e 180 with a metastable ion at m/e 155.5 for the loss of carbon monoxide, and m/e 152 with a metastable ion at 128.2 for the second loss of carbon monoxide, in agreement with the mass spectrum of anthraquinone reported by Beynon.¹⁴

Continuous extraction of the filtrate with ether gave anthraquinone (0.03 g, 0.8%). The total yield of anthraquinone was 3.5%.

The water solution was acidified with 1.5 ml of concentrated hydrochloric acid and continuously extracted with ether. Filtration of the yellow ether solution gave the photodimer of 9-anthroic acid (1.5 g, 39% yield, mp 219–220°) which was identified by infrared comparison. Evaporation of the ether gave crude 9-anthroic acid (1.3 g, 33%).

Irradiation of Sodium 9-Anthroate at Lower Concentrations. The solution of sodium 9-anthroate was made from 9-anthroic acid (2.00 g, 0.009 mole), sodium hydroxide (20 ml of 0.50 M, 0.010 mole), and enough water to make the total volume 2 l. The solution (0.0045 M, pH 11) was filtered into a Pyrex immersion well, and purified nitrogen was passed through for 2 hr. The nitrogen was purified by passage through a trap, two bottles of Fieser's solution, two traps, 18 M sulfuric acid, a trap, and finally a drying tower. The solution was irradiated for 20 hr with a Hanovia Type A, medium-pressure, mercury arc lamp.

The solution was filtered. The solid (0.2 g, 16% of the sample weight) was chromatographed on 40 g of silica gel giving anthracene (0.06 g, 4%, 206–214°), anthraquinone (0.17 g, 9%, 225–235°, $C=O$, 5.97 μ), and 10,10'-bianthrone (0.04 g, 2%, mp 243–247°, $C=O$, 6.02 μ).

The filtrate from the irradiation was acidified with 1.5 ml of concentrated hydrochloric acid and continuously extracted with ether. Filtration of the yellow ether solution after concentration gave the photodimer of 9-anthroic acid (0.62 g, 31% yield, mp 215–219°). Evaporation of the ether solution gave 9-anthroic acid (0.84 g, 42% yield, mp 212–214°).

Irradiation of Sodium 9-Anthroate with a Filter Solution. The filter solution was made by dissolving nickel sulfate (690 g of $NiSO_4 \cdot 6H_2O$) and cobalt sulfate (220 g of $CoSO_4 \cdot 7H_2O$) in water (1 l.). This solution for a 0.8-cm path length transmits 90% of the light at 300 m μ and less than 2.0% of the light from 360 to 540 m μ .

The solution of sodium 9-anthroate was made from 9-anthroic acid (2.4 g, 0.0108 mole), sodium hydroxide (1.00 g, 0.025 mole), and

(14) J. H. Beynon, G. R. Lester, and A. E. Williams, *J. Phys. Chem.*, **63**, 1861 (1959).

water to make a total volume of 3.2 l. The solution (M , $pH > 11$) was filtered into a Pyrex immersion well. Nitrogen was passed through for 1.5 hr.

Solution was irradiated for 19.5 hr with a Hanovia Type A, medium-pressure, mercury arc lamp. The highest temperature filter solution reached was 55° . The solution was filtered. 1 (0.28 g, 12% of the sample weight) was chromatographed on silica gel giving anthracene (0.02 g, 1%, mp $196-203^\circ$), quinone (0.15 g, 6.7%, mp $230-239^\circ$), and 10,10'-bianthrone (1.2%, mp $253-256^\circ$).

Filtrate was continuously extracted with ether for 3 days. 1 (0.2 g) from the evaporation of the ether was chromatographed on 20 g of silica gel giving anthracene (0.03 g, 1.5%, mp $196-203^\circ$), anthraquinone (0.09 g, 4.0%, mp $232-243^\circ$), and crude bianthrone (0.05 g, 2.4%, mp $235-240^\circ$). The total yields of three products were anthracene (2.5%), anthraquinone (6.6%), and 10,10'-bianthrone (6.6%).

Filtrate was acidified with 10 ml of concentrated hydrochloric acid and continuously extracted with ether for 3 days. The ether was evaporated to dryness. The solid was recrystallized from benzene. Filtration of the hot benzene solution gave the mother liquor of 9-anthroic acid (0.25 g, 11%). Upon cooling, the solution gave crystals of 9-anthroic acid (1.4 g, 54%).

Preparation of Sodium 9-Anthroate in a Sealed Tube. The ampoule was made from a test tube (13×100 mm) and a standard neck joint (14/20). The ampoule was filled with 5 ml of 9-anthroic acid (0.003 M) in water. The ampoule was frozen in an ice-trichloroethylene bath, evacuated to 0.025 mm, closed, and thawed. This process was repeated except before the second time it was sealed off. The ampoule was irradiated for 5 hr with a Hanovia Type A, medium-pressure, mercury arc lamp using the nickel sulfate-cobalt sulfate filter described above. The ultraviolet spectrum (Figure 1) shows the presence of the anthrol anion.

Irradiation of Sodium 9-Anthroate in a Sealed Tube to Identify Carbon Monoxide. 9-Anthroic acid (2.00 g, 0.009 mole) and 10% sodium hydroxide (50 ml) were diluted to 75 ml. The solution (0.12 M) was put in a heavy-walled, Pyrex, 100-ml capacity tube fitted with a vacuum stopcock. The tube was frozen, evacuated to 0.02 mm, closed, and thawed. This process was repeated four times. The tube was irradiated for 19 hr with a Hanovia Type A, medium-pressure, mercury arc lamp using the nickel sulfate-cobalt sulfate filter solution described above. After irradiation the product gases were expanded into an infrared gas cell. The infrared spectrum showed, in addition to the bands for the water present, a broad band at 4.7μ (lit.¹⁴ for carbon monoxide 4.67μ).

The solution was filtered giving a solid (0.02 g) which by infrared comparison was shown to be a mixture of anthraquinone and 10,10'-bianthrone. No further attempt at separation was made.

Irradiation of the Disodium Salt of the Photodimer of 9-Anthroic Acid in a Sealed Tube. The dimer of 9-anthroic acid (0.222 g, 0.0005 mole) was dissolved in 10% sodium hydroxide (20 ml) and diluted to 25 ml (0.02 M). An ampoule containing 6 ml of the solution was prepared in the manner previously described and irradiated. The ultraviolet spectrum of the solution showed the presence of sodium 9-anthroate and the anthrol anion. Filtration of the solution gave water-insoluble compounds (0.006 g, 11% of starting material). The filtrate was acidified and continuously extracted with ether. Filtration of the ether solution gave dimer (0.038 g, 71% yield) and evaporation gave 9-anthroic acid (0.007 g, 13% yield).

Acknowledgment. Portions of this research were supported by a grant from the National Science Foundation (GP-6740).

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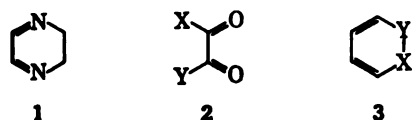
The Photorearrangement of 2,3-Dihydropyrazines

Peter Beak and John L. Miesel¹

Contribution from the W. A. Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois. Received November 28, 1966

Abstract: Six 2,3-dihydropyrazines have been found to rearrange to imidazoles upon photolysis. Data are presented in support of the proposal that the reaction proceeds through an irreversibly formed enediimine intermediate.

Comparison of the photolysis of the 2,3-dihydropyrazine system 1 with the photochemistry of structurally related and extensively studied α,β -unsaturated systems 2 and six-membered cyclic dienes 3 reveals a number of practical and theoretical interest.² Analogy



suggests 1,4³ and 1,2⁴ additions, reduction,⁵ oxida-

tion. J. G. Calvert and J. N. Pitts, "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, pp 528-530.

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B. Rubin and P. Zwiakowits, *J. Org. Chem.*, 29, 2362 (1964); J. Krauch, S. Farid, and G. O. Schenk, *Ber.*, 98, 3102 (1965); Rubin and R. G. LaBarge, *J. Org. Chem.*, 31, 3283 (1966).

tion,^{6,5} and radical formation⁶ might occur upon photolysis of 1. If 3 is allowed as an analogy, ring opening to a triunsaturated system,⁷ ring closure to a bicyclo[2.2.0] system,⁸ formation of a bicyclo[3.1.0] system,^{9,9} dimerization,¹⁰ or aromatization¹¹ might

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be expected from the irradiation of 1. Previous study of the photochemistry of imines has shown this functional group resembles the carbonyl group in its photo-reactions of reduction,¹² addition,¹³ and prototropy.¹⁴ On the other hand photoisomerization of anils,¹⁵ novel photoaddition and cyclization reactions,¹⁶ and photo-oxidation¹⁷ have been observed for the imine function. Pyrazine, a heteroaromatic imine, has been reported to photoisomerize to pyrimidine^{18a} and to undergo photo-fragmentation to acetylene and hydrogen cyanide.^{18b} Many of the possibilities suggested for the 2,3-dihydropyrazines by these analogies are intriguing. This synthetic potential and an interest in the chemical consequences of $n \rightarrow \pi^*$ excitation of diunsaturated system constrained to a six-membered ring¹⁹ prompted this study.

In this paper we report a new reaction, the photo-rearrangement of 2,3-dihydropyrazines to imidazoles.²⁰ Evidence is presented which suggests an enediimine, formed irreversibly after $n \rightarrow \pi^*$ excitation, is an intermediate in this reaction.

Results and Discussion

Spectral Properties. The low-intensity $n \rightarrow \pi^*$ bands expected for a dihydropyrazine²¹ could not be resolved for 2,3-dihydro-5,6-dimethylpyrazine (4) or 2,3-dihydro-5,6-diphenylpyrazine (5). These absorptions appear as the longest wavelength band in each

Letters, 2959 (1965); (c) H. Hart and A. J. Waring, *ibid.*, 325 (1965). In most cases these products are considered to arise from photochemical reaction of the triene produced by ring opening although it is recognized that such an intermediate is not obligatory. Cf. D. H. R. Barton, R. Bernasconi, and J. Klein, *J. Chem. Soc.*, 511 (1960).

(10) (a) L. A. Paquette and G. Slomp, *J. Am. Chem. Soc.*, **85**, 765 (1963); E. C. Taylor and R. O. Kan, *ibid.*, **85**, 776 (1963); W. Ayer, R. Hagatsu, P. de Mayo, J. T. Reid, and J. B. Stothers, *Tetrahedron Letters*, 648 (1961); (b) D. J. Valentine, N. J. Turro, and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 5202 (1964); G. O. Schenk, S. P. Mannsfeld, G. Schonberg, and C. H. Krauch, *Z. Naturforsch.*, **19b**, 18 (1964).

(11) R. Srinivisan, *J. Am. Chem. Soc.*, **82**, 5063 (1960).

(12) (a) J. Rennert and J. Weisenfeld, *Photochem. Photobiol.*, **5**, 337 (1966); (b) S. Kato, S. Minagawa, and M. Koizumi, *Bull. Chem. Soc. Japan*, **34**, 1026 (1961); (c) C. DuFraisie and E. Toromanoff, *Compt. Rend.*, **235**, 759 (1952).

(13) (a) A. Schönberg and W. Awad, *J. Chem. Soc.*, 651 (1947); (b) A. Mustafa, A. K. Mansour, and A. F. A. M. Shalaby, *J. Am. Chem. Soc.*, **81**, 3409 (1959); (c) G. Pfundt and W. M. Hardham, *Tetrahedron Letters*, 2411 (1965).

(14) (a) M. G. Cohen and G. M. J. Schmidt, *J. Phys. Chem.*, **66**, 2442 (1962); (b) D. G. Anderson and G. Wettermark, *J. Am. Chem. Soc.*, **87**, 1443 (1965).

(15) (a) E. Fischer and Y. Frei, *J. Chem. Phys.*, **27**, 808 (1957); (b) ref 11, p 460.

(16) (a) P. Cerutti and H. Schmid, *Helv. Chim. Acta*, **47**, 203 (1964); (b) *ibid.*, **48**, 1359 (1965); (c) J. S. Shannon, H. Silberman, and S. Sternhell, *Tetrahedron Letters*, 659 (1964); (d) P. J. Collin, H. Silberman, S. Sternhell, and G. Sugowicz, *ibid.*, 2063 (1965); (e) S. Searles and R. Clasen, *ibid.*, 1627 (1965); (f) E. C. Taylor, B. Forth, and M. Pfau, *J. Am. Chem. Soc.*, **87**, 1400 (1965).

(17) R. O. Kan and R. C. Furey, *Tetrahedron Letters*, 2573 (1966).

(18) (a) F. Lahmani, N. Ivanhoff, and M. M. Mayat, *Compt. Rend.*, **263**, 1005 (1966); (b) K. K. Innes, quoted in ref 2, p 460.

(19) The useful concept of electrons largely localized in σ , π , and nonbonding orbitals is retained in the present discussion except for the extended Hückel calculations. Recent comments on the localized approximation for azines have been made by R. Hoffmann, *J. Chem. Phys.*, **40**, 2745 (1964).

(20) (a) P. Beak and J. Miesel, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 95. (b) Dr. D. R. Arnold has independently discovered this reaction; D. R. Arnold, personal communication. We wish to thank Dr. Arnold for this information and for valuable discussion of this manuscript.

(21) Analogous absorptions in related molecules are of low intensity although allowed by local symmetry and affected by molecular symmetry; (a) for a general discussion see J. W. Sidman, *Chem. Rev.*, **58**, 689 (1958); M. Kasha, *Discussions Faraday Soc.*, **9**, 14 (1950); (b) for an example see K. K. Innes, J. D. Simons, and S. G. Tilford, *J. Mol. Spectry.*, **11**, 257 (1963).



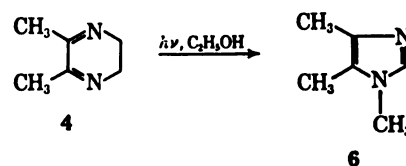
case with a broad featureless structure. By the empirical criteria of low intensity, absence of absorptions in the hydrocarbon analogs, and the shift of the absorption to shorter wavelengths in hydrogen-bonding solvents (Table I), this absorption is clearly of the $n \rightarrow \pi^*$ type.^{19,21,22} Attempts to demonstrate the disappearance of the long-wavelength band in acid were precluded by the instability of the compounds under these conditions.

Table I. The $n \rightarrow \pi^*$ Absorptions of 2,3-Dihydro-5,6-dimethylpyrazine (4) and 2,3-Dihydro-5,6-diphenylpyrazine (5)

Compound	Solvent	λ_{\max} , $m\mu$	ϵ
4	95% ethanol	337	200
	Methylene chloride	349	240
	Cyclohexane	352	215
5	95% ethanol	364	440
	Methylene chloride	371	425
	Cyclohexane	378	315

In the ultraviolet spectrum of 4 the $n \rightarrow \pi^*$ band is the only absorption above 290 $m\mu$; in the case of 5 there is a tailing absorption from 290 to 310 $m\mu$ from an absorption shoulder at 280 $m\mu$. Accordingly the use of a Pyrex filter in photochemical experiments would allow only excitation of the $n \rightarrow \pi^*$ band for 4 and mainly $n \rightarrow \pi^*$ excitation for 5. 2,3-Dihydro-5,6-diphenylpyrazine (5) did not show fluorescence in methanol at room temperature or phosphorescence in an ethanol-glycerol glass at 77°K.

Photolyses. Irradiation of 2,3-dihydro-5,6-dimethylpyrazine (4) in absolute ethanol using a 450-w high-pressure mercury resonance lamp with a Pyrex filter²³ for 5 hr yields 71% 1,4,5-trimethylimidazole (6).

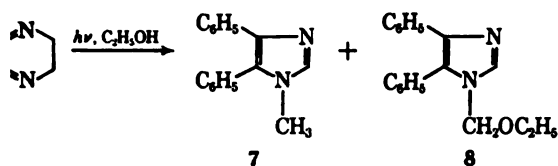


The product was identified by spectral comparison with an authentic sample and by preparation of the picrate.

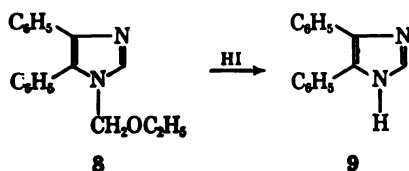
Photolysis of 2,3-dihydro-5,6-diphenylpyrazine gives 4,5-diphenyl-1-methylimidazole (7) in 75% yield. In some photolyses 4,5-diphenyl-1-ethoxymethylimidazole (8) may also be isolated in about 10% yield. The major product was identified as 7 by spectral and melting point comparisons with an authentic sample. The structure of 8 is based on analytical, infrared, ultra-

(22) The short-wavelength shift caused by conjugative substituents for the $n \rightarrow \pi^*$ band of carbonyl groups^{21a} appears to be altogether reversed in comparing the $n \rightarrow \pi^*$ absorptions of 4 with 5. The reliability of this correlation for imines is somewhat compromised by its failure to predict the "conjugative" shifts of the $n \rightarrow \pi^*$ absorptions of azo compounds: H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp 185, 430.

(23) In the following discussion these conditions should be presumed unless otherwise stated.

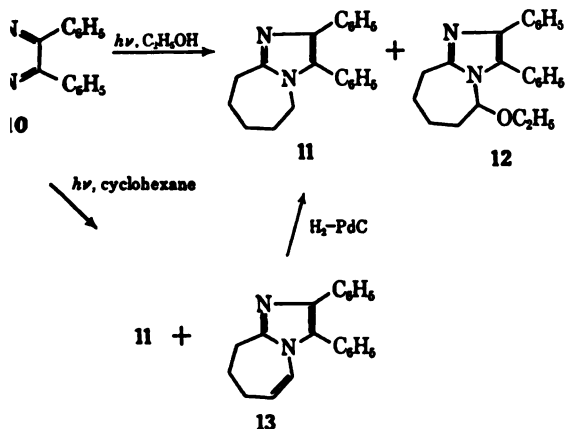


nmr, and mass spectral data as well as its conversion to 4,5-diphenylimidazole (9) in 70% yield on treatment with refluxing hydriodic acid. The quantum yield for the disappearance of 2,3-dihydro-5,6-diphenylpyrazine (5) and the appearance of 4,5-diphenyl-



ylimidazole (7) are about 0.1. Photolyses of 5 in benzene²⁵ or in absolute ethanol using a 23-watt pressure mercury resonance lamp for 3 to 6 hr gave 7 in yields ranging from 70 to 90%. The use of ethanol as a solvent for 5 with the high-pressure lamp and a Pyrex filter gives 7 (4%), 8 (8%), and 9

effect this reaction provides a method for the removal of substituents from the 2 and 3 positions of a dihydropyrazine to the 2 position and the exocyclic carbon bonded to nitrogen of an N-substituted imidazole. The availability of 2,3-dihydropyrazines from diamine precursors suggests the reaction for some synthetic convenience over present procedures for the preparation of substituted imidazoles. The synthetic potential and the variation in products obtained in the reaction may be illustrated by the synthesis of *trans*-2,3-diphenyl-5,6,7,8,9,10-hexahydro-1,2-imidazolo[1,2-*a*]azepine (10). In absolute ethanol the prod-

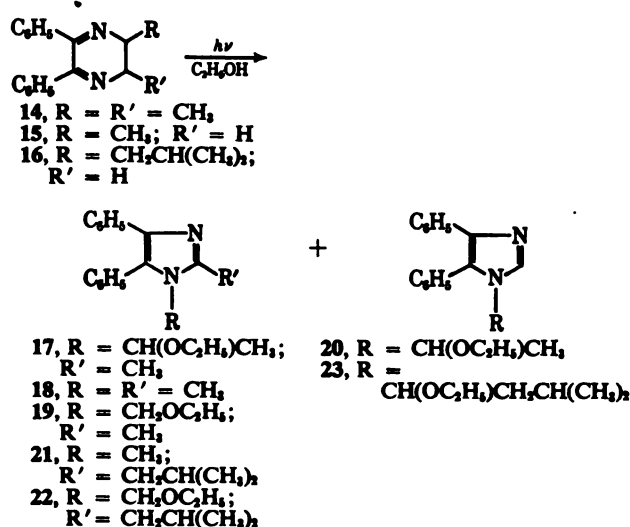


ucts 2,3-diphenyl-6,7,8,9-tetrahydro-5H-imidazo[1,2-*a*]azepine (11) in 9% yield and 2,3-diphenyl-5,6,7,8,9-tetrahydro-5H-imidazo[1,2-*a*]azepine (12) in 8% yield. In cyclohexane 11 was produced in 8% yield and 2,3-diphenyl-8,9-dihydro-7H-imidazo[1,2-*a*]azepine (13) in 19% yield. The structural assignments were based on analytical data, consistency of ultraviolet, infrared, nmr, and mass spectral data with the expected products using 7 and 8 as model compounds, and the con-

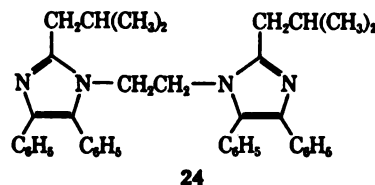
synthetically this reaction complements the conversion of 5 to 2-imidazoline with hydrogen peroxide: H. I. X. Mager and W. Rec. Trav. Chim., 84, 314 (1965).

version of 13 to 11 on catalytic hydrogenation. This appears to be the second synthesis of this type of imidazoazepine ring system.²⁶

Additional cases are provided by photolyses of 2,3-dihydro-2,3-dimethyl-5,6-diphenylpyrazine (14), 2,3-dihydro-2-methyl-5,6-diphenylpyrazine (15), and 2,3-dihydro-2-isobutyl-5,6-diphenylpyrazine (16). Irradiation of an ethanolic solution of 14²⁶ for 10 min gave 4,5-diphenyl-1-(1-ethoxyethyl)-2-methylimidazole (17) in 55% yield.²⁷ Reaction of 15 under these conditions for 8 hr gave 1,2-dimethyl-4,5-diphenylimidazole (18) (42%) and an unresolved mixture of 4,5-diphenyl-1-ethoxymethyl-2-methylimidazole (19) and 4,5-diphenyl-1-(1-ethoxyethyl)imidazole (20) (20%). Photolysis of 16 for 10 min gave 2-isobutyl-4,5-diphenyl-1-methylimidazole (21) (50%)²⁷ as well as material characterized by its spectral properties as 2-isobutyl-4,5-diphenyl-1-ethoxymethylimidazole (22) (6%)²⁷ and 1-(1-ethoxy-3-methylbutyl)-4,5-diphenylimidazole (23) (20%).²⁷ Conversion of 17 to 4,5-diphenyl-2-methylimidazole was achieved with hydriodic acid while 18 was identified by direct comparison with an authentic sample.



Irradiation of 2,3-dihydro-2-isobutyl-5,6-diphenylpyrazine (16) in cyclohexane took an unexpected course and produced 1,2-di(2-isobutyl-4,5-diphenylimidazolyl)ethane (24) (43%) in addition to the expected product 21 (26%). The infrared and ultraviolet spectra of this compound are very similar to that of 21, but the extinction coefficient in the ultraviolet was approximately



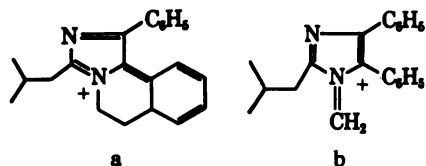
twice that of 21. The singlet assigned to the N-substituted methylene protons of 24 appears at δ 3.78 and this value compares well with the chemical shift of δ 3.30 for the N-methyl group in 21 and of δ 3.94 for the methylene of the N-ethyl group in 4,5-diphenyl-1-ethylimidazole. The mass spectrum of 24 confirmed the

(25) R. G. Glushov and O. Y. Mayidson, Dokl. Akad. Nauk SSSR, 133, 585 (1960).

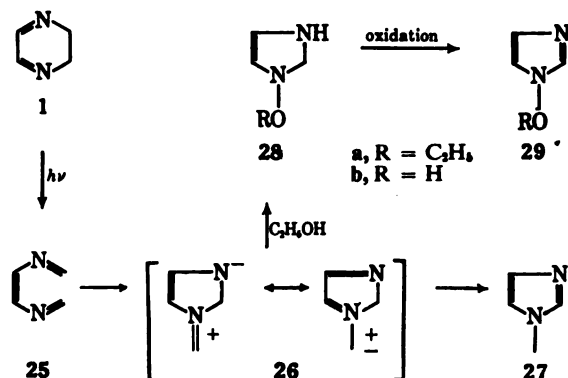
(26) The *cis* isomer and a mixture of *cis* and *trans* isomers gave the same product in separate experiments.

(27) This is based on starting material consumed.

molecular weight of 578 and gave major fragments at m/e 303 (metastable for $578 \rightarrow 303$ observed at 158.5; calcd, 159) and 289, consistent with species a and b which can be envisioned to arise from 24.



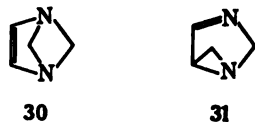
Intermediates. These conversions of 2,3-dihydropyrazines to imidazoles may be formulated for the general case as proceeding *via* an enediimine 25 formed by photolytic ring opening. Subsequent ring closure of 25 to 26 would generate an intermediate which could lead to an N-alkylimidazole (27) by proton transfer or to an N-ethoxyalkylimidazole (29a) by addition



of ethanol followed by oxidation²⁸ of the resulting imidazoline 28.

The generality of the photochemical ring opening reactions for systems isoelectronic with 1,3-cyclohexadienes was predicted by Barton 8 years ago.^{7a} Despite the formidable uncertainties involved in drawing formal analogies for photochemical reactions,^{2,29} the present case can be considered to support the empirical utility of Barton's prediction. The cyclization of 25 to 26 as a nonphotochemical reaction has reasonable precedent.²⁰

This proposal outlines the general nature of the intermediates, and the involvement of different tautomers and timing of the reactions are open to discussion. At least two species, 30 and 31, which could fulfill the function of 25, can be envisioned. Analogy^{2,29} clearly favors 25, however, and for the lack of definitive



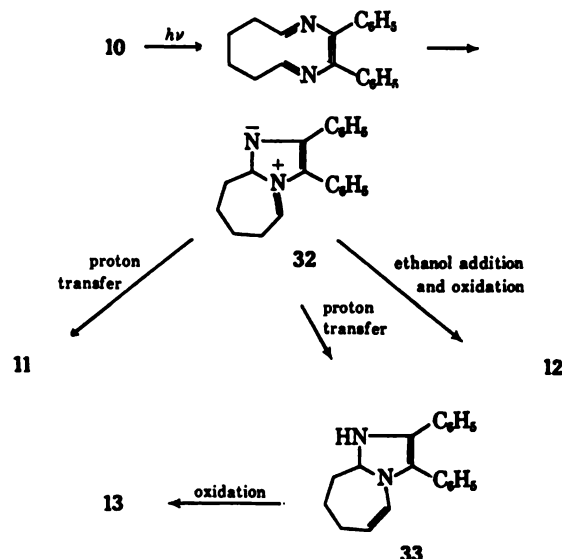
information about the alternatives, 25 will be provisionally preferred.³¹

(28) The facility of the proposed reaction is suggested by the ready oxidation of aryl-2-imidazolines: K. Hoffmann, "Imidazole and Its Derivatives," Part 1, Interscience Publishers, Inc., New York, N. Y., 1953, p 42. The oxidation could be a photoreaction due to traces of unremoved oxygen in the nitrogen used for purging or a subsequent reaction occurring in the work-up. M. Busch, *Ber.*, **64**, 1816 (1931), claims the preparation of a 4-imidazoline bearing hydrogens on both nitrogen atoms and reports this compound is readily oxidized to the corresponding imidazole.

(29) See the discussion by F. B. Mallory, C. S. Wood, and J. T. Gordon, *J. Am. Chem. Soc.*, **86**, 3094 (1964), for a cautionary note on the use of analogy for photochemical processes.

(30) G. McCoy and A. Day, *ibid.*, **65**, 2159 (1943).

The results of the photolyses of 10 can be accommodated in the proposed mechanistic framework. Production of 2,3-diphenyl-8,9-dihydro-6H-imidazo[1,2-a]zepine (13) from 10 under these conditions could occur by proton transfer of 32 to give 33 followed by oxidation.



The formation of 4,5-diphenylimidazole (9) in the photolysis of 2,3-dihydro-5,6-diphenylpyrazine (5) in 95% ethanol could result from the loss of the elements of formaldehyde from 28b or 29b formed by addition of water to 26 or by exchange with the corresponding ethers.

The product distributions in the cases of the unsymmetrically 2,3-substituted 2,3-dihydropyrazines 15 and 16 can be rationalized if the intermediates corresponding to 25 and 26 are considered to lead predominantly to imidazole products resulting from intramolecular nucleophilic addition at the most substituted imine carbon atom.³² For example, 1,2-dimethyl-4,5-diphenylimidazole (18) is formed in the photolysis of 2,3-dihydro-2-methyl-5,6-diphenylpyrazine (15) rather than 1-ethyl-4,5-diphenylimidazole.

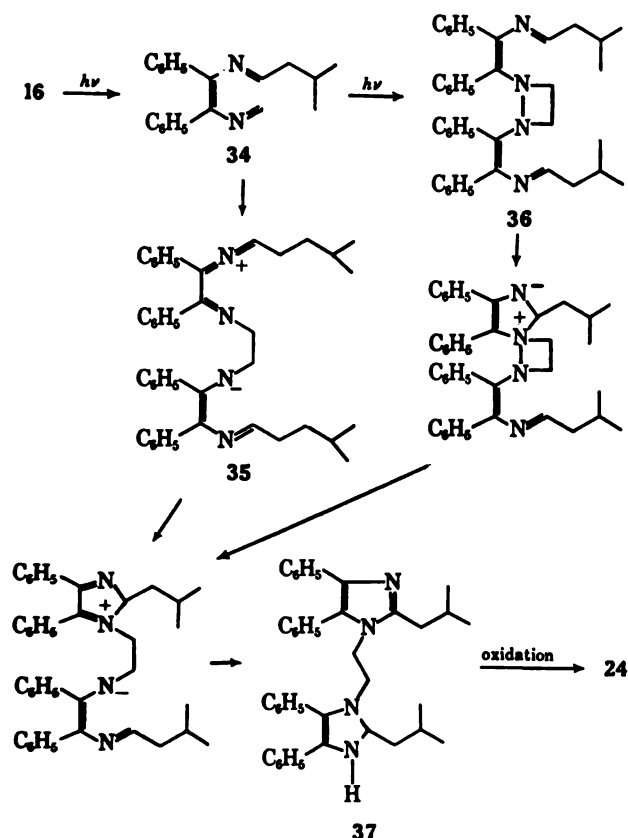
The formation of 1,2-di(2-isobutyl-4,5-diphenylimidazolyl)ethane (24) on photolysis of 16 in cyclohexane may result from the condensation of two molecules of 34 to give 35, a species which could undergo ring closure and proton transfer to yield 37, followed by oxidation. Tautomeric variants of this scheme can be envisioned. A different possibility is photoreaction of 34 to form the diazetidine 36 followed by ring closure,

(31) The assumption that changes in bond orders or overlap populations on transformation from the ground to the excited state indicate positions of bond formation and bond breaking in the excited state^{28a} may be applied to the present case by use of the extended Hückel method.^{32b} In agreement with the suggested intermediacy of the enediimine 25, bond overlap populations obtained from the calculations show a bond weakening of the 2,3 and 1,6 bonds and a bond strengthening of the 1,2 and 5,6 bonds on promotion of an electron from the highest occupied to the lowest unoccupied orbital of 2,3-dihydropyrazine (1). In contrast to this a strengthening of the 2,3 bond is obtained on promotion of an electron from the second highest occupied to the lowest unoccupied orbital of 1.

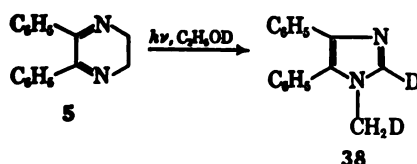
(32) (a) H. E. Zimmerman, *Pure Appl. Chem.*, **9**, 493 (1964); J. P. Malrieu, *Photochem. Photobiol.*, **5**, 291,301 (1966); R. Hoffmann, private communication. (b) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963); the program used was kindly provided by Mr. Donald Dugre. We are grateful to Mr. Dugre and Professor Hoffmann for use of the program and for advice.

(33) Although rationales can be constructed for this proposal, the limited data, as well as the fact that small energy differences of subtle origin may be involved, suggest that further speculation is not warranted.

ring opening, and proton transfer to give 37. The intermediacy of 36 is suggested by analogy to the proposals of Searles and Clasen for the photolytic conversion of anils to stilbenes and azobenzenes.^{16c} These rationales, however, do not explain the apparently anomalous formation of 24.



Support for the proposed intermediates is provided by the deuterium incorporation observed in the course of photolysis. Irradiation of 5 in ethanol-*d* (95% *d*), followed by heating the products in ethanol-*d* to complete the exchange of the labile imidazole C-2 proton, gave 4,5-diphenyl-1-methyl-*d*-imidazole-2-*d* (38) which has a minimum of 90% dideuterium incorporation. The extent of deuterium incorporation was determined by mass spectrometry, and the position of deuteration was determined by nmr analysis. Direct comparison of the spectrum of 38 with that of 7 showed the expected ratio, 10:2, of proton resonances, and the signal for the N-deuteriomethyl group at δ 3.42 had an unresolved triplet shape.³⁴ Isolation of unreacted 5 demonstrated that it did not exchange under the conditions of the experiment, while control experiments with 4,5-diphenyl-1-methylimidazole (7) showed that exchange of only the C-2 proton occurred on treatment with ethanol-*d* under



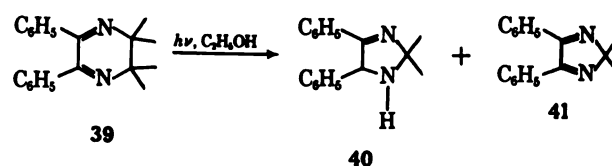
the photolysis conditions.³⁵ The incorporation of deu-

(34) The hydrogen-deuterium coupling constant would be expected to be on the order of 1–2 cps.

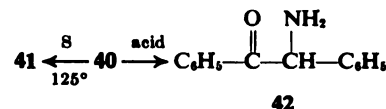
(35) H. A. Staab, M. Th. Wu, A. Mannschreck, and G. Schwalbach, *Tetrahedron Letters*, 845 (1964); T. M. Harris and J. L. Randall, *Chem. Ind. (London)*, 1728 (1965); R. O. Olofson, private communication.

terium into the N-methyl group of the product imidazole is expected for an intermediate corresponding to 26 in this reaction.

In an attempt to generate a relatively stable enediimine, the irradiation of 2,3-dihydro-5,6-diphenyl-2,2,3,3-tetramethylpyrazine (39) was investigated. The expected enediimine intermediate in this case would not be capable of imidazole formation by the prescribed pathway. Photolysis of 39 in absolute ethanol for 2.5 hr gave 2,2-dimethyl-4,5-diphenyl-3-imidazoline (40) (60%) and 2,2-dimethyl-4,5-diphenylisimidazole (41) (9%). The imidazoline 40 was identified by

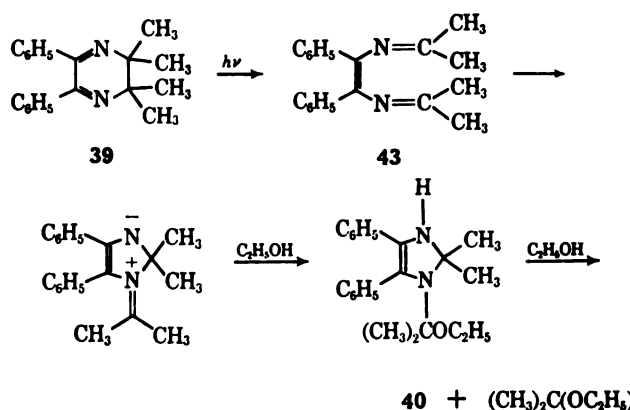


analytical, infrared, ultraviolet, nmr, and mass spectral data. The ultraviolet spectrum of 40, λ_{max} 245 m μ (ϵ 12,500), is characteristic of phenyl-substituted Schiff bases.³⁶ The nmr resonances of two methyl groups at δ 1.62 and 1.48 are consistent with the assigned structure and indicate that alternative structures bearing methyl groups on a carbon doubly bonded to nitrogen can be ruled out.³⁷ The mass spectrum shows that losses of hydrogen, a methyl group, and benzonitrile from the molecular ion, as expected for 40, are favorable processes. Chemical confirmation of this assignment was provided by the oxidation of 40 to 41 with sulfur at 125° in high yield and by the hydrolysis of 40 to desyl-



amine (42) by dilute acid. The structure of 41 was established by spectral and physical comparison with an authentic sample.

Although detection of the presumed intermediate 43 has not been possible,³⁸ the observed products are consistent with its transient existence. Ring closure



of 43 followed by loss of the nitrogen substituent, presumably with formation of acetone or acetone diethyl ketal, would lead to 40. The formation of 2,2-di-

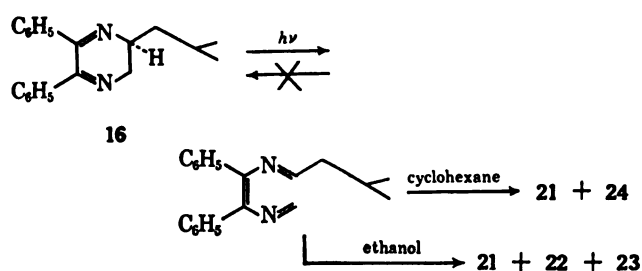
(36) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **73**, 3923 (1951).

(37) E. Arnal, J. Elyuero, R. Jacquier, C. Marzin, and J. Wyld, *Bull. Soc. Chim. France*, 877 (1965).

(38) A number of experiments, under a variety of conditions, were carried out and attempts were made to detect 43 as a nonisolable species.

methyl-4,5-diphenylisimidazole (41) in this reaction may be due to photooxidation of 40 by minor products or impurities in the system.

If the photolytic conversion of the 2,3-dihydropyrazines to imidazoles proceeds *via* an enediimine corresponding to 25, there is a reasonable possibility that the photochemical ring opening is reversible, *i.e.*, that the enediimine can re-form a 2,3-dihydropyrazine.³⁹ In principle, this process could be detected by partial photolysis of a 2,3-dihydropyrazine which is optically active by virtue of an asymmetric center at position 2 and isolation of the starting material to determine if racemization, requisite in ring closure of the planar enediimine intermediate, has occurred. Photolysis of optically active 2,3-dihydro-2-isobutyl-5,6-diphenylpyrazine (16) for 10 min in absolute ethanol or cyclohexane followed by recovery of starting material in 55 and 44% yields showed that less than 5% racemization had occurred. Accordingly, the photochemical ring opening is not reversible within the limits of detection.⁴⁰



Excited Species. On the basis of the spectral data for 4 the reaction may be formulated as occurring after $n \rightarrow \pi^*$ excitation. The photolysis of 2,3-dihydro-2,3-diphenylpyrazine (5) to give 4,5-diphenyl-1-methylimidazole (7) does not appear to be sensitized or quenched by benzophenone,⁴¹ triphenylene,⁴¹ *trans*-stilbene,⁴² naphthalene, or perylene, even when the latter is the reaction solvent. These results suggest, but do not require, that a triplet species is not an intermediate in the conversion of 5 to 7.⁴³ The reaction may provisionally be formulated as occurring in an n, π^* singlet. It is possible that a triplet which lies less than *ca.* 60 kcal/mole above its ground state could be in-

volved as could a triplet which is inefficient in energy transfer. Observation of the phosphorescence spectrum of 4 and 5 in conjunction with a quantitative study of quenching and sensitization could settle this point. Investigation of the nature of the $n \rightarrow \pi^*$ absorptions of 4 and 5 would also be of interest for a further understanding of these reactions.

Experimental Section^{44,46}

2,3-Dihydro-5,6-dimethylpyrazine (4) was prepared by the method of Ishiguru and Matsumura⁴⁷ bp 60–62° (18 mm) (lit.⁴⁷ 60–63° (18 mm)), n_D^{20} 1.4826. The nmr spectrum consists of singlets at δ 3.28 (relative area 2), CH_3 , and 2.10 (relative area 3), $C-CH_3$. The infrared and ultraviolet (λ_{max} 230 (ϵ 1740) and 337 $m\mu$ (ϵ 200)) are consistent with the established structure. 2,3-Dihydro-5,6-dimethylpyrazine is unstable to standing in air but is stable for several weeks if stored under nitrogen in the refrigerator.

Anal. Calcd for $C_6H_{10}N_2$: C, 65.42; H, 9.15; N, 25.43. Found C, 65.24; H, 9.07; N, 25.35.

2,3-Dihydro-5,6-diphenylpyrazine (5) was prepared according to Amundsen,⁴⁸ mp 162.5–163.5° (lit.⁴⁸ 161.5–162.5°). The nmr spectrum consists of an unsymmetrical multiplet centered at δ 7.3 (relative area 5), Ar-H, and a singlet at δ 3.7 (relative area 2), CH_3 . The infrared and ultraviolet (λ_{max} 224 (ϵ 15,100), 288 (ϵ 5740), and 363.5 $m\mu$ (ϵ 440)) are consistent with the established structure. The mass spectrum showed major fragment peaks at m/e 131 and 103 corresponding to the loss of the elements of benzonitrile. No fluorescence of 2,3-dihydro-5,6-diphenylpyrazine was observed in methanol solution at room temperature under conditions such that a fluorescence quantum yield of 0.01 would have been detected. No phosphorescence of 5 in a 1:1 ethanol-glycerol glass at 77°K was observed.

***trans*-2,3-Diphenyl-5,6,7,8,9,10-hexahydroquinoxaline (10).** To a solution of 2.9 g of benzil in 10 ml of absolute ethanol was added 2.18 g of *trans*-1,2-diaminocyclohexane- CO_2 adduct in 5 ml of absolute ethanol. The solution was heated at reflux on a steam bath under a positive pressure of nitrogen for 45 min. After 5–10 min, yellow plates precipitated. The reaction mixture was cooled in ice and filtered, and the solid collected was washed with portions of cold 95% ethanol. The product consisted of 3.82 g of yellow plates, mp 170.5–173° (lit.⁴⁹ 167–168°). The product was sublimed at 110° (0.1 mm) to give yellow needles, mp 171–172°. The nmr spectrum consisted of a multiplet at δ 7.24 (relative area 10), ArH, a series of multiplets at 1.20–3.00 (relative area 10), $C-H$. The infrared, mass (molecular ion at m/e 288), and ultraviolet spectra (λ_{max} 223 (ϵ 15,000), 260 (ϵ 5100), 290 (ϵ 5300), and 369 $m\mu$ (ϵ 450)) were consistent with the expected values.

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.71; mol wt, 288. Found: C, 83.26; H, 7.04; N, 9.33; mol wt, 280 (benzene).

***cis*-2,3-Dihydro-2,3-dimethyl-5,6-diphenylpyrazine (14).** *meso*-2,3-Diaminobutane was isolated from commercial 2,3-diaminobutane by the method of Dickey, Fickett, and Lucas.⁵⁰ A solu-

(39) A number of analogies for such a process may be found in the photochemistry of 1,3,5-hexatrienes. For examples, see ref 7b; R. Srinivasan, *J. Am. Chem. Soc.*, **83**, 2806 (1961); G. J. Fonken, *Tetrahedron Letters*, 549 (1962).

(40) Application of the Woodward-Hoffmann concepts to the two $n \rightarrow \pi^*$ states presumed for these purposes to be involved in the interconversion of a 2,3-disubstituted dihydropyrazine and its isomeric enediimine reveals that concerted ring opening and ring closure are allowed both as conrotatory and disrotatory processes: R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965); H. Longuet-Higgins and E. W. Abrahamson, *ibid.*, **87**, 2045 (1965). In this case, unlike that of 1,3 cyclohexadienes, the symmetry rules allow a photolytic interconversion of *cis*- and *trans*-2,3-dihydro-2,3-disubstituted pyrazines by concerted processes. Experimental demonstration of this would assume both transitions occur, the enediimine to be photostable, and photochemical ring closure of the presumed enediimine intermediate. The latter reaction was not detectable with 16. Consistent with these results, no racemization of optically active 14 or photochemical interconversion of *cis* and *trans* isomers of 14 was found in incomplete reactions.

(41) Quantitative studies were complicated by competitive absorptions.

(42) The conversion of 5 to 7 in the presence of *trans*-stilbene provides a marked contrast to the photoaddition of *o*-quinones to *trans*-stilbene *via* a triplet species.³

(43) G. S. Hammond and N. J. Turro, *Science*, **142**, 1541 (1963); G. S. Hammond, N. J. Turro, and P. A. Leermakers, *J. Phys. Chem.*, **66**, 1144 (1962); H. E. Zimmerman and J. S. Swenton, *J. Am. Chem. Soc.*, **86**, 1436 (1964); G. W. Griffin and E. J. O'Connell, *ibid.*, **84**, 4148 (1962).

(44) The melting points were determined with a Thomas-Hoover capillary apparatus and are corrected. The boiling points are uncorrected. The infrared spectra were determined on a Perkin-Elmer Model 521 infrared spectrometer using 10% chloroform solutions, unless otherwise noted. The ultraviolet spectra were measured on a Cary Model 14 M spectrophotometer and a Perkin-Elmer 202 ultraviolet-visible spectrometer using 95% ethanol solutions unless otherwise noted. The proton magnetic resonance spectra were obtained on a Varian Associates A-60 spectrometer using 10–30% chloroform-*d* solutions, unless otherwise noted, and are reported in δ (parts per million) relative to the internal standard, tetramethylsilane. The mass spectra were determined by Mr. J. Wrona on an Atlas CH4 mass spectrometer. Optical rotation measurements were performed on a Zeiss 0.01° polarimeter. Phosphorescence studies were performed using an Aminco-Bowman spectrophotofluorometer converted for phosphorescence. The fluorescence spectrum was taken on the instrument described by Weber and Bablovzian.⁴⁵

(45) G. Weber and B. Bablovzian, *J. Biol. Chem.*, **241**, 2558 (1966).

(46) The microanalyses were performed by Mr. Joseph Nemeth and associates.

(47) T. Ishiguru and M. Matsumura, *Yakugaku Zasshi*, **78**, 229 (1958); *Chem. Abstr.*, **54**, 11862 (1958).

(48) L. Amundsen, *J. Chem. Educ.*, **16**, 567 (1939).

(49) A. Einhorn and B. Bull, *Ann.*, **295**, 209 (1897).

(50) F. Dickey, W. Fickett, and H. Lucas, *J. Am. Chem. Soc.*, **74**, 944 (1952).

staining 199 mg of *meso*-2,3-diaminobutane in benzene to a solution of 445 mg of benzil (94% of theoretical) in absolute ethanol. The solution was heated at reflux under pressure of nitrogen for 2 hr. A total of 440 mg of fine, low crystals precipitated on cooling and scratching the solution. Second and third crops totaling 103 mg were obtained by concentrating the mother liquors.

Combined crude products were chromatographed on a column of 20 g of silica gel. Elution with 25% benzene-Skelly B gave unreacted benzil. Elution with 25% ether-benzene gave dihydro-2,3-dimethyl-5,6-diphenylpyrazine (14). The solid melted at 90–100° (0.15 mm) to give 400 mg of yellow needles, mp 98–99°. The nmr spectrum consisted of a multiplet at δ 7.38 (relative area 5), *ArH*, a quartet at 3.92 (relative area 1, $J = 6$ cps), $\text{N}=\text{CHN}$, and a doublet at 1.26 (relative area 3, $J = 6$ cps), $\text{C}-\text{CH}_3$, and ultraviolet (λ_{max} 224 (ϵ 14,850), 290 (ϵ 5700), and 375 m μ) spectra were consistent with the assigned structure.

Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2$: C, 82.40; H, 6.92; N, 10.68; 262. Found: C, 82.56; H, 6.96; N, 10.91; mol wt, 270. Partially resolved mixture of *cis*- and *trans*-2,3-dihydro-2,3,5,6-diphenylpyrazines (15) was also prepared. Racemic diaminobutane was resolved using *d*-tartaric acid following the method of Dickey, Fickett, and Lucas.⁵⁰ A tartrate salt of optical rotation of +0.90° was obtained and decomposed in aqueous sodium hydroxide. The amine was isolated by extraction of the aqueous solution with benzene.

A solution of 1.35 g of benzil (90% of theoretical) in 5 ml of ethanol was added to a benzene solution containing 625 mg of resolved *trans*-2,3-diaminobutane by titration. The reaction and purification were carried out as above.

Crystallization gave light yellow needles, mp 88–94°. The sublimed product was ground with a mortar and pestle to ensure sample purity. The nmr spectrum showed two different $\text{C}-\text{CH}_3$ signals at δ 1.24 and 1.48 and was consistent with a mixture of *cis-trans*-2,3-dihydro-2,3-dimethyl-5,6-diphenylpyrazines containing 26% *trans* isomer.

Optical rotation was determined using a solution of 219 mg of dihydro-2,3-dihydro-2,3-dimethyl-5,6-diphenylpyrazine in 10 ml of 95% ethanol gave $[\alpha]_D^{25} = 53 \pm 0.03^\circ$, $[\alpha]_D^{25} = -28.7 \pm 4.75^\circ$.

Dihydro-5,6-diphenyl-2-methylpyrazine (15) was prepared by the method of Strache,⁵¹ mp 116–118° (lit.⁵¹ 111–112°). The nmr spectrum consisted of a multiplet centered at δ 7.28 (relative area 10), *ArH*, 4.20–2.84 (relative area 10), $\text{N}=\text{CHN}$, and a doublet at 1.44 (relative area 3), $\text{C}-\text{CH}_3$, and ultraviolet spectra were consistent with the established structure.

Diethyl-2,3-dihydro-5,6-diphenylpyrazine (16). To a solution of 1.84 g of benzil in 5 ml of absolute ethanol was added 1.07 g of diamino-4-methylpentane.⁵² The mixture was heated at reflux under a positive pressure of nitrogen for 2.5 hr. After sufficient to clarify the solution was added, the solution was cooled by ice and precipitation occurred. A total of 1.84 g (73% yield) of light yellow crystals, mp 66–69°, was collected by filtration. Crude product was chromatographed on silica gel. Elution with 25% ether-benzene gave a yellow oil which crystallized on cooling to light yellow needles, mp 68–70°. This solid was sublimed at 60° (0.12 mm) to give light yellow needles, mp 69–71°. The nmr spectrum consisted of a multiplet centered at δ 7.28 (relative area 10), *ArH*, a multiplet centered at 4.00 (relative area 1), $\text{N}=\text{CHN}$, multiplets centered at 3.26 (relative area 2), NCH_2 , a series of multiplets at 1.30–2.20 (relative area 3), $-\text{CH}_2\text{CH}_2-$, and a doublet (relative area 6), $-(\text{CH}_3)_2$.

The infrared spectrum had strong absorptions at 2970, 1510, and 1450 cm^{-1} . The ultraviolet spectrum (λ_{max} 224 (ϵ 15,450), 288, and 369 m μ (ϵ 440)) and the mass spectrum were consistent with the structure assigned. The optical rotation was determined using a solution of 231 mg of sublimed material in 10 ml of 95% ethanol gave $[\alpha]_D^{25} = +2.13 \pm 0.07^\circ$, $[\alpha]_D^{25} = 91.90 \pm 3.3^\circ$.

Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2$: C, 82.72; H, 7.64; N, 9.65; 290. Found: C, 82.63; H, 7.57; N, 9.47; mol wt, 283 g.

Diethyl-5,5,6,6-tetramethylpyrazine (39). To a solution of benzil in toluene was added 1.65 g of 2,3-diamino-2,3-dibutane.⁵³ Anhydrous sodium sulfate and a trace of *p*-sulfonic acid were added and the mixture was heated at reflux in a drying tube. After 10-days heating at reflux the solid was removed under reduced pressure and the residue was

chromatographed on a column of 40 g of Florisil. Elution with 50% benzene-Skelly B gave fractions which contained both benzil (1660- cm^{-1} band) and 2,3-diphenyl-5,5,6,6-tetramethylpyrazine (975- cm^{-1} band) by infrared analysis. These fractions were recrystallized from ice-cold acetone solution by the addition of water. This solid was sublimed to give 1.1 g of light yellow needles, mp 92–110° (29% yield). The nmr spectrum consisted of two resonances at δ 7.40 (relative area 5), *ArH*, and 1.42 (relative area 6), CCH_3 . The infrared spectrum showed strong absorptions at 2880, 1545, 1450, 1160, and 975 cm^{-1} . The ultraviolet spectrum (λ_{max} 223 (ϵ 12,100), 290 (ϵ 4150), and 365 m μ (ϵ 420)) was also consistent with the assigned structure.

Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2$: C, 82.72; H, 7.64; N, 9.65; mol wt, 290. Found: C, 82.46; H, 7.61; N, 9.49; mol wt, 285 (benzene).

1,4,5-Trimethylimidazole (6). Crude 4,5-dimethylimidazole⁵⁴ (3.0 g) was methylated with 5.0 g of dimethyl sulfate. The product was distilled under reduced pressure to give a colorless oil which became semicrystalline during the distillation, bp 107–109° (18 mm) (lit.⁵⁴ 117° (20 mm)). The nmr spectrum consisted of singlets at δ 7.70 (relative area 1), $\text{N}=\text{CHN}$, 3.62 (relative area 3), $\text{N}-\text{CH}_3$, and 2.38 and 2.29 (relative area 3 each), $\text{C}-\text{CH}_3$. The nmr resonances of the methyl groups in benzene solution appear at δ 2.80, 2.20, and 1.72, and these compare relatively well with reported values of δ 2.63, 2.21, and 1.65.⁵⁴ The infrared and mass spectrum were consistent with the established structure,⁵⁴ with the latter showing a large molecular ion — 1 peak. The picrate, mp 219–220° (lit.^{54b} mp 218–219°), and methiodide, mp 158–160° (lit.^{54b} mp 158°), derivatives were prepared.

4,5-Diphenylimidazole was prepared by the method of Davidson, Weiss, and Jelling.⁵⁷ The crude product was recrystallized from ethanol-water to give colorless needles, mp 230–231° (lit.⁵⁷ 249°, 232–233°⁵⁸).

4,5-Diphenyl-1-methylimidazole (5) was prepared by the method of Simonev and Garnovskii,⁵⁹ mp 157.5–158° (lit.⁵⁹ 158°). The nmr spectrum consisted of a multiplet at δ 7.35 (relative area 11), *ArH* and $\text{N}=\text{CHN}$, and a singlet at 3.37 (relative area 3), $\text{N}-\text{CH}_3$. The infrared, ultraviolet, and mass spectra were consistent with the established structure.

1,2-Dimethyl-4,5-diphenylimidazole (18). To 2 g of solid 4,5-diphenyl-2-methylimidazole⁵⁷ was added 0.9 ml of dimethyl sulfate (10% excess). The mixture was heated on a steam bath for 24 hr and cooled. A solution of methanol-ammonium hydroxide was added before the solution was poured into sodium hydroxide solution. The aqueous solution was extracted with chloroform, and the chloroform extracts were combined, washed with water, and dried over anhydrous sodium sulfate. After filtration, the solvent was removed under reduced pressure. The residue was recrystallized from ether to give colorless rectangles, mp 121–24°. The nmr spectrum consisted of a multiplet at δ 7.30 (relative area 10), *ArH*, a singlet at 3.30 (relative area 3), $\text{N}-\text{CH}_3$, and a singlet at 2.44 (relative area 3), $\text{C}-\text{CH}_3$. The infrared spectrum had strong bands at 2950, 1605, and 1400 cm^{-1} .

Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.16; H, 6.31; N, 11.08.

2,2-Dimethyl-4,5-diphenylisimidazole (41) was prepared according to the method of Weiss,⁶⁰ mp 78–79° (lit.⁶⁰ 79–80°). The nmr (δ 7.46 (relative area 10), *ArH*, singlet at 1.64 (relative area 5.7), CCH_3), infrared, and mass spectra were consistent with the established structure.

General Procedure for Photolysis. The solutions were photolyzed in a Pyrex container into which the high-pressure mercury vapor lamp and filter in a quartz immersion well or the low-pressure mercury vapor lamp without a filter had been previously placed. The solution was deaerated by a stream of nitrogen before and during photolysis. The nitrogen was purified by passage through two traps of Fieser solution,⁶¹ a lead acetate solution trap, and a drying tower of mixed Molecular Sieve and indicating Drierite. The photolyses were terminated when starting material could not be detected by infrared or ultraviolet spectroscopy.

(54) H. Brederick and G. Thielig, *Ber.*, **86**, 88 (1953).

(55) H. Jowett, *J. Chem. Soc.*, **87**, 405 (1905).

(56) (a) J. Imbach and R. Jacquier, *Compt. Rend.*, **257**, 2683 (1963);

(b) R. Grindley and T. Pyman, *J. Chem. Soc.*, 3128 (1927).

(57) D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 319 (1937).

(58) I. Lamb and F. Pyman, *J. Chem. Soc.*, 125, 706 (1924).

(59) A. Simonov and A. Garnovskii, *Zh. Obshch. Khim.*, **31**, 114 (1961).

(60) M. Weiss, *J. Am. Chem. Soc.*, **74**, 5193 (1952).

(61) L. Fieser, *ibid.*, **46**, 2639 (1924).

1. Strache, *Ber.*, **21**, 2358 (1888).

2. Schnell and P. Karrer, *Helv. Chim. Acta*, **38**, 2036 (1955).

3. Syre, *J. Am. Chem. Soc.*, **77**, 6689 (1955).

The crude photolysis mixtures were usually worked up by evaporation of the solvent at reduced pressure, followed by column chromatography on either Florisil (Florian Co.) or silica gel (E. Merck AG, 0.05–0.20 mm). Unless otherwise noted, the column was eluted with solvents in the following order: 50% benzene–Skelly B, benzene, benzene–1% ether, benzene–2% ether, benzene–5% ether, benzene–10% ether, benzene–25% ether, benzene–50% ether, ether, and more polar solvents as needed. The Skelly B used for chromatography was predistilled; all other solvents used in the chromatographies were reagent grade.

Light Sources. The light sources used for photolysis were an Hanovia Type L 450-w high-pressure quartz mercury vapor immersion lamp and an Hanovia 23-w Type SC-2537 low-pressure Vycor mercury vapor immersion lamp. The Pyrex filter sleeve used to restrict the light absorbed by the sample transmits 1, 30, and 70% of the incident light at 280, 300, and 320 m μ .

Photolysis of 2,3-Dihydro-5,6-dimethylpyrazine (4). A solution of 1.27 g of 2,3-dihydro-5,6-dimethylpyrazine (4) in 420 ml of absolute ethanol was photolyzed using a Pyrex-filtered high-pressure lamp. The solvent was removed under reduced pressure and the residue distilled to give 902 mg (71% yield) of clear, colorless oil, bp 107–109° (18 mm), which crystallized on standing. The nmr in deuteriochloroform and benzene, the infrared and ultraviolet spectra, and the melting point of the picrate derivative were identical with those of authentic 1,4,5-trimethylimidazole (6).

Photolysis of 2,3-Dihydro-5,6-diphenylpyrazine (5). A solution of 1.00 g of 2,3-dihydro-5,6-diphenylpyrazine (5) in 420 ml of absolute ethanol was photolyzed using a Pyrex-filtered high-pressure mercury vapor lamp. The yellowish solid obtained by evaporation of the solvent was chromatographed on a column of 40 g of Florisil. Elution with benzene–5% ether gave 746 mg (75% yield) of light tan crystals. Recrystallization of this solid from ether gave colorless rectangular crystals, mp 159–160°. This material was identical with authentic 4,5-diphenyl-1-methylimidazole (7) by nmr, infrared, ultraviolet, mass spectral, and mixture melting point criteria.

In a later photolysis of a solution of 1.14 g of 2,3-dihydro-5,6-diphenylpyrazine in 420 ml of absolute ethanol using a Pyrex-filtered high-pressure lamp the crude product was chromatographed on a column of 20 g of silica gel. Elution with 10% ether–benzene gave a crystalline fraction (244 mg) which was rechromatographed on a column of 20 g of silica gel. Elution with 25% ether–benzene gave 100 mg of crystalline material in the first fractions, and this was recrystallized from ether to give colorless rectangles, mp 89.5–91.5°. The compound was identified as 4,5-diphenyl-1-ethoxymethylimidazole (8). The nmr spectrum consisted of a singlet at δ 7.80 (relative area 1), $\text{N}=\text{CHN}$, a broad multiplet centered at 7.25 (relative area 10), ArH , a singlet at 5.08 (relative area 2), $\text{N}-\text{CH}_2-\text{O}$, a quartet at 3.44 (relative area 2, $J = 7$ cps), CH_2CH_3 , and a triplet at 1.12 (relative area 3, $J = 7$ cps), CH_2CH_3 . The infrared, ultraviolet, and mass spectra were also consistent with the structure assigned.

Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.58; H, 6.40; N, 9.90.

A solution of 76.7 mg of 4,5-diphenyl-1-ethoxymethylimidazole in several milliliters of concentrated HI was refluxed for 7 hr. The acid solution was diluted with distilled water and neutralized with concentrated ammonium hydroxide. The colorless precipitate collected by suction filtration was 44 mg (70% yield) of impure 4,5-diphenylimidazole, mp 205–220°. The crude product was recrystallized from ethanol–water to give colorless needles, mp 228–230°, undepressed upon mixture melting point with authentic 4,5-diphenylimidazole. The infrared and mass spectra of the cleavage product were identical with those of the authentic material.

The photolysis of 5 was carried out in Skelly B, benzene, and 95% ethanol and found to give 7 in yields of 67, 90, and 4%. In the latter case 8 (8%) and 9 (33%) were also obtained. Irradiation of 5 in ethanol for 6 hr using the low-pressure mercury resonance lamp gave 7 in 80% yield.

Approximate quantum yields for the disappearance of 5 and the combined appearance of 7 and 8 were determined to be 0.13 ± 0.03 in ethanol at 25° by ultraviolet analysis with a Pyrex-filtered high-pressure mercury resonance lamp in a thermostated rotating reactor⁶² using the photoreduction of benzophenone as an actinometer.⁶³ The semiquantitative nature of this result should be

noted.⁶⁴ The ultraviolet spectra used for the determination of quantum yields did not show an isosbestic point.

Attempts were made to sensitize the photoreaction of 5 in ethanol with benzophenone, triphenylene, and *trans*-stilbene and to quench the reaction with naphthalene or by using piperylene as solvent. In all cases the reaction appeared to give the yield of 7 expected in the absence of sensitization or quenching.

Photolysis of 5 in Ethanol-*d*. About 250 ml of ethanol-*d* was prepared by the hydrolysis of diethyl sulfite with D_2O .⁶⁴ The ethanol-*d* was distilled, stored over anhydrous sodium carbonate, and redistilled. The pH of the sample was approximately that of absolute ethanol as determined with a Corning pH meter and glass microelectrodes. The deuterium incorporation was determined using the falling drop method.

Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{DO}$: 16.6 atom % excess deuterium. Found: 16.6 atom % excess deuterium.

A solution of 852 mg of 2,3-dihydro-5,6-diphenylpyrazine (5) in about 250 ml of ethanol-*d* was photolyzed using a Pyrex-filtered high-pressure lamp for 1.5 hr. After removal of the solvent the semisolid deep yellow residue was chromatographed on a column of 20 g of silica gel. Elution with 5% ether–benzene gave 215 mg of starting material 5. The mass spectrum at low ionizing voltage indicated no incorporation of deuterium. Elution with 25% ether–benzene gave 85 mg of colorless needles identified by nmr and infrared spectra as a slightly impure sample of 4,5-diphenyl-1-ethoxymethylimidazole (8). Elution with 50% ether–benzene gave 135 mg of colorless crystalline solid which was recrystallized from ether to give colorless rectangles, mp 156–159°. The nmr (multiplet at δ 7.28 (relative area 5), ArH , unresolved triplet at 3.42 (relative area 1), $-\text{CH}_2-\text{D}$) and infrared spectra were consistent with the expected product, 2-deuterio-4,5-diphenyl-1-methyl-*d*-imidazole (36). The sample of the recrystallized imidazole 36 was heated at reflux overnight in ethanol-*d* under a drying tube to ensure complete exchange of the labile imidazole ring proton⁶⁵ before mass spectral analysis. At low ionizing voltage the ratio of the molecular ion peaks of this material indicated 8.6% $\text{C}_{17}\text{H}_{13}\text{N}_2\text{D}$ and 91.4% $\text{C}_{17}\text{H}_{13}\text{N}_2\text{D}_2$. Further elution of the chromatography column with ether gave an additional 103 mg of solid, which was seen by nmr spectroscopy to be composed of about 70% dideuterated imidazole 36. Elution with ethanol gave 204 mg of light yellow solid, mp 212–228°, identified by its nmr, infrared, and mass spectra as 4,5-diphenylimidazole (9). The formation of these products suggests the deuterioethanol contained a small amount of deuterium oxide.

In a control experiment it was shown that 3,4-diphenyl-1-methylimidazole (7) gave only 2-deuterio-4,5-diphenyl-1-methylimidazole on photolysis under these conditions.

Photolysis of *trans*-2,3-Diphenyl-5,6,7,8,9,10-hexahydroquinoxaline (10). A solution of 1.10 g of *trans*-2,3-diphenyl-5,6,7,8,9,10-hexahydroquinoxaline (10) in 420 ml of absolute ethanol was photolyzed for 7 hr using a Pyrex-filtered high-pressure lamp. The solvent was removed under reduced pressure and the residue was chromatographed on a column of 20 g of silica gel.

Elution with 1% ether–benzene gave 356 mg (32.5% recovery) of light yellow crystals, found to be unreacted 10.

Elution with 2% ether–benzene gave 460 mg (53% yield) of colorless solid which was purified by sublimation at 110° (0.15 mm) to give fine colorless needles, mp 121–123°. The nmr spectrum consisted of a multiplet at δ 7.28 (relative area 10), ArH , a multiplet at 5.12 (relative area 1), $\text{O}-\text{CH}-\text{N}$, a multiplet at 3.18 (relative area 4), CH_2CH_3 , and $-\text{CH}_2\text{C}(=\text{N})$, a series of multiplets at 1.20–2.50 (relative area 6), $(-\text{CH}_2)_4-$, and a triplet at 1.06 (relative area 3), CH_2CH_3 . The infrared spectrum had strong bands at 2970, 1600, 1443, 1350, 1110, 1090, and 1065 cm^{-1} . The ultraviolet (λ_{max} 256 (ϵ 11,400) and 269 (sh) $\text{m}\mu$ (ϵ 10,200)) and mass spectra are in qualitative agreement with the structural assignment as 2,3-diphenyl-5-ethoxy-6,7,8,9-tetrahydro-5H-imidazo[1,2-*a*]azepine (12).

Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$: C, 79.48; H, 7.28; N, 8.43; mol wt, 332. Found: C, 79.32; H, 7.55; N, 8.56; mol wt, 332 (benzene).

Elution with 10% ether–benzene gave 70 mg (9% yield) of colorless solid. This material was purified by sublimation at 120–130° (0.15 mm) to give colorless crystals, mp 138–140°. The nmr spectrum consisted of a multiplet at δ 7.30 (relative area 10), ArH , a multiplet at 3.74 (relative area 2), CH_2-N , a multiplet at 3.02 (relative area 2), $-\text{CH}_2\text{C}(=\text{N})$, and a multiplet at 1.82 (relative

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(63) A. Beckett and G. Porter, *Trans. Faraday Soc.*, **59**, 2083 (1963); W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Am. Chem. Soc.*, **83**,

2789 (1961); N. J. Turro, P. A. Leermakers, H. R. Wilson, D. C. Neckers, G. W. Byers, and G. F. Vesley, *ibid.*, **88**, 2613 (1966).

(64) Reference 2, p 723 and Chapter 7.

(65) E. de Salas and C. Wilson, *J. Chem. Soc.*, 319 (1938).

($-\text{CH}_2$)₂-. The infrared spectrum showed strong absorptions at 2910, 1600, and 1350 cm^{-1} . The ultraviolet and mass spectra were consistent with the assigned structure, 2,3-diphenyl-1,4-dihydro-5H-imidazo[1,2-a]azepine (11).

Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2$: C, 83.29; H, 6.99; N, 9.71; mol wt, 282. Found: C, 83.04; H, 6.96; N, 9.56; mol wt, 282.

Elution of 1.06 g of 10 in 420 ml of cyclohexane for 5 hr under the same conditions followed by the same work-up gave (19%) of a crystalline material in the benzene-2% ether fraction. This was sublimed to give colorless needles, mp 125–127°. The nuclear magnetic resonance consisted of a multiplet at δ 7.30 (relative area 10), ArH , a doublet (with additional structure) at δ 6.24 (relative area 1, $J = 10$ cps), $\text{NCH}=\text{CH}-$, a doublet at δ 5.24 (relative area 1), $-\text{C}=\text{CHCH}_2$, a multiplet at δ 3.10 (relative area 2), $-\text{CH}_2\text{C}(=\text{N})-$, and multiplets at δ 1.76–2.60 (relative area 3), $-\text{CH}_2-\text{CH}_2$. The infrared spectrum had strong absorptions at 1600, and 1410 cm^{-1} . The ultraviolet (λ 280 m μ , ϵ 10,000) and mass spectra were consistent with the structure assigned as 2,3-diphenyl-8,9-dihydro-7H-1,2-a]azepine (13).

Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.18; H, 6.42.

Elution with benzene-10% ether gave 90 mg of 11. Elution with aromatic solvents gave other unidentified products.

Catalytic hydrogenation of 76 mg of 13 in ethanol over 10% palladium on charcoal gave, after ca. 1 equiv uptake of hydrogen, 20 mg of starting material and 31 mg of 11. This was identified by infrared, nmr, and melting point comparison.

Photolysis of *cis*-2,3-Dihydro-2,3-dimethyl-5,6-diphenylpyrazine (14). A solution of 917 mg of *cis*-2,3-dihydro-2,3-dimethyl-5,6-diphenylpyrazine (14) in 420 ml of absolute ethanol was photolyzed using a Pyrex-filtered high-pressure lamp for 10 min. The crude product was chromatographed on a column of 20 g of silica gel.

Elution with 1% ether-benzene gave 474 mg of *cis*-2,3-dihydro-2,3-dimethyl-5,6-diphenylpyrazine. No *trans*-dihydropyrazine was detected in the nmr spectrum.

Elution with 5% ether-benzene gave 239 mg (26%) of a crystalline solid purified by vacuum sublimation to give colorless crystals, mp 50–51°. The nmr spectrum consisted of a multiplet at δ 7.40 (relative area 10), ArH , a quartet at δ 5.16, quartet (relative area 1, s), $\text{OCH}-\text{CH}_2$, two overlapping quartets at δ 3.30 (relative area 1, s), CH_2CH_2 , a singlet at δ 2.66 (relative area 3), a doublet at δ 1.60 (relative area 3, $J = 7$ cps), $-\text{CHCH}_2$, a doublet at δ 1.14 (relative area 3, $J = 7$ cps), CH_2CH_2 . The infrared spectrum had strong absorptions at 2950, 1600, 1385, 1340, and 1270 cm^{-1} . The ultraviolet and mass spectra were consistent with the structure assigned as 4,5-diphenyl-1-(1-ethoxyethyl)-2-methylpyrazine (17).

Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}$: C, 78.40; H, 7.24; N, 9.14; mol wt, 305. Found: C, 78.14; H, 7.38; N, 9.14; mol wt, 319.

Photolysis of the partially resolved *cis-trans* mixture of 14 (8.7 \pm 4.75%) for 9 min in ethanol gave 17 (25%) and 14 (75%). The recovered starting material contained 27% *trans* isomer by nmr and had optical activity of $[\alpha]_D^{25} -0.68 \pm 0.02^\circ$, $[\alpha]_D^{25} \pm 3.0^\circ$.

Elution of 190 mg of 17 in 10 ml of concentrated hydriodic acid heated at reflux for 2 days. After cooling the mixture was poured into water and neutralized with concentrated ammonium hydroxide. The precipitate was collected by suction filtration to give 47 mg (97% yield) of 4,5-diphenyl-2-methylimidazole, mp 125–127°, identified by nmr, infrared, and melting point comparison with authentic sample.

Photolysis of 2,3-Dihydro-5,6-diphenyl-2-methylpyrazine (15). Elution of 1.5 g of 2,3-dihydro-5,6-diphenyl-2-methylpyrazine in 420 ml of absolute ethanol was photolyzed using a Pyrex-filtered high-pressure lamp for 8 hr. The crude product was chromatographed on a column of 20 g of silica gel.

Elution with 1% ether-benzene gave 232 mg (15% recovery) of 15. Elution with 5% ether-benzene gave 272 mg of oil. This oil was solid at 70–90° (0.15 mm) to give a colorless viscous oil. The infrared spectrum showed this to be a mixture of 4,5-diphenyl-1-(1-ethyl)imidazole (20) (singlet at δ 7.84, $\text{NCH}=\text{N}$, multiplets ArH , 5.12, $\text{O}-\text{CHCH}_2$, and 3.30, OCH_2CH_2 , doublet at δ 1.08, HCH_2 , and triplet at δ 1.08, CH_2CH_2) and 4,5-diphenyl-1-ethyl-2-methylimidazole (19) (multiplet at δ 7.30, ArH , singlet at δ 5.00, $\text{N}-\text{CH}_2-\text{O}$, multiplet at δ 3.30, $\text{O}-\text{CH}_2\text{CH}_2$, singlet at δ 2.66, and triplet at δ 1.08, CH_2CH_2) in a ratio of 4:3. The infrared and mass spectra were consistent with the assigned mixture.

Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$: C, 78.05; H, 6.90; N, 9.58. Found: C, 77.70; H, 7.11; N, 9.39.

Elution with 10% ether-benzene gave 125 mg of oil. The nmr spectrum of this oil was consistent with a mixture of 4,5-diphenyl-1-ethoxymethyl-2-methylimidazole (19) and 1,2-dimethyl-4,5-diphenylimidazole (18) in a ratio of 2:3. The infrared spectrum was consistent with this mixture.

Elution with 25% ether-benzene gave 627 mg (42% yield) of crystalline material identified as 1,2-dimethyl-4,5-diphenylimidazole (18) by comparison of the nmr and infrared spectra with those of authentic material. Sublimation of the imidazole gave colorless needles, mp 125–127°; a mixture melting point with authentic material was undepressed.

Photolysis of *d*-2-Isobutyl-2,3-dihydro-5,6-diphenylpyrazine (16). A solution of 931 mg of *d*-2-isobutyl-2,3-dihydro-5,6-diphenylpyrazine ($[\alpha]_D^{25} 91.9^\circ \pm 3.3^\circ$) in 420 ml of absolute ethanol was photolyzed using a Pyrex-filtered high-pressure lamp for 10 min. The crude product was chromatographed on a column of 20 g of silica gel.

Elution with 1% ether-benzene gave 508 mg of light yellow solid purified by sublimation to give 446 mg (50% recovery) of 16, mp 66.5–69.5°. The nmr and infrared spectra of the sublimed solid were identical with those of starting material. The optical rotation of this material determined using a solution of 228.4 mg of sublimed material in 10 ml of 95% ethanol was $[\alpha]_D^{25} +2.11 \pm 0.07^\circ$, $[\alpha]_D^{25} +92.2^\circ \pm 3.3^\circ$.

Elution with 2% ether-benzene gave 30 mg of an oil whose infrared spectrum suggested an ethoxymethylimidazole. The nmr spectrum consisted of a multiplet at δ 7.30, ArH , singlet at δ 5.04, NCH_2-O , quartet at δ 3.28, $-\text{CH}_2\text{CH}_2$, multiplet at δ 2.70, CH_2-CH , multiplet at δ 2.30, $\text{CH}_2\text{CH}(\text{CH}_3)$, doublet and triplet at δ 1.10, $\text{CH}(\text{CH}_3)$, and CH_2CH_2 , and is consistent with the structure assigned as 2-isobutyl-4,5-diphenyl-1-ethoxymethylimidazole (22).

Elution with 5% ether-benzene gave 194 mg of crystalline solid. The nmr (multiplet at δ 7.28 (relative area 10), ArH , singlet at δ 3.30 (relative area 3), NCH_2 , multiplet at δ 2.68 (relative area 2), CH_2-CH , multiplet at δ 2.18 (relative area 1), $-\text{CH}_2\text{CH}(\text{CH}_3)$, and doublet at δ 1.08 (relative area 6), $-\text{CH}(\text{CH}_3)$) spectrum was consistent with 2-isobutyl-4,5-diphenyl-1-methylimidazole (21). The imidazole was purified by sublimation at 100° (0.12 mm) to give fine colorless needles, mp 104–107°. The mass, infrared (KBr disk strong absorptions at 2980, 1600, 770, and 695 cm^{-1}), and ultraviolet spectra were consistent with the assigned structure.

Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.57; H, 7.54; N, 9.49.

Elution with 10% ether-benzene gave 60 mg of partially crystalline material which was composed of 30–40% of 21. The remainder of the material was assigned the structure 4,5-diphenyl-1-(1-ethoxy-4-methylbutyl)imidazole (23) discussed below.

Further elution with 10% ether-benzene gave 93 mg of an oil which was apparently an ethoxymethylimidazole. The nmr spectrum (singlet at δ 7.78 (relative area 1), NCHN , multiplet at δ 7.28 (relative area 10), ArH , multiplet at δ 4.98 (relative area 1), $\text{O}-\text{CH}(\text{N})-\text{CH}_2$, quartet at δ 3.30 (relative area 2), $\text{O}-\text{CH}_2\text{CH}_2$, multiplet at δ 2.68 (relative area 1), $\text{CH}-\text{CH}(\text{CH}_3)$, multiplet at δ 1.78 (relative area 2), CHCH_2CH , doublet at δ 1.08, (relative area 6), $\text{CH}(\text{CH}_3)$, triplet at δ 0.80 (relative area 3), CH_2CH_2) was consistent with an impure sample of 4,5-diphenyl-1-(1-ethoxy-4-methylbutyl)imidazole (23). Attempts to obtain analytical samples of 22 and 23 were not successful.

Photolysis of *d*-2-Isobutyl-2,3-dihydro-5,6-diphenylpyrazine (16) in Cyclohexane. A solution of 903 mg of sublimed *d*-2-isobutyl-2,3-dihydro-5,6-diphenylpyrazine (16) in 420 ml of cyclohexane (Fisher Spectral Grade) was photolyzed using a Pyrex-filtered high-pressure lamp for 10 min. The crude product was chromatographed on a column of 22 g of silica gel.

Elution with benzene gave 397 mg (40% recovery) of light yellow crystals sublimed to give 336 mg of 16, mp 68.5–70.5°. The infrared spectrum was identical with that of the starting dihydropyrazine 16. The optical rotation was determined using a 10-ml solution of 228.3 mg of the sublimed solid in 95% ethanol, $[\alpha]_D^{25} +2.08 \pm 0.08^\circ$, $[\alpha]_D^{25} +91.2^\circ \pm 3.8^\circ$.

Elution with 1% ether-benzene gave 22 mg of yellow oil which was identified as slightly impure 16 from its infrared spectrum.

Elution with 2% ether-benzene gave 107 mg of off-white solid. The infrared and nmr spectra were identical with those of 2-isobutyl-4,5-diphenyl-1-methylimidazole (21).

Further elution with 5% ether-benzene gave 218 mg of solid, mp 230–270° dec. Although the compound was only slightly soluble in all common organic solvents, it was found that it could be re-

Table II. Partial Mass Spectrum of 1,2-Di(2-isobutyl-4,5-diphenylimidazolyl)ethane (24) at 70 ev

<i>m/e</i>	% of largest peak	<i>m/e</i>	% of largest peak	Metastable peaks and transition assignments
579	44.7	269	20.8	550 578 → 563
578	100.0	261	49.0	505-506 563 → 535
523	20.4	260	51.2	495-496 578 → 535
304	26.0	259	83.0	158.5 578 → 303
303	81.0	247	23.4	
302	39.5	246	38.2	
301	20.4	245	37.4	
289	33.6	244	24.6	
288	20.0	234	76.7	
287	24.2	233	81.0	
276	22.9	232	34.0	

crystallized from acetone to give colorless rectangles, mp 269–271°. The nmr (multiplet at δ 7.26, ArH, singlet at 3.78, N-CH₂, multiplets at 1.80–2.30, CHCH₃, doublet at 0.90, CH(CH₃)₂), infrared (KBr disk, strong absorptions at 2970, 1600, 760, and 690 cm⁻¹), and ultraviolet (λ_{\max} 257.5 m μ (ϵ 23,400), λ shoulder 268 m μ (ϵ 21,100)) spectra were consistent with a 1-substituted 4,5-diphenylimidazole dimer, assigned the structure 1,2-di(2-isobutyl-4,5-diphenylimidazolyl)ethane (24). The mass spectrum (Table II) at 70 ev was consistent with the structure assigned.

Anal. Calcd for C₄₈H₄₈N₄: C, 83.06; H, 7.37; N, 9.68; mol wt, 578. Found: C, 82.93; H, 7.31; N, 9.81; mol wt, 523 (chloroform).

Photolysis of 2,3-Diphenyl-5,5,6,6-tetramethylpyrazine (39). A solution of 915 mg of 2,3-diphenyl-5,5,6,6-tetramethylpyrazine (39) in 420 ml of absolute ethanol was photolyzed using a Pyrex-filtered high-pressure lamp for 2.5 hr. The residue remaining after solvent evaporation was chromatographed on 15 g of silica gel.

Elution with 2% ether–benzene gave 71 mg (9% recovery) of 39.

Elution with 5% ether–benzene gave 474 mg (60% yield) of crystalline solid which was recrystallized from Skelly B and sublimed at 80° (0.15 mm) to give colorless needles, mp 86.5–88.5°. The nmr (multiplet at δ 7.40 (relative area 10), ArH, singlet at 5.48 (relative area 1), CH, broad singlet (removed by shaking with D₂O) at 3.14 (relative area 1), NH, singlet at 1.62 (relative area 3), CH₃, and singlet at 1.48 (relative area 3), CH₃), infrared (strong absorptions at 2980, 1635, 1500, and 1450 cm⁻¹), and ultraviolet (λ_{\max} 245 m μ (ϵ 12,500)) spectra of the photoproduct are consistent with the assigned structure, 2,2-dimethyl-4,5-diphenyl-3-imidazoline

Table III. Partial Mass Spectrum of 2,2-Dimethyl-4,5-diphenyl-3-imidazoline at 13 ev

<i>m/e</i>	% of largest peak
250	2.8
248	3.1
235	4.7
148	12.7
147	100.0
145	10.0

(40). The mass spectrum (Table III) was consistent with the assigned imidazoline structure.

Anal. Calcd for C₁₇H₁₈N₂: C, 81.56; H, 7.25; N, 11.19; mol wt, 250. Found: C, 81.70; H, 7.38; N, 11.06; mol wt, 271.

The presence of ca. 9% 2,2-dimethyl-4,5-diphenylisimidazole was shown by nmr analysis of the crude reaction mixture.

Dehydrogenation of 2,2-Dimethyl-4,5-diphenyl-3-imidazoline (40). A sample of 120 mg of purified 2,2-dimethyl-4,5-diphenyl-3-imidazoline was heated with an equimolar quantity of elemental sulfur for 3 hr at 95° and 1 hr at 125°. The sample was dissolved in ether, the unreacted sulfur was removed by filtration, and the solvent was removed under reduced pressure to leave 100 mg (83% yield) of pinkish crystals. The nmr, infrared, and ultraviolet spectra were identical with those of 2,2-dimethyl-4,5-diphenylisimidazole (41). The compound was sublimed to give colorless needles, mp 78–79.5° (lit.⁶² 78–79°). A mixture melting point with authentic 41 was undepressed.

Acid Hydrolysis of 2,2-Dimethyl-4,5-diphenyl-3-imidazoline (40). A sample of 220 mg of 2,2-dimethyl-4,5-diphenyl-3-imidazoline was hydrolyzed by heating for 1 hr in a few milliliters of 2 *N* hydrochloric acid. The solution was neutralized with sodium carbonate and the impure desylamine was collected by filtration; mp 85–90° (lit.⁶⁴ 109°).

A sample of the hydrolysis product was dissolved in warm dilute hydrochloric acid and aqueous picric acid was added. The precipitate was recrystallized from water to give yellow needles, mp 185–186° dec. A mixture melting point with authentic desylamine picrate was undepressed.⁶⁷ The infrared spectrum of this picrate was identical with that of the authentic sample.

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Thermal Reactions of Azidoformates

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Abstract: Kinetic studies have shown that azidoformates decompose thermally in a variety of solvents in a clean first-order reaction, the rate-determining step being evolution of nitrogen and formation of a nitrene. The nitrene reacts with saturated hydrocarbons by insertion into a C–H bond and by abstraction of two hydrogen atoms from adjacent carbons. The insertion reaction is highly selective, the primary:secondary:tertiary reactivity being in the ratio of 1:10:32. The mechanisms of these reactions are discussed.

In a search for new reactions of saturated hydrocarbons, our attention was focused on the reactions of several of Curtius's "starre" or nonrearranging azides: azidoformates, sulfonyl azides, and aryl azides.¹ It was felt that, if these compounds decompose by loss of nitrogen and formation of an electron-deficient nitrene

(1) A. Bertho, *J. Prakt. Chem.*, [2] **120**, 89 (1929).

species, the nitrene might insert into a carbon–hydrogen bond, in analogy to the well-known carbene reaction. If the reaction followed this course, monofunctional compounds could be used to introduce polar groups into saturated hydrocarbon polymers, such as polyethylene and polypropylene, while difunctional derivatives could be used as cross-linking agents for these polymers as

s for saturated hydrocarbon elastomers, such as neopropylene copolymers and polyisobutylene. High peroxides can be used to cross-link polyne and ethylene-propylene copolymers, free radicals are known to degrade polypropylene and isobutylene when used in small quantities.² This paper describes our experience with azidoformates.³ When this work was initiated, the literature was devoid of any pertinent references. Methyl,^{4,5} *n*-butyl⁶ and *t*-butyl⁷ azidoformates had been described, except for the work of Curtius and Klavehn⁸ on 1,3-dicyclopentadiene cycloaddition of the azide group to acetylenic bonds, the references described essentially only the nucleophilic displacement of the azide group from the azidoformate.⁹

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Our preliminary experiments showed that the thermal decomposition of an alkyl azidoformate in diphenyl ether did indeed give an *N*-cyclohexylcarbamate as one of the products of the reaction, a study of the kinetics of azidoformate decomposition in a variety of solvents was initiated. The kinetic runs were carried out by determining the increase in pressure at constant volume by means of a transducer connected to a recorder; a read-out device enabled one to take individual data points. *n*-Octadecyl azidoformate was chosen because it could be purified by recrystallization, it is a liquid and its low volatility simplified the kinetics; tetramethylene bis(azidoformate) was chosen as a diatomic compound.¹¹

A representative run with *n*-octadecyl azidoformate in diphenyl ether is illustrated in Figure 1. The reaction is clearly first order to 95% reaction; at 120°, *n*-octadecyl azidoformate has a half-life of 48.1 min. Figure 1 shows that the rate constant is independent of concentration at two different temperatures and that the reaction is essentially quantitative. Tetramethylene bis(azidoformate), in which the two azidoformate groups are separated by only four carbon atoms, gives exactly the same rate. The aromatic bis(azidoformate), 2,2-bis(4-azidocarbonyloxyphenyl)propane, is much less stable; at 120° it has a half-life of 33.4 min. The decomposition of both the *n*-octadecyl and the tetramethylene azidoformates ΔH^\ddagger is 29.9 kcal/mole S^\ddagger is +4.7 eu.

The first-order decomposition of azidoformates is catalyzed by a wide variety of reagents. Potassium hydroxide, *p*-toluenesulfonic acid, fatty acid salts of sodium, calcium, zinc, cadmium, copper, lead, manganese, cobalt, and nickel, titanium(IV) naphthenate,

D. Jones in "Chemical Reactions of Polymers," E. M. Fettes, Interscience Publishers, Inc., New York, N. Y., 1964, p. 250. A portion of this work was described in a preliminary communication, J. Prosser, A. F. Marcantonio, C. A. Genge, and D. S. Breslow, *Carbon Letters*, 2483 (1964).

Curtius and K. Heidenreich, *J. Prakt. Chem.*, [2] 52, 454

Bertho, *ibid.*, [2] 116, 101 (1927).

O. Forster and H. E. Fierz, *J. Chem. Soc.*, 93, 72 (1908).

A. Carpino, *J. Am. Chem. Soc.*, 79, 4427 (1957).

Curtius and W. Klavehn, *J. Prakt. Chem.*, [2] 125, 498 (1930).

For example, L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Am. Chem. Soc.*, 81, 955 (1959).

We are indebted to Dr. F. A. Fritz for the design and construction of the apparatus.

Methyl azidoformate and tetramethylene bis(azidoformate) were found to be somewhat shock sensitive. Explosions during distillation of the former have since been reported.¹²

L. J. Cotter and W. F. Beach, *J. Org. Chem.*, 29, 751 (1964).

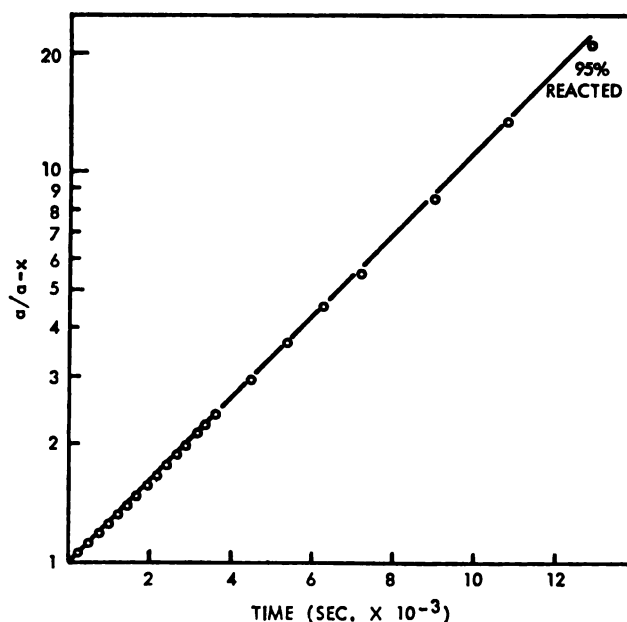


Figure 1. Decomposition of 0.1 *M* *n*-octadecyl azidoformate in diphenyl ether at 120°.

and aluminum and magnesium acetylacetonates at the 10 mole % level, as well as equal weights of carbon black and calcium carbonate, had no effect on the rate of thermal decomposition of *n*-octadecyl azidoformate in diphenyl ether.

Table I. Decomposition of Azidoformates in Diphenyl Ether

Azidoformate	Concn, <i>M</i>	Temp, °C	$k_1 \times 10^4$, sec ⁻¹	N ₂ evolved, % of theory
ODAF ^a	0.02	133.3	8.70	98.5
	0.10	133.3	9.00	99.5
	0.02	120.0	2.44	97.4
	0.10	120.0	2.40	100
	0.10	100.0	0.267	102.7
TBAF ^b	0.02	133.3	8.48	
	0.10	133.3	9.00	97.0
	0.02	120.0	2.26	98.2
	0.10	120.0	2.34	
	0.10	100.0	0.261	101
BPAF ^c	0.02	120.0	3.46	97.5

^a *n*-Octadecyl azidoformate. ^b Tetramethylene bis(azidoformate). ^c 2,2-Bis(4-azidocarbonyloxyphenyl)propane.

Table II lists the first-order rate constants for the decomposition of *n*-octadecyl azidoformate in a variety of solvents. Good first-order plots were obtained to better than 75% reaction in most of these solvents; deviations from first order were observed in the fatty acid after 50% and in 2-heptanone after 65%. Since the excess gas in the fatty acid run was identified as carbon dioxide, apparently a concurrent reaction disturbed the normal first-order kinetics; the reason for the low gas yield and the poor kinetics in 2-heptanone has not been explained. The less than fourfold variations in rate can undoubtedly be attributed to the widely varied nature of the solvents rather than to different mechanisms.¹³

(13) Huisgen and Blaschke¹⁴ have recently reported similar results for the thermal decomposition of *n*-propyl azidoformate in anethole,

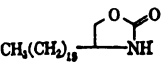
Table II. Decomposition of *n*-Octadecyl Azidoformate in Various Solvents at 120.0°*

Solvent	$k_1 \times 10^4$ sec ⁻¹	Relative rate	Gas evolved, % of theory
Diphenyl ether	2.40	1	100
Mineral oil	2.15	0.90	103
1-Octadecene	3.76	1.57	97.7
Indene	5.88	2.45	100.8
Bis(2-methoxyethyl) ether	3.32	1.39	101.2
1-Octanol	7.40	3.18	107.2
2-(<i>n</i> -Butoxyethoxy)- ethanol	4.04	1.68	91.7
Phenol	3.74	1.56	97.4
C ₈ -C ₁₈ fatty acid	2.02	0.84	119
Diethyl sebacate	2.52	1.05	101
2-Heptanone	2.96	1.23	93.8

* 0.10 *M* in *n*-octadecyl azidoformate.

To determine the products of the reaction, an attempt was made to obtain a complete material balance in the reaction of *n*-octadecyl azidoformate with cyclohexane. Separations were made using a "Scanalyzer," a liquid-solid chromatographic apparatus in which the polarity of the eluting solvent is increased automatically; the previously described apparatus¹⁵ was modified to monitor fractions by infrared rather than by ultraviolet, as described in the Experimental Section. The results obtained by heating a 1.25% solution of the azidoformate in cyclohexane at 130° are given in Table III; it

Table III. Reaction of *n*-Octadecyl Azidoformate with Cyclohexane at 130°

Fraction	Product	— Mole % of — initial azide	
		<i>m</i> -C ₆ H ₄ (NO ₂) ₂ absent	<i>m</i> -C ₆ H ₄ (NO ₂) ₂ present
I	[CH ₂ (CH ₂) ₁₇ O] ₂ CO		
II	CH ₂ (CH ₂) ₁₇ OCONHC ₆ H ₁₁	59.8	72.6
III	CH ₂ (CH ₂) ₁₇ OCONH ₂	22.6	14.7
IV		5.0	5.0
V	C ₁₉ H ₃₇ O ₂ N	7.7	8.1
		95.1	100.4

was gratifying to be able to account for 95% of the initial azide. Fraction I was identified as *n*-octadecyl carbonate, an impurity present in this sample of azidoformate. The major product of the reaction, *n*-octadecyl *N*-cyclohexylcarbamate (fraction II), is formed by insertion of the nitrene moiety into a C-H bond of cyclohexane. However, there is also a considerable amount of the hydrogen abstraction product, *n*-octadecyl carbamate (fraction III).¹⁶ Fractions I-III were identified

ethyl 10-undecenoate, benzonitrile, phenylacetylene, diphenylacetylene, diphenyl ether, mesitylene, and paraffin. Although their rates seemed to be about one-third slower than ours and their result in paraffin was abnormal, their rate constants varied by only a factor of 4 in the different solvents.

(14) R. Huisgen and H. Blaschke, *Chem. Ber.*, **98**, 2985 (1965).

(15) W. C. Kenyon, J. E. McCarley, E. G. Boucher, A. E. Robinson, and A. K. Wiebe, *Anal. Chem.*, **27**, 1888 (1955).

(16) Lwowski and Mattingly¹⁷ have recently reported a 51% yield of *N*-cyclohexylurethan and a 12% yield of urethan from the photolysis of ethyl azidoformate in cyclohexane. Huisgen and Blaschke¹⁴ reported a

by comparison with authentic specimens. Fractions IV and V, which accounted for 12.7% of the initial azide, are isomeric materials which analysis showed to be C₁₉H₃₇O₂N; they are therefore intramolecular condensation products of the nitrene. Fraction IV was shown to be 4-*n*-hexadecyl-2-oxazolidinone by comparison of its infrared and nmr spectra with those of an authentic sample of the 4-ethyl derivative. Thus, both compounds showed carbonyl absorption at 1760 cm⁻¹. In very similar nmr spectra, both compounds showed four hydrogens in addition to those in the alkyl side chain, a multiplet (2 H) centered at about τ 6.4 for the two hydrogens adjacent to oxygen, a multiplet (1 H) centered at about τ 5.9 for the one hydrogen adjacent to nitrogen, and a broad line (1 H) for the amide hydrogen at about τ 2.4.

Although fraction V would be expected to be the corresponding six-membered ring compound, 4-*n*-pentadecyltetrahydro-2H-1,3-oxazin-2-one, comparison with the analogous 4-methyl derivative probably excludes this structure. Thus, the 4-methyl derivative showed carbonyl absorption at 1704 cm⁻¹, while fraction V in various samples absorbed in the 1725-cm⁻¹ region. The presence of an absorption band at 3250 cm⁻¹ typical of N-H in a secondary amide together with the complete absence of an amide II band indicates a cyclic amide structure. In the nmr spectrum, the 4-methyl derivative showed the expected pattern: a multiplet (2 H) centered at τ 8.14 for the middle methylene hydrogens, a multiplet (2 H) centered at τ 6.64 for the two hydrogens adjacent to oxygen, a multiplet (1 H) centered at τ 5.58 for the one hydrogen adjacent to nitrogen, and a broad line (1 H) for the amide hydrogen at τ 2.76. Fraction V showed only three types of hydrogen in addition to those in the side chain: a broad line (1 H) at τ 6.86, a broad line (2 H) at τ 5.90, and a broad line (1 H) at τ 2.06. The absence of the expected middle methylene peak is not significant, since, if present, it would have been buried under the large side-chain peak. The difficulty arises from the peak for the two hydrogens being downfield from that for the one hydrogen, the direct inverse of the pattern for the 4-methyl derivative. Unfortunately, lack of material precluded further investigation.

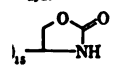
On the basis of the assumption that hydrogen abstraction might be a radical reaction, the decomposition of *n*-octadecyl azidoformate in cyclohexane was carried out in the presence of a small amount (0.25% based on cyclohexane) of a potential radical trap, *m*-dinitrobenzene. The results, shown in Table III, were quite surprising. Although the yield of hydrogen-abstraction product was indeed decreased, the yield of insertion product was increased. There was no reaction with the *m*-dinitrobenzene; all the azidoformate added could be accounted for by reaction with cyclohexane or with itself.

That the results with *m*-dinitrobenzene are well outside of experimental error was demonstrated by carrying out the decomposition in methylcyclohexane, without added nitro compound. Although the various insertion isomers were not separated from each other, the yields of the different types of products were prac-

78% yield of *N*-cyclohexylurethan in the same experiment, but details are lacking.

(17) W. Lwowski and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **87**, 1947 (1965).

Reaction of *n*-Octadecyl Azidoformate with
Cyclohexane and with Methylcyclohexane

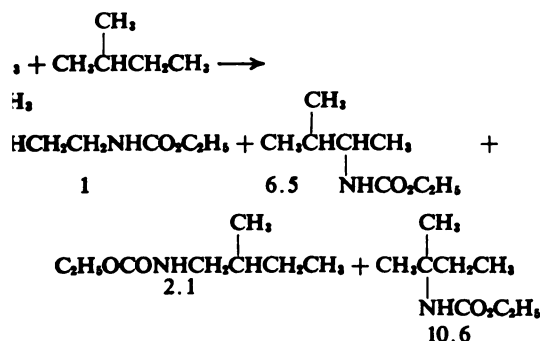
Product	Mole % of initial azide	
	Cyclohexane	Methyl- cyclohexane
$\text{H}_{37}\text{OCONHC}_6\text{H}_{11}$	59.8	...
$\text{H}_{37}\text{OCONHC}_7\text{H}_{13}$...	60.4
$\text{H}_{37}\text{OCCNH}_2$	22.6	24.4
	5.0	4.5
C_6H_8	7.7	7.9

identical with those obtained in cyclohexane.

able results were obtained in the decomposition of tetramethylene bis(azidoformate) in cyclohexane. 2% yield of tetramethylene bis(N-cyclohexyl-), from C-H insertion at both ends, 36% of ethylene N-cyclohexyldicarbamate, from insertion at one end and hydrogen abstraction at the other, 3% of tetramethylene dicarbamate, from abstraction at both ends, were isolated. Based on the 11% of azidoformate groups, 50% of the reaction was C-H insertion and 27% hydrogen abstraction, in good agreement with the *n*-octadecyl azidoformate results, considering that only 77% of the material was accounted for.

To determine the source of the hydrogen in the inserted carbamate, the decomposition of an 11% of *n*-octadecyl azidoformate in cyclohexane was investigated. Cyclohexene was identified in the reaction by mass spectrographic analysis; as the same amount of unsubstituted carbamate was used as in the more dilute reaction, the cyclohexene formed, based on the amount of *n*-octadecyl azidoformate, was 42%. The low yield is not surprising in view of the finding by Lwowski and ¹⁷ that the double bond in cyclohexene reacts preferentially with ethoxycarbonylnitrene 36 times faster than do the nonallylic methylene groups; therefore no attempt was made to isolate the exocyclic imine. No trace of bicyclohexyl could be detected by either gas chromatographic or mass spectrographic analysis.

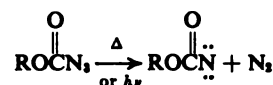
To determine the relative reactivities of different C-H bonds toward insertion, ethyl azidoformate was used in 2-methylbutane, the products being identified by gas chromatography. After correction for the number of hydrogens, the relative reactivities



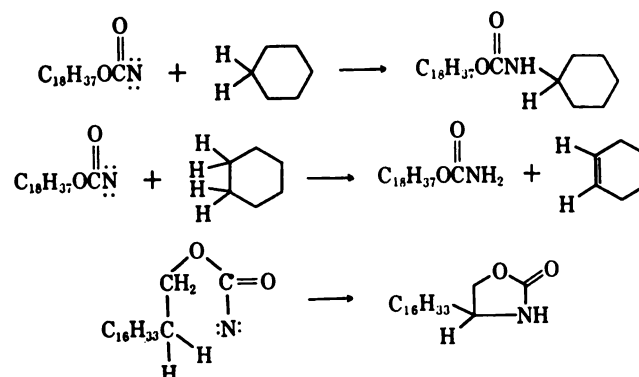
of secondary:tertiary C-H bonds were found to be 32:1.

Discussion

There would appear to be little doubt from the kinetic results that the rate-determining step in the thermal decomposition of azidoformates is the loss of nitrogen and the formation of an electron-deficient nitrene species, in complete agreement with the elegant work of Lwowski and his co-workers on the photochemical decomposition. The reaction of *n*-octadecyl azido-



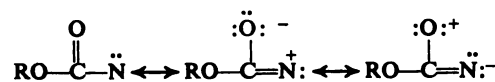
formate with cyclohexane can then be pictured as follows:



About 65% of the azidoformate undergoes insertion, either intra- or intermolecularly, and about 20% undergoes hydrogen abstraction by a process of removing two hydrogen atoms from adjacent carbons.

Several examples of 2-oxazolidinone formation have been reported recently. Thus, Smolinsky and Feuer¹⁸ obtained a 68% yield of the 4-methyl-4-ethyl derivative by vapor-phase decomposition of 2-methylbutyl azidoformate, conditions under which intermolecular reactions would be minimized. The fact that *t*-butyl azidoformate, upon irradiation in the reactive solvent, *t*-butyl alcohol, cyclizes to the 4,4-dimethyl derivative in 60–75% yield^{19,20} is probably a reflection of the well-known *gem*-dimethyl effect, while the complete absence of 2-oxazolidinone in the decomposition of ethyl azidoformate under a variety of conditions¹⁷ is probably a result of the lower activity of a primary as compared to a secondary C-H bond. Although it appears rather unlikely that the unknown isomer in the reaction is the six-membered cyclic carbamate, intramolecular nitrene insertion to give a six-membered ring is not without precedent; several examples of δ -lactam formation by photolysis of carbonyl azides have been reported.^{21,22}

The reactivity of a formyl nitrene toward insertion into a C-H bond is remarkably independent of its modes of formation. As shown in Table V, essentially identical results are obtained by azide thermolysis, by azide photolysis, and by α elimination. In view of the quite high selectivity found, there must be considerable resonance stabilization of the nitrene, *e.g.*



(18) G. Smolinsky and B. I. Feuer, *J. Am. Chem. Soc.*, **86**, 3085 (1964).

(19) R. Kreher and G. H. Bockhorn, *Angew. Chem.*, **76**, 681 (1964).

(20) R. Puttner and K. Hafner, *Tetrahedron Letters*, 3119 (1964).

(21) J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962).

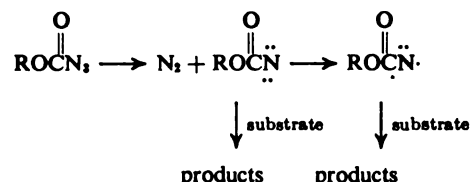
(22) W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, **28**, 2859 (1963).

Table V. Insertion of Carboethoxynitrene into the C-H Bonds of 2-Methylbutane

Method of formation	Type of bond		
	Primary	Secondary	Tertiary
Azide thermolysis	1	10	32
Azide photolysis ^a	1	9	34
α elimination ^a	1	11	27

^a W. Lwowski and T. J. Maricich, *J. Am. Chem. Soc.*, **87**, 3630 (1965).

Some progress is being made in determining the nature of the nitrene, singlet or triplet, responsible for its different reactions. Considering the relatively low temperature at which nitrene can be formed from azide, it is highly likely that nitrene is formed initially as a singlet.²³ This can then react with substrate to give products, or it can decay to ground-state triplet²⁵



which in turn can react with substrate. The facts that tetramethylene bis(azidoformate) cross-links polyisobutylene,³⁰ whereas radicals are known to lead to degradation,² and that the insertion reaction can be highly stereospecific,^{18,31} argues for singlet nitrene being involved in C-H insertion. However, recent work with cyanogen azide³² indicates that a triplet nitrene can insert nonstereospecifically. Thus, the spin multiplicities involved in C-H insertion seem to parallel quite closely those involved in addition to a carbon-carbon double bond. Here, too, Lwowski and McConaghy³³ concluded that both singlet and triplet nitrene add, the former stereospecifically and the latter nonstereospecifically.

There is much less evidence available at present regarding hydrogen abstraction. It seems to be fairly certain from our results that two hydrogen atoms are abstracted from adjacent carbon atoms in a concerted fashion,³⁴ or at least in rapid consecutive reactions, since the formation of free cyclohexyl radicals would have been expected to lead to the formation of at least some bicyclohexyl. Although there is no *a priori*

reason for eliminating the possibility of this being a singlet reaction, it is easier to explain our results with *m*-dinitrobenzene on the basis of hydrogen abstraction involving a triplet nitrene. Although the mechanism of action of nitroaromatics as inhibitors of free-radical reactions may be uncertain, they appear to inhibit by reacting with free radicals.³⁵ Although the yield of hydrogen abstraction product was indeed reduced by the addition of *m*-dinitrobenzene, all of the azidoformate was accounted for as reaction products with cyclohexane or with itself. If the same nitrene species (singlet or triplet) were responsible for both insertion and abstraction, one would have expected *m*-dinitrobenzene to decrease the insertion yield as well, whereas in actual fact the yield of insertion product in the presence of *m*-dinitrobenzene actually increased over that obtained in its absence. If one assumes that C-H insertion under these conditions involves a singlet nitrene, then hydrogen abstraction probably involves a triplet.

Experimental Section

Preparation of Chloroformates. Several different procedures were used to prepare the chloroformates. *n*-Octadecyl chloroformate was prepared as follows. To 198 g (2 moles) of phosgene in a flask connected to a Dry Ice condenser was added 270.5 g (1 mole) of molten 1-octadecanol over a period of 90 min, the reaction being kept at 5–10° by external cooling. The cooling bath was then removed and the reaction stirred for 5 hr. The Dry Ice condenser was removed and the excess phosgene was allowed to evaporate overnight, the last traces being removed *in vacuo*. A quantitative yield of chloroformate was obtained as a clear yellow oil; the absence of a hydroxyl band in the infrared spectrum indicated the completeness of the reaction.

To 70 ml of carbon tetrachloride in a flask attached to a Dry Ice condenser was added 45 g (0.5 mole) of tetramethylene glycol while 114 g (1.15 moles) of phosgene was passed in. The reaction was kept at 10–15° during the addition, which took 45 min. The reaction mixture was stirred at 15° for an additional 4.5 hr, the Dry Ice condenser was removed, and the solution was refluxed to remove excess phosgene. Stripping the solvent *in vacuo* left 106 g of tetramethylene bis(chloroformate), an essentially quantitative yield. Although pure enough for subsequent reaction, the material could be further purified by distillation, bp 126° (5–6 mm).

A solution of 46 g (0.2 mole) of 2,2-bis(4-hydroxyphenyl)propane in 300 ml of ether was added to 49 g (0.5 mole) of phosgene cooled below 0° in an ice-salt bath. To the stirred and cooled resulting white slurry was then added dropwise 60.5 g (0.5 mole) of dimethylaniline. The mixture was stirred in the cooling bath for an additional hour and allowed to warm to room temperature overnight, and the solvent and excess phosgene were removed *in vacuo*. The residual solid was suspended in 400 ml of ether and poured onto ice, and the organic layer was separated. After being washed once with 5% hydrochloric acid and then with water, the solution was dried over sodium sulfate and the solvent evaporated. There was thus obtained 60 g (85%) of 2,2-bis(4-chlorocarbonyloxyphenyl)propane, mp 93–96°. Recrystallization from heptane gave a 77% yield of product melting at 96.5–98.5°.

Preparation of Azidoformates. A solution of 16.7 g (0.05 mole) of *n*-octadecyl chloroformate in 100 ml of chloroform was added dropwise to a vigorously stirred solution of 6.5 g (0.10 mole) of sodium azide in 15 ml of water at room temperature. The reaction mixture was stirred vigorously at room temperature for 3 days, and the organic layer was separated, washed several times with water, and dried over a mixture of magnesium and sodium sulfates. Removal of the solvent yielded 16.5 g (97%) of crystalline *n*-octadecyl azidoformate, mp 37.8–38.8°.

Anal. Calcd for C₁₉H₃₇N₃O₂: C, 67.21; H, 10.99; N, 12.38; O, 9.43. Found: C, 67.54; H, 11.07; N, 12.16; O, 9.07. For the kinetic runs, a sample was recrystallized several times from methanol, mp 41.0–41.5°.

(35) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 169.

(23) If the law of spin conservation is to be obeyed, a nitrene triplet can be the initial product if singlet azide decomposes into triplet nitrene and triplet nitrogen, or if singlet azide is first converted into triplet azide, which then decomposes into triplet nitrene and singlet nitrogen. Neither path seems very likely at decomposition temperatures in the vicinity of 100°.²⁴

(24) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 178 (1964).

(25) Evidence is accumulating that all nitrenes have triplet ground states. This has been demonstrated for HN₃,²⁶ NCN,²⁷ alkyl azides,²⁸ aryl azides,²⁹ and sulfonyl azides.²⁹

(26) G. Herzberg, "Molecular Spectra and Molecular Structure," D. Van Nostrand Co., New York, N. Y., 1950, p 369.

(27) A. G. Anastassiou, *J. Am. Chem. Soc.*, **87**, 5512 (1965).

(28) E. Wasserman, G. Smolinsky, and W. A. Yager, *ibid.*, **86**, 3166 (1964).

(29) G. Smolinsky, E. Wasserman, and W. A. Yager, *ibid.*, **84**, 3220 (1962).

(30) D. S. Breslow, U. S. Patent 3,284,421 (1966).

(31) S. Yamada, S. Terashima, and K. Achiwa, *Chem. Pharm. Bull. (Tokyo)*, **13**, 751 (1965).

(32) A. G. Anastassiou, *J. Am. Chem. Soc.*, **88**, 2322 (1966).

(33) W. Lwowski and J. S. McConaghy, Jr., *ibid.*, **87**, 5490 (1965).

(34) A referee has suggested that a concerted reaction is unlikely because the two C-H bonds are skew. In view of the rapid interconversion of cyclohexane structures, we do not consider this a valid objection.

same procedure, tetramethylene bis(chloroformate) was into tetramethylene bis(azidoformate) in 96% yield, after recrystallization from ethanol-hexane.

Calcd for $C_4H_8N_4O_4$: C, 31.58; H, 3.53; N, 36.84; Found: C, 31.57; H, 3.27; N, 37.05; O, 28.19.

4-azidocarbonyloxyphenylpropane was obtained in 92% 69–70.5° after recrystallization from ethanol.

Calcd for $C_{17}H_{14}O_4N_4$: C, 55.74; H, 3.86; N, 22.93; Found: C, 56.29; H, 3.72; N, 23.16.

Runs. The reactor consisted of a 200-ml creased flask with neck ending in a 29/42 standard-taper female joint. The joint was a side arm closed off by a pressure stopcock; this was a glass-enclosed magnet on which the sample cup. The entire apparatus was immersed in an oil bath controlled $\pm 0.01^\circ$; the reaction was stirred by a magnetic stirring magnet drive being placed just below the oil bath. The transducer built into a stainless-steel 29/42 standard-taper joint was used to determine pressure changes. The connection through the side arm to a thermostated gas line also to a 100-cm, closed-end manometer to determine pressure; the entire system could be evacuated or filled with inert gas.

For each run, the desired volume of solvent was placed in the side arm of the azidoformate, in a small glass sample cup, was set in place. After the transducer was inserted and clamped, the apparatus was alternately evacuated to about 2 mm and filled with an inert gas, nitrogen or argon, to a pressure of about 1 atm.

Finally, the apparatus was filled with inert gas to a pressure in excess of 1 atm, and the reactor was lowered into the oil-bath temperature bath. During equilibration, the reactor was, as required, to maintain the pressure at about 780 mm. When the pressure had become constant (usually 0.5–1 hr), the bar was retracted, and the sample cup was dropped into the hot oil bath. Pressure was recorded automatically on a strip chart recorder at 2 in./hr. For rapid reactions, the pressure was read from a digital read-out system. At the end of the run, the reactor was cooled in the reaction was bled to the thermostated gas line. After equilibration, the pressure in the system was adjusted by manipulating the mercury level in the gas line. The theoretical reaction gas volume was calculated in the usual way from the known sample weight, and temperature data.

Chromatographic Separations. The products from reaction of azidoformate with cyclohexane or methylcyclohexane were separated on adsorbent columns 17 cm long and 1.8 cm i.d., containing 100 parts by weight of Woelm neutral alumina and 6 parts by weight of 60/80 mesh Porapak Q.

The two-bottle gradient solvent system comprised about 100 ml of a relatively nonpolar solvent in a 9.6-cm i.d. bottle and 100 ml of a more polar solvent in a 5.2-cm i.d. bottle.

Chromatographic separations were made in an automated system which used an infrared spectrophotometer (Perkin-Elmer Model 237-B) as the detector. This was set to scan over the carbonyl region, 1850–1650 cm^{-1} . This apparatus is similar to the "analyzer" previously described¹⁸ which used an ultraviolet spectrophotometer as the detector. A typical run produced 10 cuts which were stored in a fraction collector. A strip chart recorded the carbonyl absorbance of each chromatographic fraction. The several components of a sample were isolated by selectively combining the pertinent cuts and evaporating solvent. Weight per cent analysis was obtained; typical recoveries of sample were 95–98 wt %.

Different solvent systems were used in these chromatographic separations. One system used 0.4 vol % ethanol in chloroform in the 9.6-cm bottle and 1.6 vol % ethanol in chloroform in the smaller 5.2-cm bottle. Another system was obtained by passing Mallinckrodt analytical reagent chloroform through an alumina column. This gave good separation of fractions I–III but did not separate fractions IV and V (Table III); the presence of these two in a combined elution band was readily apparent because of the difference in carbonyl frequencies, 1760 vs. 1730 cm^{-1} .

In earlier work, this mixture of fractions IV and V was separated by chromatography, again on the alumina and 6% water using *n*-heptane as the nonpolar solvent and 10 vol % alcohol in *n*-heptane as the polar solvent. In later work, complete resolution of all five components in the mono-*n*-octadecyl-hydrocarbon reaction mixture was achieved using a mixture consisting of 1 vol % of acetonitrile in carbon tetrachloride in the larger bottle and 20 vol % of acetonitrile in carbon tetrachloride in the smaller bottle.

Reaction of *n*-Octadecyl Azidoformate with Cyclohexane.

n-Octadecyl carbamate was prepared by passing ammonia into a cold solution of 1 g of *n*-octadecyl chloroformate in 250 ml of ether. Filtration to remove ammonium chloride, evaporation of the solvent, and recrystallization of the residue from aqueous acetone yielded 1.2 g (82% of theory) of product, mp 101.5–103°.

Anal. Calcd for $C_{19}H_{37}O_2N$: C, 72.78; H, 12.54; N, 4.47; Found: C, 72.68; H, 12.54; N, 4.56.

n-Octadecyl *N*-cyclohexylcarbamate was prepared by refluxing a solution of 2.71 g (10 mmoles) of 1-octadecanol, 1.38 g (11 mmoles) of cyclohexyl isocyanate,³⁶ and 0.27 g of triethylamine in 25 ml of chloroform. Removal of solvent and recrystallization from acetone yielded 3.26 g (83% of theory) of white solid, mp 68.5–69.5°.

Anal. Calcd for $C_{24}H_{44}O_2N$: C, 75.88; H, 12.48; N, 3.54; Found: C, 75.98; H, 12.87; N, 2.94.

4-Ethyl-2-oxazolidinone was prepared in 47% yield from 2-amino-1-butanol and ethyl carbonate according to the procedure of Homeyer,³⁷ bp 129–131° (0.5 mm), n_D^{20} 1.4637, mp 17° (lit.³⁷ n_D^{20} 1.4631, mp 16.0–16.5°).

Anal. Calcd for $C_6H_{10}O_2N$: N, 12.17. Found N, 12.20.

4-Methyltetrahydro-2H-1,3-oxazin-2-one was prepared in the same fashion from 3-amino-1-butanol. Recrystallization from acetone gave a 39% yield of product, mp 98.5–99.5° (lit.³⁸ mp 91°).

Anal. Calcd for $C_8H_{12}O_2N$: C, 52.16; H, 7.88; N, 12.17; Found: C, 52.13; H, 7.89; N, 12.14.

Solutions of 1.00 g (2.95 mmoles) of *n*-octadecyl azidoformate in 100 ml of cyclohexane (Eastman Kodak Spectro Grade) were heated at 130° under nitrogen in capped pressure bottles for 16 hr. Eight such runs were combined, using chloroform to rinse the bottles. Removal of the solvent *in vacuo* left 8.745 g of solid.

The acetonitrile-carbon tetrachloride solvent system gave five fractions (Table III). Fraction I (1.9 wt %) had an infrared spectrum very similar to that of decyl carbonate; it is presumably octadecyl carbonate, present as a minor impurity in the azidoformate, and the yield calculations were corrected accordingly. Fraction II (62.6 wt %) analyzed correctly for *n*-octadecyl *N*-cyclohexylcarbamate, and its melting point and infrared spectrum agreed with those of an authentic sample. In the same way fraction III (18.7 wt %) was identified as *n*-octadecyl carbamate. Fraction IV (4.1 wt %) was identified as 4-*n*-hexadecyl-2-oxazolidinone, mp 60.5–62° after recrystallization from aqueous acetone.

Anal. Calcd for $C_{19}H_{37}O_2N$: C, 73.25; H, 11.97; N, 4.50; mol wt, 311. Found: C, 72.94; H, 12.10; N, 4.36; mol wt (Rast), 295.

The infrared and nmr spectra of fraction IV were very similar to those of 4-ethyl-2-oxazolidinone. Fraction V (6.7 wt %), mp 75.5–77° after recrystallization from aqueous acetone, was an isomer of fraction IV.

Anal. Calcd for $C_{19}H_{37}O_2N$: C, 73.25; H, 11.97; N, 4.50; mol wt, 311. Found: C, 73.45; H, 12.25; N, 4.43; mol wt (Rast), 309.

To determine the source of the hydrogen in the unsubstituted carbamate, 1.00 g of *n*-octadecyl azidoformate was decomposed in 10 ml of cyclohexane as described above. Mass spectral analysis showed the presence of 0.30 ± 0.05 mole % of cyclohexene.³⁹ This corresponds to a 42% yield of cyclohexene, if a 22% yield of unsubstituted carbamate is assumed.

Reaction of *n*-Octadecyl Azidoformate with Cyclohexane in the Presence of *m*-Dinitrobenzene. A solution of 2.00 g of *n*-octadecyl azidoformate and 0.50 g of *m*-dinitrobenzene in 200 ml of cyclohexane was heated for 17 hr at 130° as described above. Removal of solvent left 2.750 g of residue.

Chromatographic separation of the product gave fractions II–V; *n*-octadecyl carbonate, previously separated as fraction I, was apparently absent from this sample of azidoformate. Fraction II, *n*-octadecyl *N*-cyclohexylcarbamate, did contain a yellow contaminant which did not show carbonyl absorbance. Rechromatography on a similar column, using carbon tetrachloride and 5 vol % of diethyl ether in carbon tetrachloride in the 9.6- and 5.2-cm

(36) A. Skita and H. Rolfes, *Ber.*, 53B, 1248 (1920).

(37) A. H. Homeyer, U. S. Patent 2,399,118 (1946).

(38) A. M. Paquin, *Z. Naturforsch.*, 1, 518 (1946).

(39) We are indebted to P. W. Shearer of this laboratory for this determination. Since cyclohexane has a small peak contribution at $M - 2$ (m/e 82, the parent ion for cyclohexene), a fresh calibration sample of cyclohexane (Eastman Kodak Spectral Grade) was run immediately preceding the questioned samples. This calibration pattern was then used to apply the proper correction on the $M - 2$ (m/e 82) peak, leaving the residual m/e 82 free for calculating cyclohexene. Relative sensitivities for constituents reported were based on our instrumental parameters.

bottles, respectively, separated the yellow contaminant from fraction II. Infrared indicated that most of this contaminant was *m*-dinitrobenzene, but unidentified material was present also. Fractions II-V were identical by infrared with the analogous components discussed above and accounted for 100.4 mole % of the initial azidoformate. Thus, the contaminants, 14.2 wt % of the sample, apparently were not derived from the azidoformate.

Reaction of *n*-Octadecyl Azidoformate with Methylcyclohexane. Solutions of 1.00 g of azidoformate in 100 ml of methylcyclohexane were treated as described above. From eight runs, 8.20 g of yellow-white solid was obtained.

Chromatographic separative analysis of the reaction product also produced five fractions (Table IV). Fraction I was *n*-octadecyl carbonate (2.5 wt %). Fraction II was a mixture of isomeric *n*-octadecyl *N*-methylcyclohexylcarbamates (66.1 wt %).

Anal. Calcd for $C_{28}H_{51}O_2N$: C, 76.22; H, 12.55; N, 3.42; mol wt, 410. Found: C, 75.74; H, 12.30; N, 3.28; mol wt (Rast), 400.

Rechromatographing fraction II on neutral alumina and 6% water with 2.0 vol % of diethyl ether in petroleum ether (bp 45–70°) in the 9.6-cm solvent bottle and 8.0 vol % of diethyl ether in petroleum ether in the 5.2-cm bottle showed the presence of at least three components. One component (25%) was resolved from the mixed elution band containing the other two. The latter were approximately in the ratio of 2:3 in order of elution. Infrared spectra of these three components showed differences, but these were not readily interpreted in terms of structure. Fractions III (20.4 wt %), IV (3.8 wt %), and V (6.6 wt %) were identical with those described above.

Reaction of Tetramethylene Bis(azidoformate) with Cyclohexane. Tetramethylene bis(carbamate) was prepared from the chloroformate and ammonia in 92% yield according to Rabjohn,⁴⁰ mp 197–198°.

Tetramethylene bis(*N*-cyclohexylcarbamate) was prepared from 1.00 g (11 mmoles) of 1,4-butanediol, 3.20 g (26 mmoles) of cyclohexyl isocyanate,⁴¹ and 2 drops of triethylamine. The resulting white solid was filtered and recrystallized several times from aqueous acetone, yielding 2.66 g of product (71% of theory), mp 178.5–180.5°.

Anal. Calcd for $C_{18}H_{32}O_4N_2$: C, 63.49; H, 9.47; N, 8.23. Found: C, 63.48; H, 9.62; N, 8.94.

Solutions of 1.00 g of azidoformate in 100 ml of cyclohexane were treated as described above. From eight runs there was obtained 9.95 g of yellow-white solid. This material was incompletely soluble in chloroform; 1.00 g gave 53 mg of crystalline solid whose analysis, melting point, and infrared spectrum identified it as tetramethylene bis(carbamate).

Oils and other extraneous matter in the soluble portion of the sample were removed by passage through a chromatographic column of activated charcoal (Darco G60) 10 cm high and 1.8 cm in diameter; 87% of the sample was recovered by chloroform elution. This material was chromatographed on the alumina and 6% water

column in the "Scanalyzer" with the ethanol-chloroform solvent system. The first fraction eluted accounted for 38.9 wt % of the original sample. Comparison of analysis, melting point, and infrared spectrum with those of a synthetic sample showed this fraction, recrystallized from acetone-*n*-heptane, was tetramethylene bis(*N*-cyclohexylcarbamate). It accounted for 32.3 mole % of the initial azidoformate.

The second fraction eluted in the "Scanalyzer" run, 35.9 wt %, was indicated by its infrared spectrum to be tetramethylene *N*-cyclohexylcarbamate.

Anal. Calcd for $C_{18}H_{32}O_4N_2$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.98; H, 8.73; N, 10.79.

The infrared spectrum indicated the presence of both $-\text{CONH}_2$ and $-\text{CONHC}_6\text{H}_{11}$. The same four N-H bands shown by tetramethylene bis(carbamate) at 3410, 3300, 3245, and 3200 cm^{-1} were present, indicating NH_2 . Except for the 3300- cm^{-1} band, these bands were in the correct ratios of intensities. The more intense 3300 cm^{-1} , which was exhibited also by the tetramethylene bis(*N*-cyclohexylcarbamate), indicated the presence of $-\text{NHC}_6\text{H}_{11}$ in this second fraction. Corroborating evidence for the $-\text{CONH}_2$ grouping was the amide II band at 1615 cm^{-1} . The presence of a $-\text{CONHC}_6\text{H}_{11}$ grouping was indicated by the amide II band at 1530 cm^{-1} .

An additional elution band containing at least two components (two carbonyl bands at 1760 and 1700 cm^{-1}) was isolated. Limited work on rechromatographing this mixed fraction was unsuccessful in attaining adequate separation.

Reaction of Ethyl Azidoformate with 2-Methylbutane. Isoamylamine, 2-methylbutylamine, and *t*-amylamine were commercial materials (K & K Laboratories). 2-Amino-3-methylbutane was prepared by the reductive amination of 3-methyl-2-butanone according to the procedure of Schwoegler and Adkins,⁴¹ bp 86.5–86.8°, n_D^{25} 1.4032. The amines were then converted to the corresponding urethans by reaction with ethyl chloroformate according to the procedure of Hartman and Brethen.⁴² Gas chromatography indicated the compounds to be 94–98% pure without distillation. One sample was purified by preparative-scale gas chromatography and was shown to have an infrared spectrum identical with that of the crude material, indicating that no decomposition had taken place on the chromatographic column.

To determine reactivities, a solution of approximately 1.5 g of ethyl azidoformate in 40 ml of 2-methylbutane was heated for 4 hr at 120° under nitrogen in a 110-ml stainless-steel bomb. The solvent was then stripped and the residue was analyzed by gas chromatography. The results shown in Table V are averages of two runs. The gas chromatographic analyses were carried out on an F & M Model 500 temperature-programmed instrument. A 12-ft stainless steel column packed with UCON 75H on Chromosorb W was used. The initial column temperature was 100°, and this was raised to 200° at a rate of 11°/min. The fact that the two primary isomers were obtained in the expected 2:1 ratio was a good check on the analytical procedure.

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A Fluorine Nuclear Magnetic Resonance Shielding Study of Substituent Effects on π -Charge Distributions in Benzophenone and Its Lewis Acid Adducts^{1a}

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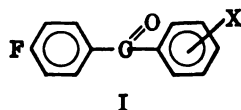
Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania. Received December 3, 1966

Abstract: Fluorine nuclear magnetic resonance (F nmr) shielding has been investigated for an extensive series of *ortho*-*m'*- and *-p'*-substituted benzophenones and their Lewis acid complexes in methylene chloride solution. This study appears to be the first systematic study of substituent nmr shielding effects in both the reactant and the product of a chemical reaction under common conditions. The *p*-fluorophenyl label is used to measure π -charge density at the carbonyl carbon atom. It is concluded that the change in π -charge density at the carbonyl carbon induced by the polar effect of the *m'*- or *p'*-substituted phenyl group is directly proportional to the product of the σ of the substituent and the carbonyl carbon atom charge density in the unsubstituted derivative. This result gives strong support for the hypothesis of Hammett.

Substituent effects on fluorine nuclear magnetic resonance shielding (F nmr) in *para*-substituted benzophenones have been related to the changes in charge density at the fluorine atom and its carbon atom.² HMO calculations further show approximately linear relationships in *p*-fluorobenzophenones, *p*-FC₆H₄COX, between the π -charge densities at the carbonyl carbon and *p*-fluorocarbon atom.³ The expected consequence of these relationships is that F nmr shielding in the *p*-fluorophenyl label may be utilized to measure changes in charge density which occur at the carbonyl carbon atom.

Polar effects of *meta*- and *para*-substituted benzophenones on chemical reactivities follow with high precision the modified $\sigma\rho$ relationship.⁴ Such effects are encountered when the measured effects are of direct conjugation. Hammett supports the quantity $-\sigma$ measures the change in charge density produced by the substituent at the reaction center.⁵ In this paper we have substituted the Hammett hypothesis to directly test in the following

shielding in an extensive series of *p*-fluoro-*m'*-substituted benzophenones (structure I) and their Lewis acid complexes has been determined.



In this series, the polar effects of the *m'*- and *p'*-substituted phenyl groups on the F nmr shielding are expected to follow the $\sigma^o\rho$ relationship,⁴ confirming

This work was performed at the Pennsylvania State University in part by the Office of Naval Research and is gratefully acknowledged. (b) Department of Chemistry, University of California.

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Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p 196.

the Hammett hypothesis. The values of ρ for the uncomplexed ketone and for several Lewis acid adducts have been determined by the procedure of Taft and Lewis.⁶ A direct relationship is found between the ρ values and the π -electron density at the carbonyl carbon atom of unsubstituted *p*-fluorobenzophenone and its adducts. The relationship bears an analogy to Hine's τ relationship.⁷ The results have important application to substituent effects on the thermodynamic properties for formation of the Lewis acid adducts of I. This is the subject of the following companion paper.

F nmr shielding in the formation of 1:1 adducts of BF₃, BCl₃, and BBr₃ with *p*-fluorophenyl-labeled bases has been found to be ideal for the present objectives. Thus the shielding parameters of both uncomplexed base and the 1:1 adduct are obtained in a common pure solvent (CH₂Cl₂). The shielding for the adduct is found to involve little or no medium effect. In the present work results similar to that previously obtained with *p*-fluorobenzonitrile⁸ have been found for the *p*-fluorobenzophenones, I. At room temperatures the adducts are rapidly dissociated giving rise to a single time-average fluorine signal. The signal is the weighted average of the shielding parameters for complexed and uncomplexed base.⁹ The observed shieldings for a series of methylene chloride solutions having an approximately constant concentration (~ 0.4 M) of the *p*-fluorobenzophenone, and increasing concentrations of Lewis acid display a limiting downfield shift at a stoichiometric acid-base ratio of unity (*cf.* Figure 2 of ref 8 as a typical result). With the weaker acids or bases employed in this study an acid-base ratio of 3-10 is required to obtain the limiting shift (the shielding parameter for the adduct).

The proton adducts of compounds such as series I ketones have F nmr shieldings which are highly medium sensitive.¹⁰ It is, therefore, impossible to obtain the

(6) R. W. Taft and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).

(7) (a) J. Hine, *ibid.*, **82**, 4877 (1960); (b) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 4.

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(9) J. S. Pople, W. A. Schneider, and H. J. Bernstein "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p 218.

(10) R. W. Taft and P. L. Levins, *Anal. Chem.*, **34**, 436 (1962).

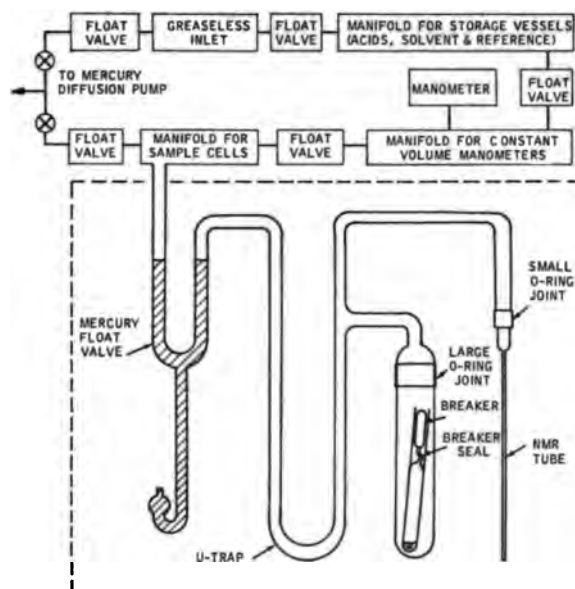


Figure 1. Vacuum line schematic.

shielding parameters for the proton adducts and the uncomplexed ketones in a common solvent. In this work we have obtained the shielding parameters of the protonated forms of I as they occur in 99.8% (wt) H_2SO_4 containing the ketone ($\sim 0.4 M$).

Experimental Section

Preparation of *m*- and *p*-Fluorobenzophenones. *p*-Fluorobenzophenone. To a solution of 5 g of benzoyl chloride and 10 ml of fluorobenzene in 25 ml of carbon disulfide, 6 g of AlCl_3 was added in several portions with stirring. Stirring was continued for 3 hr and then the mixture was warmed on a steam bath for 1 hr. The solvent was removed and the residue decomposed with ice and hydrochloric acid. The oily product was extracted with ether and washed with aqueous sodium hydroxide solution and water. The ether was evaporated and the residue purified through an alumina column. Recrystallizations from petroleum ether gave 5.5 g of the ketone (mp 49–50°, lit.¹¹ mp 48.2–48.7°).

***m*-Fluorobenzophenone.** This ketone was obtained by the condensation of 4 g of *m*-fluorobenzoyl chloride with benzene in carbon disulfide solution in the presence of AlCl_3 . The product was recrystallized from petroleum ether (mp 54.5–55°, lit.¹² mp 55°).

The following ketones were prepared in the same manner from fluorobenzene and the correspondingly substituted benzoyl chlorides. The products were purified by repeated recrystallizations from aqueous ethanol, ethanol, and petroleum ether: *p,p'*-difluorobenzophenone (mp 107°, lit. mp 106–107°, ¹¹ 107.5–108.5°), *m,p'*-difluorobenzophenone (mp 61.0–61.5°), *p*-fluoro-*m'*-chlorobenzophenone (mp 77.5–78°), *p*-fluoro-*m'*-trifluoromethylbenzophenone (mp 45–46°), *p*-fluoro-*p'*-trifluoromethylbenzophenone (mp 100.5–101.5°), *p*-fluoro-*p'*-nitrobenzophenone (mp 88–88.5°), *p*-fluoro-*m'*-bromobenzophenone (mp 84.5°).

***p*-Methoxy-*p'*-fluorobenzophenone.** To a solution of 18 g of anisole and 15 g of *p*-fluorobenzoyl chloride in 75 ml of carbon disulfide, 15 g of AlCl_3 was added dropwise under moderate refluxing. After standing for 2 hr at room temperature the solvent was removed and the residue decomposed with hydrochloric acid and ice. The resulting mixture was heated on a steam bath for 1 hr and the crystalline product collected on a filter and washed with water. The product was purified by recrystallizations from ethanol (mp 97–97.5°, lit. mp 94.5–95.5°, ¹⁴ 96.0–96.5°).

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(13) W. Funasaka, T. Ando, H. Osaki, and K. Murakami, *Yuki Gosei Kagaku Kyokai Shi*, **17**, 334 (1959).

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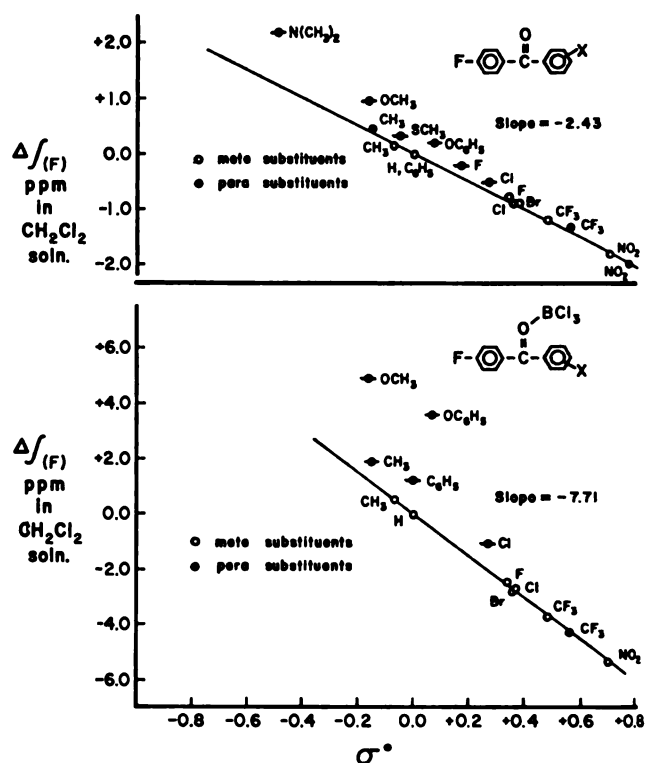


Figure 2. Polar effects of 3' and 4' substituents and conjugation effects of 4' substituents in *p*-fluorobenzophenones and their BCl_3 adducts on fluorine nuclear magnetic resonance shielding.

***p*-Methoxy-*m'*-fluorobenzophenone** was obtained in the same way from *m*-fluorobenzoyl chloride and recrystallized from aqueous ethanol and ethanol (mp 69.5–70°).

The following ketones were prepared similarly by the Friedel-Crafts reaction of *m*- or *p*-fluorobenzoyl chloride with substituted benzenes in carbon disulfide solution. The products were purified by repeated recrystallizations from aqueous ethanol, ethanol, and petroleum ether: *p*-methyl-*p'*-fluorobenzophenone (mp 97.5–98°, lit.¹³ mp 98–99°) and *p*-methyl-*m'*-fluorobenzophenone (mp 53–54°) were obtained from toluene; *p*-ethyl-*p'*-fluorobenzophenone (mp 69.5–70°) and *p*-ethyl-*m'*-fluorobenzophenone [bp 139–141° (2 mm)] from ethylbenzene; *p*-butyl-*p'*-fluorobenzophenone (mp 75–75.5°) and *p*-*t*-butyl-*m'*-fluorobenzophenone (mp 30–31°) from *t*-butylbenzene; *p*-chloro-*p'*-fluoro- (mp 113–114°, lit.¹⁴ mp 115°) and *p*-chloro-*m'*-fluorobenzophenone (mp 79.5–80°) from chlorobenzene; *p*-bromo-*p'*-fluorobenzophenone (mp 108.5–109°, lit.¹⁴ mp 107–108°) and *p*-bromo-*m'*-fluorobenzophenone (mp 87–88°) from bromobenzene in poor yields; *p*-ethoxy-*p'*-fluorobenzophenone (mp 87.5–88°, lit.¹³ mp 86.5–87.5°) and *p*-ethoxy-*m'*-fluorobenzophenone [bp 176° (4 mm)] from phenyl ethyl ether; *p*-phenoxy-*p'*-fluorobenzophenone (mp 101.5–102°) and *p*-phenoxy-*m'*-fluorobenzophenone (mp 61–62°) from diphenyl ether; *p*-thiomethyl-*p'*-fluorobenzophenone (mp 105–106°, lit.¹⁴ mp 105.5–106.5°) and *p*-thiomethyl-*m'*-fluorobenzophenone (mp 78–79°) from thioanisole; *p*-phenyl-*p'*-fluorobenzophenone (mp 148.5–149°) and *p*-phenyl-*m'*-fluorobenzophenone (mp 104–105°) from biphenyl.

***m*-Methyl-*m'*-fluorobenzophenone.** To a Grignard solution prepared from 14 g of *m*-fluorobromobenzene and 2.2 g of magnesium, 9 g of *m*-methylbenzotrile diluted with an equal amount of ether was added dropwise under cooling in ice-salt bath. The reaction mixture was allowed to stand overnight, warmed under gentle reflux for 1 hr and decomposed with ice and hydrochloric acid. The aqueous mixture was heated on a steam bath for 1 hr and left overnight. The organic material was dissolved in ether, washed with aqueous sodium hydroxide solution, dilute hydrochloric acid, and water, and dried over calcium chloride. Distillation yielded 12 g of the ketone (bp 130–130.5° at (2 mm)).

***m*-Methyl-*p'*-fluorobenzophenone** was prepared in the same way. A center fraction, 137–139° (2 mm), was recrystallized from petroleum ether (mp 46.5–47°).

(15) W. Funasaka, T. Ando, K. Kondo, and S. Kodama, *Yuki Gosei Kagaku Kyokai Shi*, **17**, 717 (1959).

-fluoromethyl-*m*'-fluorobenzophenone (mp 37–38°) and bromomethyl-*p*'-fluorobenzophenone (mp 45–46°) were obtained by the reaction of *m*-trifluoromethylbenzonitrile with the corresponding reagents of the corresponding fluorobromobenzenes. *m*-bromo-*m*'-fluorobenzophenone. A Grignard solution prepared from 15 g of *m*-fluorobromobenzene in 30 ml of ether was slowly (1 hr) to a cold solution of *m*-chlorobenzoyl chloride, 12.5 ml of ether. After addition of the reagent, the mixture was allowed to stand overnight at room temperature. The mixture was refluxed for 0.5 hr and decomposed with ice and hydrochloric acid. The aqueous mixture was heated on a steam bath for 1 hr. The organic layer was taken up with ether and washed with aqueous sodium hydroxide, and water. After drying over calcium chloride, the ether was removed, and the resulting product was dissolved in alcohol and precipitated by adding water. Three recrystallizations from light petroleum gave 11 g of the ketone (mp 55–56°).

The same procedure was applied for the preparations of *m,m*'-difluorobenzophenone (mp 58.5–59°, recrystallization from petroleum ether), *m*-bromo-*m*'-fluorobenzophenone from *m*-bromochlorobenzene (67–67.5°, recrystallization from aqueous ethanol, 1-petroleum ether mixture), and *p*-trifluoromethyl-*m*-fluorobenzophenone from *p*-trifluoromethylbenzoyl chloride (mp 56°) in aqueous ethanol and petroleum ether.

Samples of the ketones which were used to prepare the Lewis acid adducts were sublimed and stored in a desiccator.

Acids. Commercial samples of BF₃, BCl₃, and BBr₃ were purified by trap distillation on the vacuum line. Appropriate baths were used in the traps until a fraction was obtained with the following pressures: BF₃, 290 mm (–112°); BCl₃, 470 mm (0°); BBr₃, 14 mm (20°). AlCl₃(C₂H₅)₂ and AlCl₃(C₂H₅)₃ were purchased from Texas Alkyls Inc. and were distilled before use. Purified samples of AlCl₃ and BI₃ were kindly supplied by Mr. J. W.

Preparation of Nmr Samples. All solutions were prepared on a vacuum line at 10^{–5} mm in the general manner indicated earlier.⁸ Pictures of the vacuum line scheme. The essentially nonvolatile fluorobenzophenones were weighed into a small capillary tube which was sealed in the nmr tube and evacuated to ~10^{–6} mm. The Lewis acids (BF₃, BCl₃, or BBr₃), the nmr reference (TCTFCB),¹⁴ and the solvent (CH₂Cl₂) were measured quantitatively as vapors from constant-volume manometers. Transfer from the manometer was made through appropriate Hg float valves into the U trap subsequently into the nmr tube by means of a liquid N₂ bath. Highly volatile acids (BI₃, AlCl₃, AlCl₃(C₂H₅)₂, and AlCl₃(C₂H₅)₃) were protected from contact with air and moisture by the magnetic breaker seals. The breakers were filled with the appropriate amount of acid required in a separate operation and in a tube and attached to the line. After evacuation, the seal was broken and the acid transferred from the breaker seal to trap and finally into the nmr tube with the benzophenone. The amount of acid was determined by weighing the breaker seal and after the sample preparation. Solvent and nmr reference were transferred subsequently as described above. In every case a prepared nmr tube was sealed off under vacuum and stored in liquid N₂ until its spectra were obtained at 25 ± 1°. In each case the solution displayed a single *p*-fluorophenyl signal. The procedure used in preparing the samples of uncomplexed ketone and the H₂SO₄ solutions¹⁷ is that described earlier. The procedure followed in obtaining the shielding parameters also has been previously described.¹⁴

is

Table I are listed the shielding parameters (relative to internal fluorobenzene), \int_H^{p-X} , for a series of

acid adducts of *p*-fluorobenzophenone in methylene chloride solution at 25°. The shielding parameters have been obtained from at least three separate experiments with stoichiometric acid to base ratio (*a/b*) of 5. The limiting shifts from these experiments are precise to ±0.08 ppm. For the uncomplexed ketone the precision is ±0.03 ppm. The BF₃ and AlCl₃

R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and J. Davis, *J. Am. Chem. Soc.*, **85**, 709 (1963).
I. R. Fox, P. L. Levins, and R. W. Taft, *Tetrahedron Letters*, **7**, 61.

Table I. Fluorine Nmr Shielding Parameters for Lewis Acid Adducts of *p*-Fluorobenzophenone

Acid	\int_H^{p-X} , ppm	Acid	\int_H^{p-X} , ppm
None (uncomplexed)	6.69	AlCl ₃ (C ₂ H ₅) ₂	21.77
AlCl ₃ (C ₂ H ₅) ₂	17.20	AlCl ₃	22.40
BF ₃	17.62	BBr ₃	22.85
BCl ₃	21.20	BI ₃	23.62

(C₂H₅)₂ results are about 0.3 ppm upfield from the limiting value at *a/b* = 1, presumably because of a small amount of dissociation. For these, the limiting shift was obtained at *a/b* = 3–5. A titration curve for BF₃ (*a/b* = 0.17–5.3) gave results similar to those reported with *p*-fluorobenzonitrile.⁸ Analysis by the Ehrenson computer program¹⁸ gave the limiting shift indicated and a dissociation equilibrium constant (in *M* units) $K_D = 0.004 \pm 0.002$.

Table II lists the 3'- and 4'-polar substituent shielding effects for the *p*-fluorobenzophenone and its BF₃, BCl₃, BBr₃, and H₂SO₄ adducts. All except the latter were obtained in methylene chloride solution at 25°. The latter are from measurements in 99.8% H₂SO₄. The symbol $\Delta\delta$ represents the shielding relative to the unsubstituted *p*-fluorobenzophenone derivative. For the methylene chloride solutions, the shielding parameter relative to internal fluorobenzene may be obtained, of course, by combining $\left(\int_H^{p-X} = \int_H^{p-X_0} + \Delta\delta\right)$ the results of Tables I and II.

The shielding parameters for the BF₃ adducts given in Table II were obtained utilizing the Ehrenson computer program to analyze for each ketone the results of five to seven experiments with *a/b* = 0.3 to 8.0. For the *p*-CF₃ substituent, for example, this analysis gave $\Delta\delta = -3.60$ ppm and $K_D = 0.018 \pm 0.008$. This may be compared with $\Delta\delta = -3.52$ ppm observed in an experiment with *a/b* = 7.71. The values for K_D obtained for the other BF₃ adducts of Table II were within the range 0.002–0.02.

The shielding parameters for the BCl₃ and BBr₃ adducts given in Table II are the limiting shifts obtained from two or three experiments with *a/b* = 3–7. The precision is approximately ±0.08 ppm for each. The precision of the H₂SO₄ results is comparable.

Table III lists the shielding effects of conjugating *p*' substituents for *p*-fluorobenzophenone and its BF₃, BCl₃, BBr₃, and H₂SO₄ adducts under the same conditions as for the corresponding results in Table II. The shielding parameters for the BF₃, BCl₃, and BBr₃ adducts were obtained as the limiting shifts for two or three experiments with *a/b* = 1 to 4. The precision is ±0.08 ppm.

Table IV lists the shielding effects of *m*' and *p*' substituents for *m*-fluorobenzophenone in benzene and H₂SO₄ solutions. For comparison the corresponding *p*-fluorobenzophenone shielding effects are also shown. It is apparent from Table IV that *p*-F shielding effects in the uncomplexed ketone are uniformly about threefold greater than for corresponding *m*-F shielding effects. A substantial number of similar results were

(18) Cf. R. W. Taft, G. B. Klengensmith, and S. Ehrenson, *J. Am. Chem. Soc.*, **87**, 3620 (1965).

Table II. Polar Effects of 3' and 4' Substituents on Fluorine Nmr Shielding (ppm) in *p*-Fluorobenzophenone and Its BF₃, BCl₃, BBr₃, and H₂SO₄ Adducts

Subst	σ^0	Uncomplexed ketone		— BF ₃ adduct —		— BCl ₃ adduct —		— BBr ₃ adduct —		— H ₂ SO ₄ adduct —	
		$\Delta \int_{\text{exptl}}^{\text{H}}$	$\Delta \int^a$	$\Delta \int_{\text{exptl}}^{\text{H}}$	$\Delta \int^a$	$\Delta \int_{\text{exptl}}^{\text{H}}$	$\Delta \int^a$	$\Delta \int_{\text{exptl}}^{\text{H}}$	$\Delta \int^a$	$\Delta \int_{\text{exptl}}^{\text{H}}$	$\Delta \int^a$
<i>m</i> '-CH ₃	-0.07	+0.15	+0.17	+0.57	+0.45	+0.53	+0.54	...	+0.54	+0.53	+0.49
H	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
<i>m</i> '-F	0.34	-0.75	-0.82	-1.96	-2.18	-2.44	-2.62	-2.25	-2.81	-2.25	-2.39
<i>m</i> '-Cl	0.37	-0.88	-0.89	...	-2.37	-2.66	-2.85	...	-3.07	-2.62	-2.59
<i>m</i> '-Br	0.36	-0.89	-0.86	-2.15	-2.30	-2.80	-2.77	-2.58	-2.98	-2.70	-2.52
<i>m</i> '-CF ₃	0.48	-1.17	-1.17	...	-3.07	-3.70	-3.70	-3.67	-3.97	-3.20	-3.36
<i>p</i> '-CF ₃	0.54	-1.32	-1.31	-3.60	-3.46	-4.25	-4.16	-4.20	-4.47	-3.80	-3.78
<i>m</i> '-NO ₂	0.70	-1.79	-1.72	...	-4.48	-5.33	-5.40	-5.61	-5.79	-5.65	(+0.81) ^b
<i>p</i> '-NO ₂	0.82	-2.01	-1.99	...	-5.25	...	-6.31	...	-6.80	-6.78	(+0.97) ^b
$\bar{\rho} = \int_{\text{H}}^{p-X_0} / 2.75$			-2.43		-6.40		-7.71		-8.27		(-7.00) ^c

^a $\Delta \int_{\text{H}}^{\text{exptl}} = \sigma^0 \bar{\rho} = \int_{\text{H}}^{p-X_0} (1 + \sigma^0/2.75)$; cf. eq 9 and Discussion. ^b Calculated values of σ^0 in H₂SO₄. It is noteworthy that these values meet the usual relationship, $^4 (\sigma^0_{(m)} - \sigma^0_{(p)}) / (\sigma^0_{(p)} - \sigma^0_{(I)}) \cong 0.5$. ^c Observed value of $\bar{\rho}$.

Table III. Effects of Conjugating *p*' Substituents on the Fluorine Nmr Shielding of *p*-Fluorobenzophenone and Its BF₃, BCl₃, BBr₃, and H₂SO₄ Adducts^a

Subst	σ^+	Uncomplexed ketone		BF ₃ adduct		BCl ₃ adduct		BBr ₃ adduct		H ₂ SO ₄ adduct	
		$\Delta \int_{\text{exptl}}^{\text{H}}$	σ^+	$\Delta \int_{\text{exptl}}^{\text{H}}$	σ^+	$\Delta \int_{\text{exptl}}^{\text{H}}$	σ^+	$\Delta \int_{\text{exptl}}^{\text{H}}$	σ^+	$\Delta \int_{\text{exptl}}^{\text{H}}$	σ^+
<i>p</i> '-N(CH ₃) ₂	-1.7	+2.19	-0.90
<i>p</i> '-OCH ₃	-0.78	+0.91	-0.38	+4.38	-0.68	+5.05	-0.66	+5.41	-0.65	+6.10	-0.87
<i>p</i> '-OC ₂ H ₅	...	+1.01	-0.42	+7.00	-1.00
<i>p</i> '-OC ₃ H ₇	-0.5	+0.45	-0.19	+3.26	-0.51	+3.66	-0.48	+3.30	-0.49
<i>p</i> '-CH ₃	-0.31	+0.45	-0.19	+1.79	-0.28	+1.88	-0.24	+2.21	-0.27	+2.38	-0.34
<i>p</i> '-C ₂ H ₅	-0.29	+0.44	-0.18	+1.89	-0.30	+1.90	-0.25	+2.38	-0.34
<i>p</i> '- <i>i</i> -C ₄ H ₉	-0.26	+0.41	-0.17	+1.70	-0.27	+1.85	-0.24	+2.04	-0.25	+2.05	-0.29
<i>p</i> '-SCH ₃	-0.65	+0.34	-0.14	+5.75	-0.82
<i>p</i> '-C ₆ H ₅	-0.22	+0.02	-0.01	+1.12	-0.18	+1.25	-0.16	+1.48	-0.18	-0.30	+0.04
<i>p</i> '-F	-0.07	-0.19	+0.08	+0.83	-0.12
<i>p</i> -Cl	+0.11	-0.52	+0.21	-0.54	+0.08	-1.05	+0.14	-0.85	+0.10	-0.45	+0.07

^a $\sigma^+ = \Delta \int_{\text{exptl}}^{\text{H}} / \bar{\rho}$; $\bar{\rho}$ value is given in Table II. Values in ppm.

Table IV. Comparison of Shielding Effects of 3' and 4' Substituents in *m*-Fluorobenzophenones and *p*-Fluorobenzophenones in Benzene and Sulfuric Acid Solutions

Subst	— C ₆ H ₆ soln, ppm —		— H ₂ SO ₄ soln, ppm —	
	$\Delta \int_{\text{H}}^{m-F}$	$\Delta \int_{\text{H}}^{p-F}$	$\Delta \int_{\text{H}}^{m-F}$	$\Delta \int_{\text{H}}^{p-F}$
<i>p</i> '-OCH ₃	...	+0.86	+0.70	+6.10
<i>p</i> '-CH ₃	+0.18	+0.42	+0.23	+2.38
<i>p</i> '-SCH ₃	+0.08	+0.26	+0.70	+5.75
<i>m</i> '-CH ₃	+0.06	+0.10	+0.16	+0.53
H	(0.00) ^a	(0.00) ^b	(0.00)	(0.00)
<i>p</i> '-Cl	-0.21	-0.56	0.00	-0.50
<i>m</i> '-Cl	-0.36	-0.90	-0.63	-2.62
<i>m</i> '-Br	-0.39	-0.90	-0.55	-2.70
<i>m</i> '-CF ₃	-0.70	-3.20
<i>p</i> '-CF ₃	-0.42	-1.36	-0.70	-3.80

^a $\int_{\text{H}}^{m-C_6H_5CO} = -0.99$ ppm. ^b $\int_{\text{H}}^{p-C_6H_5CO} = -6.13$ ppm.

obtained previously.¹⁹ In the proton adducts in H₂SO₄ it is also apparent that this factor increases to about 5.5 for polar substituent effects. For conjugat-

(19) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963).

ing *p*' substituents the factor increases further to approximately ninefold (cf. following discussion, in particular concerning eq 5).

Discussion

Theoretical treatments of substituent effects on fluorine shielding in *meta*- and *para*-substituted fluorobenzene have given the relationship²⁰

$$\int_{\text{H}}^{p-X} = C_1 \Delta q_F + C_2 \Delta p_{C-F} + C_3 \Delta I \quad (1)$$

where \int_{H}^{p-X} is the shielding parameter for the *para*-substituted fluorobenzene relative to internal fluorobenzene, Δq_F is the change (relative to C₆H₅F) in π -electron charge density at the fluorine atom, Δp_{C-F} is the change in the C-F π -bond order, ΔI is the change in ionic character of the C-F σ bond which is induced by the polar substituent, and C_1 , C_2 , and C_3 are constants. By using the shielding of the *para*-substituted fluorobenzene relative to that of its *meta* isomer, \int_{m-X}^{p-X} ,

(20) (a) M. Karplus and T. P. Das, *J. Chem. Phys.*, **34**, 1683 (1961); (b) F. Prosser and L. Goodman, *ibid.*, **38**, 374 (1963).

term very generally vanishes for most practical cases. Further, HMO theory anticipates linear relationships between corresponding values of Δq_F , Δq_{C-F} , and Δq_{C-O} , where the latter is the change (relative to benzene) in π -electron density at the carbon atom with the fluorine is bonded,³ i.e.

$$\int_{m-X}^{p-X} = C_4 \Delta q_{C-F} \quad (2)$$

constant C_4 is estimated from experimental results (120 ppm/e).¹⁹

A simple model HMO calculations for *p*-fluorophenyl derivatives, *p*-FC₆H₄COX, where X is a carbonyl atom of Coulomb integral -0.5 to $+2.0 \beta$ relative to benzene carbon, the substituent effect of X tends to produce uniformly a sevenfold greater change in the π -charge density at the carbonyl carbon than at the *para* carbon atom.³ This result is quite generally for *p*-fluorobenzoyl derivatives

$$\Delta q_{C-F} = C_5 q_{C-O} + C_6 \quad (3)$$

q_{C-O} is the π -charge density at the carbonyl carbon, and C_5 and C_6 are constants. Combination of eqs 2 and 3 indicates that the *p*-fluorophenyl label is used to study the π -electron density changes at the carbonyl carbon, i.e.

$$\Delta \int_{m-X}^{p-X} = C_7 \Delta q_{C-O} \quad (4)$$

$C_7 \cong 40$ ppm/e. Equation 4 may be simplified by the present experimental investigation. It has been shown¹⁹ experimentally that for restricted families of similar substituents, such as the ketone series I or Lewis acid adducts (cf. Table IV and comments), the following relationships hold.

$$\Delta \int_H^{p-X} = C_8 \Delta \int_H^{m-X} \quad (5)$$

$$\Delta \int_{m-X}^{p-X} = [(C_8 - 1)/C_8] \Delta \int_H^{p-X}$$

C_8 is a constant. Combining eq 4 and 5 gives

$$\Delta \int_H^{p-X} = C_9 \Delta q_{C-O} \quad (6)$$

$\Delta \int_H^{p-X}$ refers to the shielding of a *p*'-substituted *p*-fluorobenzophenone (or acid adduct) relative to unsubstituted *p*-fluorobenzophenone (or adduct), and C_9 is the corresponding change in the π -charge density at the carbonyl carbon, and $C_9 = C_8 C_7 / (C_8 - 1)$, a constant.

Interpretation of the *meta*- and *para*-substituent effects on rates and equilibria for side-chain derivatives of benzene which are described by the $\sigma\rho$ relationship, Hammett⁵ supposed that the quantity $-\sigma$ measures the change in charge density produced by the substituent at the side-chain reaction center, i.e., for example, for ketone I $\Delta q_{CO} \propto (-\sigma)$. By the application of ^{19}F nmr shielding in series I ketones and their acid adducts, it follows that the Hammett hypothesis is satisfied by the relationship

$$\Delta \int_H^{p-X} = -\bar{\rho}\sigma \quad (7)$$

where ρ is used to distinguish the shielding series constant for a given series of ketone derivatives from the usual reactivity series constant, ρ .

In Figure 2 are plotted $\Delta \int_H^{p-X}$ values from Tables III and IV for *m*'- and *p*'-substituted *p*-fluorobenzophenones and their BCl₃ adducts vs. σ^0 values.⁴ In general, a linear trend is clearly discernible. Linear relationships of excellent precision, however, encompass only the *m*' and nonconjugating *p*' substituents. The crossed-circle points for *p*' substituents represent significant deviations from eq 7 according to the criterion of Taft and Lewis.⁶ The results in Figure 2 have the same characteristics, for example, as a plot of Brown's σ^+ values²¹ vs. σ^0 . We conclude that Hammett's hypothesis is confirmed for the polar effects of *m*' and *p*' substituents.

The additional effects of direct conjugation between $-R$ *p*' substituents and the carbonyl group lead to deviations from eq 7 as might be expected by Brown's σ^+ treatment.²¹ The latter parameters, however, do not generally suffice quantitatively to describe the observed combination of polar and conjugative effects. This result is seen by comparison of corresponding σ^+ values and the "effective" $\bar{\sigma}^+$ ($\equiv \Delta \int_H^{p-X} / \bar{\rho}$) values which are listed in Table III for conjugating *p*' substituents. For *p*'-OCH₃ and *p*'-SCH₃, the $\bar{\sigma}^+$ values for uncomplexed ketone and for the BF₃, BCl₃, and BBr₃ adducts are significantly less negative than Brown's σ^+ values. In H₂SO₄, however, the $\bar{\sigma}^+$ for these two substituents are significantly more negative than Brown's σ^+ values. For all of the *p*' substituents of Table III the $\bar{\sigma}^+$ value of the uncomplexed ketone is substantially less than Brown's σ^+ value. On the other hand, Brown's σ^+ values for *p*-OC₆H₅, *p*-CH₃, *p*-C₂H₅, *p*-*t*-C₄H₉, and *p*-Cl apply quite satisfactorily for all of the Lewis acid adducts of Table III.

In Hine's τ relationship⁷ the reaction constant, ρ , for polar reactivity effects of *meta* and *para* substituents is directly related to the change in the σ value of the side-chain reaction center. Thus the Hammett and the Hine hypotheses suggest that the π -charge density of the carbonyl carbon of the unsubstituted ketone derivative determines the susceptibility of this center to changes in charge density produced by substituent polar effects. This condition and eq 2, 3, and 5 lead to the relationship

$$-\sigma = \int_H^{p-X_0} / k \quad (8)$$

where $\int_H^{p-X_0}$ is the shielding of the unsubstituted *p*-fluorobenzophenone derivative relative to internal fluorobenzenes (Table I) and k is a constant for a series of carbonyl derivatives.

Equation 8 is confirmed by the excellent agreement between $\Delta \int_{\text{exptl}}^{p-X}$ and $\Delta \int_{\text{calcd}}^{p-X}$ values given in Table II

(21) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957); **80**, 4979 (1958).

for the uncomplexed ketones and their BF_3 , BCl_3 , and BBr_3 adducts; $\Delta \int_{\text{H}}^{\text{p-X}} \text{calcd}$ is obtained as $\left(\int_{\text{H}}^{\text{p-X}_0} / 2.75 \right)$. ($-\sigma^0$), i.e., $k = 2.75$. The generality and precision of eq 8 (which is illustrated in Table II) indicates that this relationship may be used reliably to predict $\int_{\text{H}}^{\text{p-X}}$ values for the other Lewis acid adducts of Table I with additional well-behaved polar substituents of known σ^0 value. For these, the shielding of m' - and p' -substituted p -fluorobenzophenone derivatives relative to fluorobenzene is given by

$$\int_{\text{H}(\text{calcd})}^{\text{p-X}} = \int_{\text{H}(\text{obsd})}^{\text{p-X}_0} + \sigma^0 \rho = \int_{\text{H}}^{\text{p-X}_0} \left(1 + \frac{\sigma^0}{2.75} \right) \quad (9)$$

The corresponding relationship for π -charge density given by eq 4 is

$$q_{\text{CO}} = q_{\text{CO}}^0 [1 + (\sigma^0/2.75)] \quad (10)$$

where q_{CO}^0 is the carbonyl carbon π -charge density in unsubstituted p -fluorobenzophenone.

Using the relationships established previously between σ values and F nmr substituent shielding effects in *meta*- and *para*-substituted fluorobenzenes, the present results may be used to calculate the σ values for the COC_6H_5 , $\text{CO}(\text{BF}_3)\text{C}_6\text{H}_5$, and $\text{CO}(\text{BCl}_3)\text{C}_6\text{H}_5$ substituents.^{16, 19}

$$\sigma_{(\rho)} = \sigma_{\text{I}} + \sigma_{\text{R}} \quad (11)$$

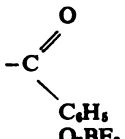
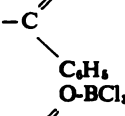
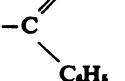
$$\int_{m-X}^{\text{p-X}} = -29.5 \sigma_{\text{R}} \quad (12)$$

$$\int_{\text{H}}^{m-X} = -7.1 \sigma_{\text{I}} + 0.6 \quad (13)$$

In methylene chloride solutions, the additional shielding parameters have been obtained for *m*-fluorobenzophenone ($\int_{\text{H}}^{m-X} = -0.81$ ppm), its BF_3 adduct ($\int_{\text{H}}^{m-X} = -2.88$ ppm), and its BCl_3 adduct ($\int_{\text{H}}^{m-X} = -3.81$ ppm). These shieldings and the

corresponding p -fluorobenzophenone results (Table I) yield the σ values listed in Table V. It is further illustrated by the $\bar{\rho}/6.3$ values given in Table V that the $\bar{\rho}$ values of Table II are essentially directly proportional to the $\sigma_{(\rho)}$ values as required by the discussion above.

Table V. σ Values from F Nmr Shielding Results

Substituent	σ_{I}	σ_{R}	$\sigma_{(\rho)}$	$\bar{\rho}/6.3$	$\Delta\sigma_{(\rho)}$
	+0.20	+0.20	0.40	0.39	...
	+0.49	+0.50	0.99	1.02	0.59
	+0.62	+0.59	1.21	1.22	0.81

It is clear from these results, eq 6, and $\Delta \int_{\text{H}}^{\text{p-X}}$ values for uncomplexed and complexed ketones (Tables II and III) that the change in σ value or charge density for the carbonyl functional group on formation of a Lewis acid adduct is *not* independent of the 3' or 4' substituent. However, by consideration of eq 10: for the carbonyl carbon of the uncomplexed ketone, $q_{(\text{u})} = q_{(\text{u})}^0 [1 + (\sigma^0/2.75)]$; for the carbonyl carbon of the complex, $q_{(\text{c})} = q_{(\text{c})}^0 [1 + (\sigma^0/2.75)]$. Therefore, for formation of the complex, $\Delta q = q_{(\text{c})} - q_{(\text{u})} = \Delta q^0 [1 + (\sigma^0/2.75)]$. Thus, for the substituent effect on formation of the complex, $\Delta q - \Delta q_0 = \Delta q^0 (\sigma^0/2.75) \propto (\Delta\sigma_{\rho})\sigma_{\text{X}}^0$, where $\Delta\sigma_{\rho}$ = the change in $\sigma_{(\rho)}$ value for the unsubstituted functional group (cf. Table V) and σ_{X}^0 is the σ value for the 3'- or 4'-polar substituent. Further consideration of matters relevant to complex formation is given in the following companion paper.

Evaluation of Ground-State Electronic Energy from Fluorine Nuclear Magnetic Resonance Shielding. I. Prediction of Enthalpies of Reaction for Formation of Lewis Acid Adducts of Benzophenones¹

C. S. Giam and R. W. Taft

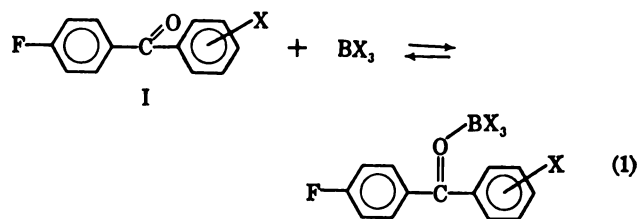
Contribution from the Department of Chemistry, University of California, Irvine, California 92640. Received December 3, 1966

Abstract: The previously proposed linear fluorine nuclear magnetic resonance shielding electronic energy (SEE) relationship for *p*-fluorophenyl derivatives is shown to provide satisfactory prediction of the standard enthalpy of reactions of *m*'- and *p*'-substituted *p*-fluorobenzophenones with the Lewis acids BCl₃ and BBr₃. This result indicates that *p*-fluorophenyl shielding in appropriate systems provides a useful approximation to the evaluation of the ground-state electronic energy change needed for *a priori* prediction of rather complex organic equilibria from spectroscopic data. Using Arnett's calorimetric procedure, standard enthalpies of reaction have been measured for the formation of a substantial series of the Lewis acid adducts in methylene chloride. The observed values, ranging from -11.5 to -20.6 kcal/mole, are in good agreement with the predicted values. The linear SEE relationship has been used to obtain a novel analysis of the contributions of substituent perturbations in reactant and product states to the observed thermodynamic substituent effects.

In a previous paper,² it was proposed that substituent effects on fluorine nuclear magnetic resonance (nmr) shielding in related *p*-fluorophenyl derivatives are linear with the substituent effect on the corresponding standard electronic energy change. This relationship has a theoretical basis in linear relationships between conjugative substituent effects on: (a) *p*-fluorophenyl nmr shielding, (b) the LCAO-MO theory of large substituent density at the *para* carbon atom (bonded to (c) the molecular ionization potential.²

The proposed linear shielding electronic energy (SEE) relationship has been confirmed experimentally for the large substituent effects involved in the oxidation of *ex*-arylethanes to 4,4''-disubstituted *p*-fluorotriphenylethyl (*p*-fluorotriptyl) cations² and in their reduction of 1'- and 4'-substituted *p*-fluorotriptyl anions.³ The substituent effects on the standard free energy change of these processes are taken to be close estimates of the corresponding electronic energy effects.^{2,3} The mean value of the energy-shielding coefficient obtained from these two reaction series is 1.0 kcal/mole ppm,^{2,3} in good agreement with the order of magnitude value anticipated by the theory.²

The formation of complexes with strong Lewis acids, such as BCl₃, is a reaction which has been investigated in detail.⁴ The standard enthalpy of adduct formation apparently may be taken as a satisfactory estimator of the standard electronic energy change.⁴ In reaction 1, the formation of BCl₃ and BBr₃ adducts of 3'- and 4'-substituted *p*-fluorobenzophenones (series I ketones) is a close analogy to the formation of the above mentioned *p*-fluorotriptyl cations.



In the companion paper⁵ the shielding parameters for series I ketones and their Lewis acid adduct in methylene chloride solution (relative to internal fluorobenzene) are reported. In this paper we report the determination of the standard enthalpies of adduct formation of series I ketones in methylene chloride solution using the calorimetric procedure recently described by Arnett.⁶ The predicted values of the enthalpies of complex formation obtained from the linear SEE relationship are found to be in quite satisfactory agreement with the experimental values. A novel analysis of the origin of the substituent effects on the standard enthalpies of reaction 1 has been obtained from the shielding parameters for series I ketones and their Lewis acid adducts through the use of linear SEE relationship.

Experimental Section

Materials. Cf. ref 5.

Procedure. The calorimeter used was essentially that described by Arnett, *et al.*,⁶ and was purchased from the Guild Corp., Bethel Park, Pa. A Leeds and Northrup Model 8687 potentiometer and a Model 153 Honeywell 1-mv recorder were utilized.

The calorimeter consisted of a 300-ml dewar flask (4.5 in. deep and 2.5 in. i.d.). It was fitted tightly with a Teflon stopper which held in place in the dewar a 5000-ohm thermistor and a 100-ohm electric heating coil. Additional holes in the stopper were used to accommodate syringe ports and a sealed-glass tubing stirrer with a Teflon blade. The stirrer was driven by a constant speed motor. Plastic insulating tape was wrapped around the seal between the Teflon stopper and the dewar to reduce any heat leakage.

(5) R. G. Pews, Y. Tsuno, and R. W. Taft, *J. Am. Chem. Soc.*, **89**, 2391 (1967).

(6) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. McDugleby, *ibid.*, **87**, 1541 (1965).

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R. W. Taft and L. D. McKeever, *J. Am. Chem. Soc.*, **87**, 2489 (1965).

L. D. McKeever and R. W. Taft, *ibid.*, **88**, 4544 (1966).

F. G. A. Stone, *Chem. Rev.*, **58**, 101 (1958); H. C. Brown, D. McDaniel and O. Hafziger in "Determination of Organic Structure by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1956, p 567.

Methylene chloride (210 ml, dried by distilling from CaH₂) was placed in the dewar. In order to minimize hydrolysis of BCl₃ or BBr₃, the dewar was first flushed with dry nitrogen followed by the boron halide and then dry nitrogen. A known volume of BCl₃ was measured with a gas buret and introduced in the gas washing bottle containing the dry methylene chloride. The resulting solution was then transferred under N₂ to the dewar. Two or more syringes containing the samples for heat measurements were firmly wedged in the holes in the Teflon stopper so that the injection ends of the syringes were just below the liquid in the dewar.

When equilibrium conditions were established (25 ± 1°), heating curves were taken. Typically, using a heating period of 15 sec with the heater current at 0.1 amp, ~1-mv, deflection on the recorder was obtained. When two or more successive heating curves did not vary more than 2–3%, samples were introduced for determination of heats of solution or of reaction. Following sample injection, heating curves were again repeated which usually did not vary more than 5% from the initial results.

Reaction heats were determined by successive injections of base into methylene chloride solutions containing on the order of 100-fold excess of the acid. The initial acid concentration was 0.1–0.3 M. The base was injected either as pure liquid or solid or a methylene chloride solution. In the former cases, the reaction heats were obtained by correcting for the heat of solution of the base in methylene chloride as measured in separate experiments. Liquid samples were injected by hypodermic-type syringes. Solid samples were placed in polypropylene syringes. The injection ends of these syringes were sliced off and replaced by Teflon plugs in order to obtain a wide opening through which the solid could be forced. In injection of solutions, typically 0.2–1.0 ml of a 0.1–0.3 M stock solution of base in methylene chloride was used. The reaction heat obtained in this manner was corrected, if necessary, for the small heat of dilution of the acid solution. After the first or second injection of base into the acid solution, it was found that heats of acceptable precision and reproducibility were obtained (cf. Table I). The result of the first or second injection was generally erratic and was not considered in obtaining the mean value. The $\Delta H^\circ_{f(\text{exptl})}$ values of Table I as the mean of a least two (generally 3–5) acceptable values.

Results

In Table I are listed the standard enthalpies (and their precision measures) of complex formation, ΔH°_f , obtained for series I ketones with BCl₃ and BBr₃

Table I. Experimental and Predicted Values of the Standard Enthalpy of Formation (Reaction 1) of BCl₃ and BBr₃ Adducts or *m'*- and *p'*-Substituted *p*-Fluorobenzophenones in Methylene Chloride Solution at 25°

	$-\Delta H^\circ_{f(\text{exptl})}$, kcal	$-\Delta$, ppm	$-\Delta H^\circ_{f(\text{calcd})}$, ^a kcal
BCl₃ Adducts			
<i>p</i> -OCH ₃	19.0 ± 0.1	10.40	19.3
<i>p</i> -OC ₂ H ₅	18.4 ± 0.1	11.30	18.4
<i>p</i> - <i>t</i> -C ₄ H ₉	16.7 ± 0.2	13.07	16.6
H	15.1 ± 0.2	14.51	15.2
<i>p</i> -Cl	14.5 ± 0.2	15.04	14.7
<i>m</i> -F	13.6 ± 0.2	16.20	13.5
<i>m</i> -Br	13.5 ± 0.1	16.42	13.3
<i>m</i> -CF ₃	12.6 ± 0.2	17.04	12.7
<i>p</i> -CF ₃	12.3 ± 0.2	17.44	12.3
<i>m</i> -NO ₂	11.5 ± 0.3	18.05	11.7
BBr₃ Adducts			
<i>p</i> -OCH ₃	...	11.74	21.3
<i>p</i> -OC ₂ H ₅	20.6 ± 0.3	12.56 ^b	20.5
<i>p</i> - <i>t</i> -C ₄ H ₉	18.8 ± 0.2	14.50	18.6
H	17.2 ± 0.3	16.16	16.9
<i>p</i> -Cl	17.1 ± 0.3	16.49	16.6
<i>m</i> -F	...	17.66	15.4
<i>m</i> -Br	...	17.85	15.2
<i>m</i> -CF ₃	14.9 ± 0.4	18.66	14.4
<i>p</i> -CF ₃	...	19.04	14.0
<i>m</i> -NO ₂	14.8 ± 0.1	19.98	13.1

^a Calculated from eq 7. ^b Calculated from eq 9 of ref 5 using $\sigma^+ = -0.49$.

in methylene chloride solution. Values are also listed for the corresponding change in the F nmr shielding parameter, Δ , between complexed and uncomplexed ketone, i.e., $\Delta = \int_{H(c)}^{p-X} - \int_{H(u)}^{p-X} = \int_H^{p-X_0} + \Delta f_{(c)} - \Delta f_{(u)}$, where the latter shieldings are as designated and listed in Tables I–III of ref 5. The predicted values of ΔH°_f obtained from the linear SEE relationship (eq 7, below) are given also. In general the agreement between calculated and observed values of ΔH°_f is within the combined uncertainties. The only exception occurs for the enthalpy figure for the 3'-nitro-*p*-fluorobenzophenone-BBr₃ adduct. With BBr₃ the precision of ΔH°_f was generally poorer than for BCl₃, but the deviation in this case is beyond experimental error. In view of the generally satisfactory agreement in Table I, the only suggestion which we can offer for the larger observed than predicted enthalpy change is the possibility that there is a contribution to $-\Delta H^\circ_{f(\text{obsd})}$ resulting from interaction of BBr₃ with the nitro group in the adduct which occurs at the very high acid-base ratio (>100) employed in the enthalpy determination.

Discussion

The proposed linear SEE relationship is expressed by

$$\int_H^{p-X} = mE^\circ + b' \quad (2)$$

where \int_H^{p-X} is the shielding parameter for the *p*-fluorophenyl derivative relative to internal fluorobenzene, E° is the molecular electronic stabilization energy (cf. subsequent Discussion) and m and b are constants characteristic of the related series of *p*-fluorophenyl derivatives. For reaction 1 application of eq 2 gives

$$\Delta E^\circ = E^\circ_{(c)} - E^\circ_{(u)} = m \int_{H(c)}^{p-X} - m \int_{H(u)}^{p-X} + b = m\Delta + b \quad (3)$$

where Δ is the difference in the shielding parameter between complexed and uncomplexed ketone. It is assumed for present purposes that for reaction 1 $\Delta E^\circ \cong \Delta H^\circ_f$ (298°K).

In the present application of eq 3 two types of structural variations are being considered, i.e., variable Lewis acid and variable m' and p' substituents. With *p*-fluorobenzonitrile it was found⁷ (qualitatively) that m has positive sign, i.e., increasing $-\Delta H^\circ_f$ is accompanied by increasing $-\Delta$. A similar sign of m is expected for the Lewis acid adducts of *p*-fluorobenzophenone. On the other hand, with increased electron withdrawal by the m' or p' substituent, $-\Delta$ increases but $-\Delta H^\circ_f$ decreases (as expected); i.e., m has a negative sign for the substituent effect.

Thus the following two relationships are generated from eq 3: for various Lewis acid adducts of *p*-fluorobenzophenone

$$\Delta H^\circ_f \cong \Delta E^\circ = m\Delta_0 + b \quad (4)$$

and for the substituent effect (relative to unsubstituted *p*-fluorobenzophenone)

$$\int_R \Delta H^\circ_f \cong \int_R \Delta E^\circ = -m \int_R \Delta = m(\Delta_0 - \Delta) \quad (5)$$

(7) R. W. Taft and J. W. Carten, *J. Am. Chem. Soc.*, **86**, 4199(1964).

where Δ refers to the substituted fluorobenzophenone and Δ_0 to unsubstituted *p*-fluorobenzophenone. Combining eq 4 and 5 gives

$$\Delta H^\circ_f = \Delta E^\circ + \int_R \Delta E^\circ = m(2\Delta_0 - \Delta) + b \quad (6)$$

on the assumption that the magnitude of m is the same (1.00 kcal/ppm; cf. introductory section) for both types of structural dependence.

In order to obtain an independent evaluation of the constant b in eq 3 we have determined Δ and ΔH°_f for reaction 1 for the formation of the BCl_3 adduct of *p*-fluoroacetophenone. We believe the value of b obtained with the use of the latter ketone will be essentially correct for use with *p*-fluorobenzophenone adducts since acetophenone and benzophenone are of essentially identical base strength.⁸ Values of $\Delta = -18.20 \pm 0.06$ ppm and $-\Delta H^\circ_f = 18.9 \pm 0.2$ kcal/mole have been obtained with *p*-fluoroacetophenone from which $b = -0.7$ kcal/mole. Equation 6 may be reduced then to the following simplified explicit form for reaction 1

$$\Delta H^\circ_f = 2\Delta_0 - \Delta - 0.7 \text{ (in kcal/mole)} \quad (7)$$

The success of eq 7 is displayed in Table I in the comparison between observed and predicted values of $-\Delta H^\circ_f$ for reaction 1. It is to be emphasized that the predictions of eq 7 depend in no way upon the correlations made in the companion paper.⁵ Further, the correlation of Δ values with σ^0 is limited to substituents which involve no direct conjugative effects⁵ whereas the confirmed predictions of eq 7 include both strongly conjugating and nonconjugating substituents.

Equation 7 and similar relationships derived from the linear SEE relationship promise to be of great utility in obtaining values of ΔH°_f which are difficult or impossible to obtain by direct experimental determination. In our hands, Δ has been found generally to be a more precisely and easily measured quantity than ΔH°_f .

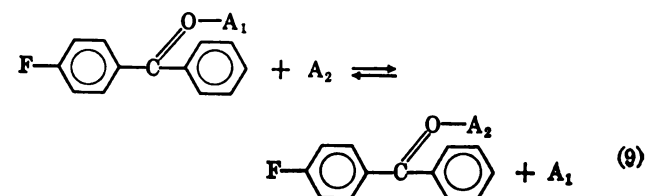
Equation 7 may be combined with the polar substituent effect relationship,⁵ $\Delta = \Delta_0[1 + (\sigma^0/2.75)]$, to obtain the (limited) relationship

$$-\Delta H^\circ_f = \Delta_0[\sigma^0/2.75] + 0.7 \quad (8)$$

Equation 8 may be used (where applicable) to calculate ΔH°_f values for any of the Lewis acid adducts for the series I ketones for which Δ_0 (cf. Table I, ref 5 for acids, e.g., $\text{AlCl}(\text{C}_2\text{H}_5)_2$, BI_3 , etc.) and σ^0 values are available. While these uses of F nmr shielding for predictions of reactivities must be regarded as having substantial consequences, the greatest significance of the linear SEE relationship is probably in the unique extra-thermodynamic analysis of substituent effects on reactivities which it permits.

The electronic stabilization energy which is measured according to eq 2 by the F nmr shielding parameter is extrathermodynamic.⁹ That is, in terms of the theoretical models used to derive eq 2 the perturbation on the π electronic energy levels of *p*-fluorobenzophenone is measured but the energy content of the substituent is not included. The relevant changes in E° may be

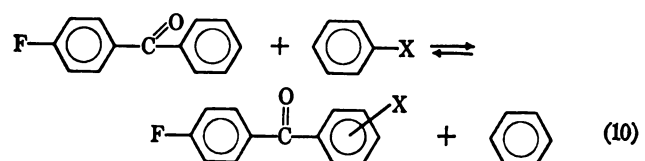
approximated (for conceptual purposes) by the following model thermodynamic exchange reactions:



for variable Lewis acid

$$\Delta E^\circ_{(9)} \cong E^\circ_{\text{A}_2} - E^\circ_{\text{A}_1} = \int_R E^\circ$$

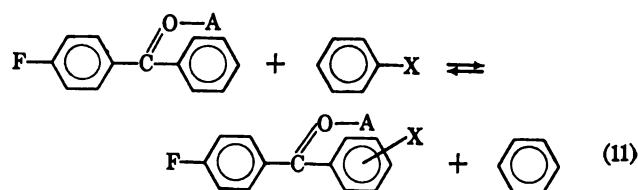
for variable substituent in base



$$\Delta E^\circ_{(10)} \cong E^\circ_{\text{X(u)}} - E^\circ_{\text{H(u)}} =$$

$$\int_R E^\circ_{(u)} \equiv -(\text{SE})_{(u)} = -\Delta \int_{(u)}$$

for variable substituent in adduct

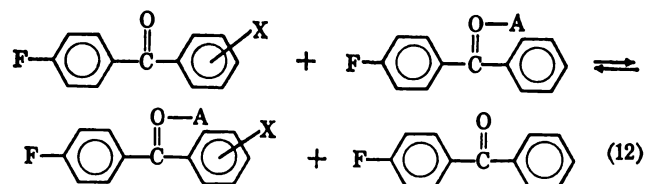


$$\Delta E^\circ_{(11)} \cong E^\circ_{\text{X(c)}} - E^\circ_{\text{H(c)}} =$$

$$\int_R E^\circ_{(c)} \equiv -(\text{SE})_{(c)} = -\Delta \int_{(c)}$$

Although values of $\Delta E^\circ_{(9)}$, $\Delta E^\circ_{(10)}$, and $\Delta E^\circ_{(11)}$ represent fundamental quantities, there is little immediate prospect that precise values of these quantities will become available by thermodynamic means.

The thermodynamic substituent effects measured in this investigation, $\int_R \Delta H^\circ_f$, correspond to the following reaction.



$$\int_R \Delta H^\circ_{f(1)} = \Delta H^\circ_{f(12)} \cong \Delta E^\circ_{(12)} = (\text{SE})_u - (\text{SE})_c =$$

$$\Delta E^\circ_{(11)} - \Delta E^\circ_{(10)}$$

Values of the substituent stabilization energies (as defined above) for uncomplexed and complexed ketone obtained from the linear SEE relationship therefore permit a novel analysis of the origin of the thermodynamic substituent effects. Specifically, the relative contributions of the substituent perturbations on the reactant and product states of reaction 1 is obtained.

(8) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 378 (1963).

(9) J. E. Leffer and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York N. Y., 1963, Chapter 6.

The results of this analysis for formation of the BCl_3 adducts are given in Table II. Similar analysis may be made with other data from Table I and Tables II and III of ref 5.

Table II. Analysis of the Contributions of Substituent Effects on the Stabilization Energy of m' - and p' -Substituted p -Fluorobenzophenones and Their BCl_3 Adducts to the Thermodynamic Substituent Effects (kcal/mole)

Subst	Reactant state $\text{SE}_{(u)} = -\Delta f_{(u)}$	Product state $\text{SE}_{(e)} = -\Delta f_{(e)}$	State change $-\int_R \Delta E^\circ = -\int_R \Delta H^\circ_{f(\text{obsd})}$	State change measured $(\pm 0.2-0.3)$
p' - OCH_3	+0.99	+4.90	+3.91	+3.9
p' - OC_6H_5	0.45	+3.66	+3.21	+3.3
p' - $i\text{-C}_4\text{H}_9$	0.41	+1.85	+1.44	+1.6
H	(0.00)	(0.00)	(0.00)	(0.0)
p' -Cl	-0.52	-1.05	-0.53	-0.6
m' -F	-0.75	-2.44	-1.69	-1.5
m' -Br	-0.89	-2.80	-1.91	-1.6
m' - CF_3	-1.17	-3.70	-2.53	-2.5
p' - CF_3	-1.32	-4.25	-2.93	-2.8
m' - NO_2	-1.79	-5.33	-3.54	-3.6

The identification of the substituent stabilization energies for uncomplexed and complexed ketone with the quantities $\Delta f_{(u)}$ and $\Delta f_{(e)}$, of course, does involve the assumption that $m = 1.00$ kcal/mole ppm as found for the $\Delta E^\circ_{(12)}$ (Δ) process. This assumption is supported by the well-behaved $\sigma^0\bar{p}$ behavior displayed by both the substituted uncomplexed and complexed ketones⁶ and the fact that the range in Δ values involved (cf. Table I) of about 10 ppm is of similar order of magnitude as the range of \int_H^{p-X} values between the uncomplexed p' - OCH_3 compound and the BBR_3 complexed m' - NO_2 compound (about 22 ppm). In view of this and subsequent discussion it is highly unlikely that any errors due to this assumption exceed 20% of the result listed in Table II and smaller error seems probable.

It is clear from the results in Table II that the thermodynamic substituent effects are the resultants of substantial effects in both complexed and uncomplexed ketone, although effects in the former state do predominate. While the substituent effects are qualitatively parallel in both states, there is no fixed factor which quantitatively relates the effects of either state to the observed thermodynamic properties. However, for those substituents which exert only a polar (σ^0) effect, fixed factors are applicable. These are obtained from the ratios of the \bar{p} values given in ref 5.

It is apparent from the above discussion and results that the linear SEE relationship provides also the prediction of the reaction constant, ρ for reaction 1. That is, for the relationship $\int_R \Delta H^\circ_f = \sigma^0 \rho$ (for polar effects) the predicted values of ρ (in kcal/mole $-\sigma^0$ units) are obtained as $\rho = -\Delta_0/2.75$, where $\Delta_0 = \int_{H(e)}^{p-X_0} - \int_{H(u)}^{p-X_0}$ (values of these parameters are given in Table I of ref 5 for the acids $\text{AlCl}(\text{C}_2\text{H}_5)_2$, BF_3 , BCl_3 , $\text{AlCl}_2\text{C}_2\text{H}_5$, AlCl_3 , BBR_3 , and BI_3).

Limitations of the Linear SEE Relationship. LCAO-MO theory *does not* indicate completely general linear relationships between local charge density and electronic energy.¹⁰ Consequently the SEE relationship,

(10) C. A. Coulson, *Proc. Phys. Soc. (London)*, **A65**, 933 (1952); L. Goodman and H. Shull, *J. Chem. Phys.*, **23**, 33 (1955).

which makes a specialized use of such linearity,² is anticipated to have structural limitations. These limitations are not well defined by present theory and, in any case, must be subjected to experimental determination.

The results of this and previous investigations,^{2,11} leave little doubt that the SEE relationships are satisfactorily linear for p -fluorophenyl substitution at a fixed functional group (within the usual context of such usage). It is not necessary, however, that the energy shielding coefficient, m , be a universal constant of precisely 1.00 kcal/mole ppm.

In the formation of trityl cations from their carbinols¹¹ $m = 0.70$ kcal/mole ppm, while in the ethane reduction to trityl anions^{3,12} $m = 1.30$ kcal/mole ppm. These results suggest that m increases (in magnitude) as the p -fluorophenyl label is substituted at substantially more "saturated" (less sensitive) functional centers. Unpublished results of Dr. M. G. Schwartz¹³ and Dr. D. Gurka¹⁴ with adducts of p -fluorophenol and of Mr. A. A. Grey¹⁴ with adducts of p -fluorophenylboron dichloride definitely confirm this trend.

In the application of eq 4 to the present study nearly equivalent results to those listed in Table I are obtained with $m = 1.05$ kcal/mole ppm and $b = 0$ whereas in the application of eq 5 $m = 1.00$ or slightly smaller. However, the differences in the alternate treatments are not significant. Consequently, as a working hypothesis, m is taken to be a constant for each broadly defined functional group, (e.g., the carbonyl group in series I ketones and their Lewis acid adducts).

Thermodynamic Considerations. The assumed approximation $\Delta H^\circ_f \cong \Delta E^\circ_{\text{elect}}$ more accurately must be replaced by the relationship

$$\Delta H^\circ_f = T\Delta[(H^\circ - E_0^\circ)/T] + \Delta E_0^\circ$$

where $\Delta[(H^\circ - E_0^\circ)/T]$ represents the sum of the thermodynamic function for the products of reaction 1 minus that for the reactants, and $\Delta E_0^\circ = \Delta E^\circ_{\text{elect}} + \Delta E^\circ_{\text{vibr}}$ where $\Delta E^\circ_{\text{vibr}}$ is the zero point vibrational energy change for reaction 1.

Since the thermodynamic functions and $\Delta E^\circ_{\text{vibr}}$ can be evaluated from vibrational and rotational spectroscopic data, it follows that the linear SEE relationship provides in principle a means of precise prediction of ΔH°_f from the various spectroscopic measurements and statistical thermodynamic relationships. A similar conclusion applies with respect to the *a priori* prediction of the equilibrium constant through the relationship

$$\Delta F^\circ_f = RT \ln K = T\Delta[(F^\circ - E_0^\circ)/T] + \Delta E^\circ_{\text{elect}} + \Delta E^\circ_{\text{vibr}}$$

In practice, the application of this precise relationship must await the evaluation of the precision of

(11) For shielding in substituted trityl cations cf. ref 2. Substituent shielding effects in the corresponding carbinols have been obtained: L. D. McKeever, Ph.D. Thesis, University of California, Irvine, Calif., Sept 1966. The latter shieldings parallel those obtained in the trityl cations but are only 3% as large.

(12) Cf. ref 3. The substituent shielding effects in the ethanes have been approximated as those observed in the corresponding triaryl-methanes. The latter shielding effects are approximately 7% as large as for corresponding shieldings in the trityl anions.

(13) M. G. Schwartz, Ph.D. Thesis, The Pennsylvania State University, Dec 1965.

(14) Work in progress at University of California, Irvine, Calif.

$\Delta E^{\circ}_{\text{elect}}$ obtained by the linear SEE relationship. In the meanwhile, the linear SEE relationship appears to provide an extremely valuable approximate relationship as discussed above.

Acknowledgment. We are pleased to acknowledge the helpful assistance of Professor Arnett, Dr. C. Douthy, and Mr. T. Murty in obtaining preliminary results with their calorimeter.

Analysis of the Nuclear Magnetic Resonance Spectra of Some 2,6-Bridged Bicyclo[2.2.1]heptane Derivatives

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Contribution from the Research and Development Department of the ARCO Chemical Company, a Division of Atlantic Richfield Company, Glenolden, Pennsylvania, and the Department of Chemistry, The Catholic University of America, Washington, D. C. Received December 15, 1966

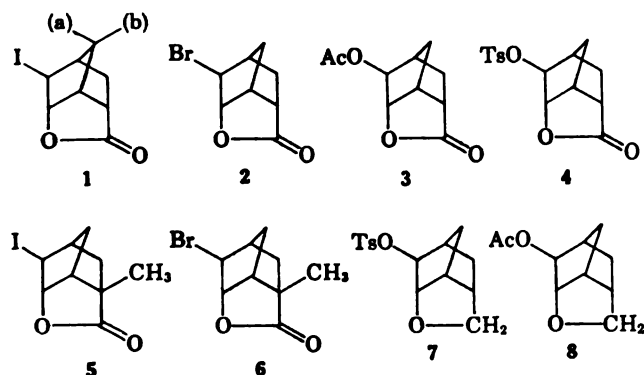
Abstract: The 60- and 100-Mc/sec nuclear magnetic resonance spectra of several bridged bicyclo[2.2.1]heptane derivatives have been analyzed in detail. These compounds possess the common structural feature of a 2,6 oxygenated bridge which may be either a lactone as in 5-*exo*-iodo-6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (1) and the 5-*exo*-bromo (2), 5-*exo*-acetoxy (3), 5-*exo*-tosyloxy (4), 2-*exo*-methyl-5-*exo*-iodo (5), 2-*exo*-methyl-5-*exo*-bromo (6) derivatives; or the 2,6 bridge may be an oxido unit as in 4-*exo*-tosyloxy-6-oxatricyclo[3.2.1.1^{3,5}]nonane (7) and 4-*exo*-acetoxy-6-oxatricyclo[3.2.1.1^{3,5}]nonane (8). Chemical shifts for all the protons in these structures have been assigned, and the geminal and vicinal couplings measured. Aromatic solvent shifts observed for compounds 1, 5, and 7 are discussed in terms of solvent-solute collisional complexes of defined stereochemistry. Long-range couplings for the proton pairs: 1-4, 3-*endo*-7(a), 5-*endo*-7(b), 2-*exo*-6-*exo*, 1-3-*exo*, 2-*exo*-4, and 6-*exo*-4 in compound 1 were observed and most of these were confirmed using spin-decoupling techniques. For the C₅-*endo* proton doublet in the lactone derivatives it is noteworthy that the principal coupling is with the C_{7(b)} proton; this amounts to about 2.5 cps while the C₅-*endo*-C₆-*exo* vicinal coupling is negligibly small (0.3 cps) and the C₅-*endo*-C₄-vicinal ranges from 0.5 to 1.0 cps. The nmr spectra of the 5-keto and 7-keto derivatives in the 2,6 lactone series are discussed in relationship to the changes in chemical shifts relative to the precursor secondary alcohols. The alcohol-ketone pairs are 5-*exo*,6-*endo*-dihydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (9) and 5-keto,6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (10); 6-*endo*,7(b)-dihydroxybicyclo[2.2.1]heptane-2-*endo* carboxylic acid lactone (11) and 7-keto,6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (12).

The norbornyl system has served as a substrate for the generation and evaluation of numerous mechanistic hypotheses in modern organic chemistry. Mechanistic conclusions originating from studies in the norbornyl series frequently have been based upon the structures of rearranged products. Detailed nuclear magnetic resonance spectral analyses in this series obviously are of importance in facilitating the elucidation of rearrangement products. Moreover, due to the conformational rigidity of these systems, long-range

couplings which are often of an unexpectedly large magnitude may be detected. This paper presents detailed analyses of the spectra of compounds 1-8. The compounds included in this study are of current and particular interest because of uncertainties of interpretation^{2a} and previous erroneous assignments.^{2b}

Chemical Shifts

In a preliminary communication of a portion of this work,² we pointed out that the chemical shifts of the C₁- and C₂-*exo* protons in compound 1 were anomalous in the sense that the C₁ proton appeared at a lower field position relative to the C₂-*exo* proton which is attached to the carbon atom bearing the carbonyl group of the lactone. This assignment was required to explain the magnitude of the couplings associated with the C₆-*exo* proton. An earlier interpretation of the spectrum of 2 used the reverse assignment of the chemical shift of the C₁- and C₂-*exo* protons.^{2b} This incorrect assignment was used recently by Jensen and Miller^{2a} who corrected stereochemical assignments of Traylor and Factor for the structure of the oxymercuration product derived from 5-norbornene-2-*endo*-car-



(1) (a) The ARCO Chemical Co., Glenolden, Pa.; (b) The Catholic University of America, Washington, D. C.

(2) (a) F. R. Jensen and J. J. Miller, *Tetrahedron Letters*, **40**, 4861 (1966); (b) E. Crundwell and W. Templeton, *J. Chem. Soc.*, 1400 (1964).
(3) R. M. Moriarty, H. Gopal, H. G. Walsh, K. C. Ramey, and D. C. Lini, *Tetrahedron Letters*, **38**, 4555 (1966).

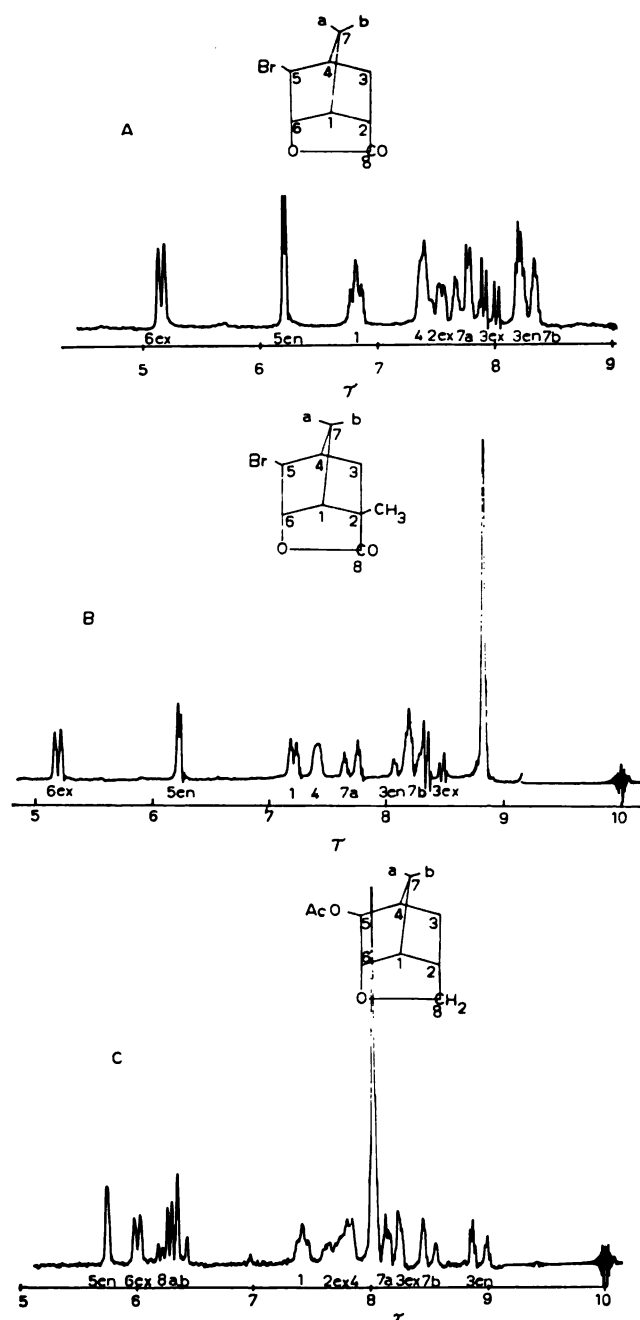


Figure 1. 100-Mc/sec nmr spectra of: A, compound 2; B, compound 6, and C, compound 8, in solution in CDCl_3 .

boxylic acid.^{4a,b} The incorrect chemical shift assignments used by Jensen and Miller for the C_1 - and C_2 -*exo* protons, however, do not influence the validity of their conclusions with respect to the configuration of the C_6 -*endo* proton in compounds 1 and 2 which they studied.

Figure 1A-C presents the 100-Mc/sec nmr spectra of compounds 2, 6, and 8, respectively (Table I presents chemical shifts). For lactones 2 and 6 one may immediately discern a similarity; namely, three resonances equivalent to one proton each appear at downfield positions and these resonances are clearly

(4) (a) T. G. Traylor and A. Factor, Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p 36N. (b) Professor Traylor informed us of his revision of the stereochemistry originally proposed by him and Factor^{4a} for the oxymercuration product of 5-norbornene-2-*endo*-carboxylic acid on Nov 20, 1964, in a seminar in this department.

separated from the complex upfield absorption. The absorptions around τ 5.1 and 6.1 are logically assigned to the C_6 -*exo* and C_5 -*endo* protons, respectively. The resonance at τ 6.75 in 2 might be due to the C_2 -*exo* proton but this assignment leads to a number of unreasonable interactions. For example, spin-decoupling experiments revealed that the proton in 2 at τ 6.75 was coupled with the C_6 -*exo* proton to the extent of 5 cps. This would be an unprecedentedly large long-range coupling for such protons. This coupling was clearly better accommodated by a vicinal rather than a 1,3 arrangement of these interacting protons. The spectrum of 6 clarifies this point in that a methyl group occupies the site in this derivative of the C_2 -*exo* proton present in 1 and 2, yet a resonance still occurs at τ 7.20. Accepting this alternative assignment, i.e., that C_1 proton gives rise to the absorption at τ 7.2, appearance of this proton in 6 as principally a doublet is due to the absence of a proton at C_2 for coupling. Furthermore, any reasonable analysis of spectra in this series, as will be shown below, demands these relative assignments of the C_1 - and C_2 -*exo* protons.

The reason for this unexpected reversal in the chemical shifts of the C_1 - and C_2 -*exo* protons is based upon a model in which the C_1 proton is axial with respect to the lactone ring and is located in the region of maximum deshielding resulting from the ring current associated with the lactone carbonyl group. This interpretation is also consistent with the results obtained for compounds 5 and 6. The upfield shifts of about 0.4 ppm for the C_1 proton in compounds 5 and 6 is probably due to the anisotropy of the carbon-carbon σ bond of the methyl group at C_2 .⁵ Accordingly, the C_3 -*exo* proton in 1 should also experience extra shielding, and reference to the data in Table I bears out this prediction. The difference in magnitude of the upfield shift is associated with the dihedral angle between the C_2 - CH_3 bond and the C_1 -H, C_3 -*exo*-H, and C_3 -*endo*-H bonds. The maximum upfield shift is experienced by the C_3 -*exo* proton, $\Delta\delta \text{C}_3$ -*exo*(1)- C_3 -*exo*(5) = +0.54. The dihedral angle here is close to 0° . The C_2 - CH_3 and C_1 -H dihedral angle is about 40° and $\Delta\delta \text{C}_1$ (1)- C_1 (5) = +0.44. The dihedral angle for the C_2 - CH_3 - C_3 -*endo*-H is about 120° and $\Delta\delta \text{C}_3$ -*endo*(1)- C_3 -*endo*(5) = -0.42. Thus, this proton suffers a large deshielding effect due to the anisotropy of the C- CH_3 bond. The effect upon the C_6 -*exo* and C_7 (b) protons is very small. Replacement of the carbonyl group of the lactone by a methylene group, as in compounds 7 and 8, causes a further upfield shift of the C_1 protons relative to the position in the lactones.

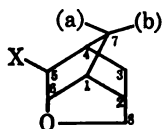
The spectrum of 8, Figure 1C, exhibits a typical AB part of an ABX pattern for protons 8(a) and 8(b). Inspection of models reveals that only one of the C_8 methylene protons has the correct geometry for spin-spin coupling with the C_2 -*exo* proton.

In most cases the assignment of resonances corresponding to the C_3 -*exo*, C_3 -*endo*, and 7(a), 7(b) proton pairs was straightforward. The expected larger value of $J_{3\text{-exo-3-endo}}$ over $J_{7(a)-7(b)}$ as found by Laszlo and Schleyer was of diagnostic value here.⁶ Differentiation of the chemical shifts of the individual protons of these

(5) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Chem. Commun.*, 359 (1966).

(6) P. Laszlo and P. von R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1171 (1964).

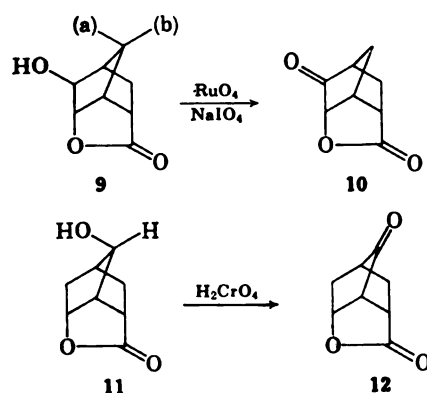
Chemical Shifts for Some Bicyclo[2.2.1]heptane Derivatives



pd	1	6 _{ex}	5 _{en}	4	3 _{ex}	3 _{en}	2 _{ex}	7(a)	7(b)
	6.78	4.88	6.08	7.30	7.94	8.48	7.46	7.68	8.18
	6.75	5.06	6.13	7.35	7.89	8.25	7.48	7.72	8.26
	6.80	5.51	5.45	7.50	7.97	8.28	7.45	8.01	8.38
	6.87	5.52	5.75	7.51	8.04	8.43	7.60	8.02	8.43
	7.22	4.93	6.15	7.34	8.48	8.06	8.83 (CH ₃)	7.64	8.12
	7.20	5.15	6.21	7.41	8.41	8.19	8.84 (CH ₃)	7.71	8.24
	7.48	5.95	5.91	7.76	8.21	9.10	7.76	8.15	8.53
	7.38	5.94	5.68	7.78	8.17	8.90	7.70	8.10	8.48

Chemical shifts for the protons in the 8 positions are τ 6.53, and 6.47 for compound 7 and 6.19 and 6.34 for compound 8. ^b Note numbering of the oxido methylene group as C₈ is not correct as far as nomenclature is concerned; *i.e.*, compounds 7 and 8 are tri-1^a,4^anonane derivatives. However, we use the above incorrect nomenclature in order to focus on the relationship of these compounds with their norbornyl analogs.

Analysis was accomplished by analysis of stereospecific long-range coupling using decoupling techniques *vide infra*. The assignments of the C₂-*exo*, C₃-*endo*, and C₄ protons were implied from previous work which showed that the spin-spin coupling of the endo C₃-*exo* protons should be relatively large, 11.5 cps, while the coupling of the C₄ proton with C₃-*exo*, C₃-*endo*, C₅-*endo*, C_{7(a)}, and C_{7(b)} protons would be comparatively smaller.^{7a,b} Confirmation of the above chemical shift assignments derive from the nmr spectra of compounds 9 and 12.



In the case of alcohol 9 the C₅-*endo* proton at 6.08 appears as a singlet peak at τ 6.30. The peak half-height is 2.8 cps. The C₆-*exo* proton appears as a doublet at τ 5.5. The principal coupling of the endo proton is with the C_{7(b)} proton, while the coupling, 5.0 cps, for the C₆-*exo* proton is with the C₁ proton. Oxidation of 9 to 10 removes the proton absorption. The C₆-*exo* proton is shifted by +0.55 ppm. Similarly, for 11, the C_{7(b)} proton appears as a singlet with peak width at a half-height of 4 cps. The C₁ proton appears as a doublet of with further small splitting ($J_{6-exo-1} \sim 5$ cps, $J_{7(b)-1} \sim 1.5$ cps, $J_{1-4} \sim 1$ cps). Oxidation of 11 to 12 removes the C_{7(b)} resonance and the coupling is essentially unshifted. The small coupling also vanishes as expected.

L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963). (b) These assignments agree with theoretically derived ones: J. Karplus, *J. Chem. Phys.*, **31**, 1 (1959).

Further points of interest with respect to chemical shifts as presented in Table I are (a) the C_{7(b)} proton resonates at higher field than its C_{7(a)} counterpart; (b) the C₃-*endo* proton occurs at higher field position than the C₃-*exo* except in the case of the C₂ methyl derivatives. Again this may be explained in terms of the anisotropy of the carbon-carbon σ bond of the methyl group; (c) reasonable consistency prevails for the relative chemical shifts of structurally related protons. Finally, since these assigned chemical shifts are largely based on spin-spin decoupling this aspect of the work will be discussed next.

Spin-Spin Decoupling. Figures 2 and 3 show expanded sweeps at 100 Mc/sec of the upfield and downfield portions of the spectrum of compound 2 in benzene solution. Relative to the spectrum of this compound shown in Figure 1, a considerable simplification of the overlapping resonances is immediately apparent. Advantage was taken of this solvent-induced separation of proton chemical shifts, and spin-decoupling experiments were performed using benzene solutions.

Based upon the discussion presented above, the chemical shifts of the C₅-*endo* and C₆-*exo* protons can be assigned with strong certainty. These two resonances were used as probes for assigning other protons in the more complicated high-field portion of the spectrum. While the chemical shift of the C₁ proton also appeared secure on the basis of arguments presented above, we nonetheless attempted an analysis based upon the assignments of Crundwell and Templeton;^{2b} *i.e.*, the three downfield resonances would correspond to protons C₆-*exo*, C₅-*endo*, and C₂-*exo* with increasing field strength, respectively. This set of assignments together with the assignments of protons C₁ and C₄ to the resonances at τ 7.35 and 7.48 for 2 used in conjunction with the other assignments as listed in Table I yielded a number of unreasonable interactions such as $J_{4-3-exo} = 10.5$ cps, $J_{2-exo-4}$ and $J_{2-exo-6-exo} \cong 5$ cps. These results, which indicate that the three downfield resonances are correctly assigned (Table I), were used with spin decoupling to assign the upfield components of the spectra.

The expanded spectrum of the C₆-*exo* and C₅-*endo* protons of 2 is shown in Figure 4. Part a depicts the normal C₆-*exo* proton with coupling constants of 5

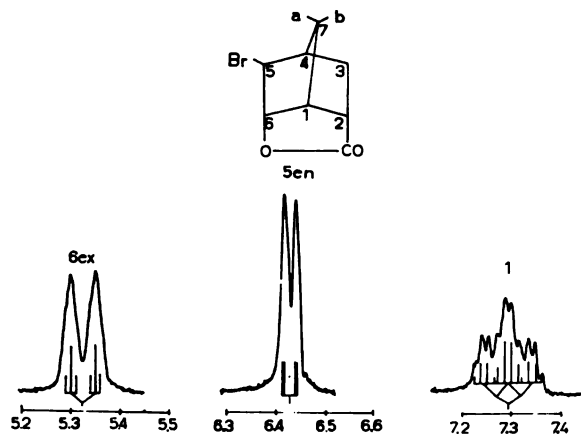


Figure 2. Downfield portion of the nmr spectrum of compound 2 in solution in C_6H_6 .

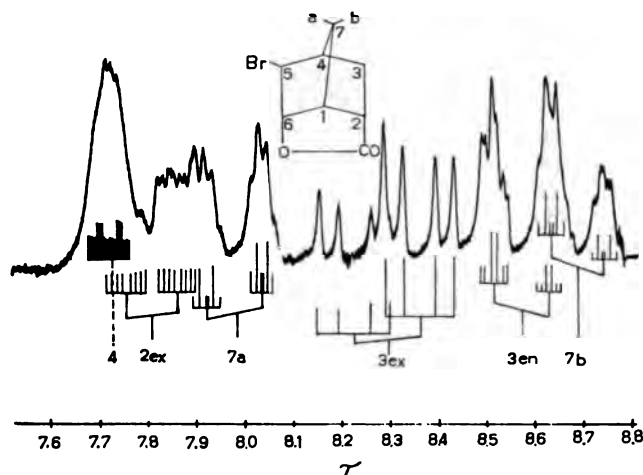


Figure 3. Upfield portion of the nmr spectrum of compound 2 in solution in C_6H_6 .

and 1 cps. Part b shows the C_6 -*exo* proton absorption upon irradiation of the C_1 proton at τ 7.29. Thus, the 5-cps coupling between the C_1 - and C_6 -*exo* proton is established clearly. Irradiation of the C_2 -*exo* proton at 7.83 cps (part c) eliminates the long-range 1.0-cps $J_{6-exo-2-exo}$, as well as $J_{6-exo-4}$. Irradiation of the C_5 -*endo* proton at τ 6.43 does not alter the resonance of the C_6 -*exo* proton. Hence $J_{6-exo-5-endo}$ is less than 0.3 cps. Turning to the C_5 -*endo*, Figure 4, part d, shows the unperturbed resonance of the C_5 -*endo* proton; it exhibits a 2.4- and a 0.5-cps coupling. Surprisingly irradiation of the C_4 proton (part b) did not remove the 2.4-cps, but rather only the 0.5-cps coupling. Assuming a zigzag geometric requirement for long-range coupling over four bonds, only the C_1 and $C_{7(b)}$ protons bear such a relationship to the C_5 -*endo* proton.

Irradiation at τ 8.69 removes the 2.4-cps coupling, as shown in part e of Figure 4. Since the chemical shift of the C_1 proton is known, and the resonance in the τ 8.7 region possesses the appearance of a member of an AB pattern, the $C_{7(b)}$ proton is fixed. Furthermore, the chemical shift of the $C_{7(a)}$ proton is revealed as the other part of the C_7 AB pattern. In Figure 5, are shown typical decoupled spectra obtained using the frequency sweep technique. Part A shows the upfield part of the normal spectrum of 2 in benzene solution; part B shows the spectrum obtained upon irradiation of

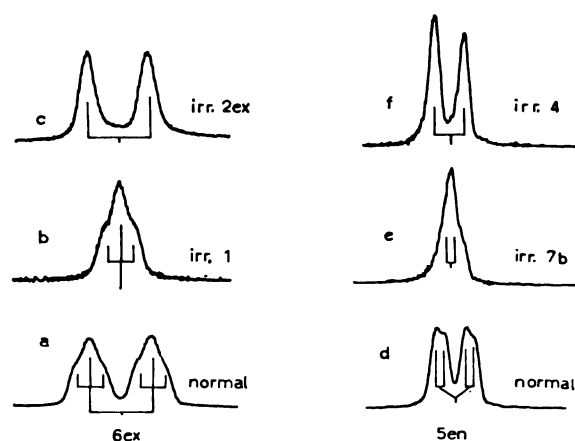


Figure 4. Expanded sweep of C_6 -*exo* resonance of compound 2: a, normal; b, decoupled from proton 1; c, decoupled from proton 2-*exo*; and d, normal resonance of C_5 -*endo* of compound 2; e, decoupled from proton 7(b); and f, decoupled from proton 4.

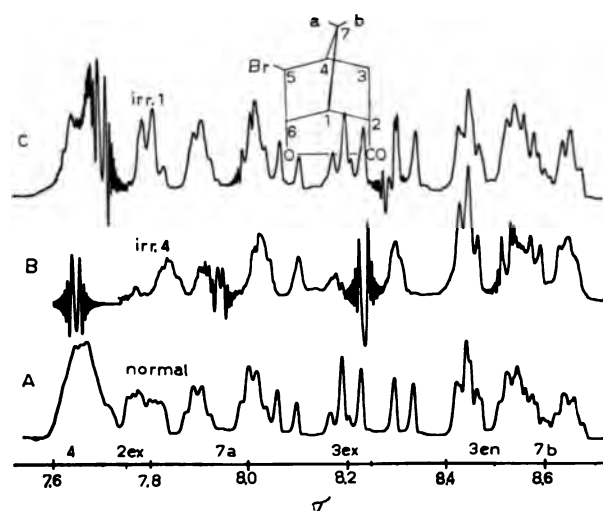


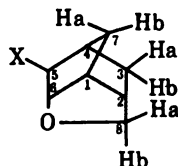
Figure 5. Upfield portion of the spectrum of compound 2 in solution in C_6H_6 : A, normal; B, decoupled from proton 4; and C, decoupled from proton 1.

the C_4 proton at τ 7.65. First to be noted in going from left to right is the beat note at τ 7.65 which is recorded at reduced amplitude. This indicates the position of irradiation. It is followed by a distorted region extending about 30 cps in both directions from the point of irradiation. Secondly, the appearance of the 7(a) resonance, particularly the upfield part, confirms the interaction $J_{7(a)-4} = 1.4$ cps. Next and more clearly, despite the beat note in the region, $J_{3-exo-4} = 3.8$ cps is confirmed. Lastly, in the upfield region both $J_{3-endo-4} = 0.8$ cps and $J_{7(b)-4} = 1.5$ cps are confirmed. Part C shows the spectrum resulting from irradiation of the C_1 proton at τ 7.3. The overlap of the beat note and the resonance of the C_4 complicates the interpretation, but nevertheless protons C_1 and C_2 obviously interact. The resonance of the C_2 -*exo* proton confirms the 4.9-cps interaction with the C_1 proton, and also a 1.4-cps coupling of proton C_1 with proton $C_{7(a)}$.

The spectra shown in Figure 5 are meant to be representative. In order to confirm the various interactions indicated, the individual resonance under study was expanded to 50 cps and decoupled.

geminal and vicinal coupling constants for the series of compounds are collected in Tables II and III, respectively. The omissions in Table III correspond to those in which accurate values could not be obtained due to unresolvable overlap.

II. Geminal C_3 , C_7 , and C_8 Coupling Constants for bicyclo[2.2.1]heptane Derivatives

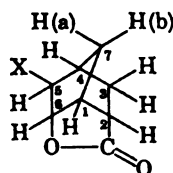


mpd	J, cps		
	3-exo-3-endo	7(a)-7(b)	8(a)-8(b)
1	13.4	11.2	...
2	13.2	11.4	...
3	13.0	11.0	...
4	13.4	11.0	...
5	13.6	11.1	...
6	13.6	11.1	...
7	13.0	10.6	8.2
8	13.2	10.6	8.2

III. Vicinal Coupling Constants for Some Bicyclo[2.2.1]heptane Derivatives

mpd	Coupling constant, J, cps											
	1-6-exo	1-2-exo	5-endo-4	3-exo-4	3-endo-4	3-endo-2-exo	3-exo-2-exo	7(a)-1	7(a)-4	7(b)-1	7(b)-4	8(a)-2-exo
1	5.4	5.0	0.5	3.6	0.5	3.0	10.2	1.6	1.8	0.6	1.5	...
2	5.0	4.9	0.5	3.8	0.8	2.0	10.6	1.4	1.4	1.5	1.5	...
3	4.6	4.6	0.8	3.8	10.5	1.5	...	1.6
4	4.8	5.0	1.1	4.0	10.3	1.8	...	1.8
5	5.1	...	1.0	4.7	0.7	1.4	1.6	1.6	1.6	...
6	5.0	...	0.6	4.1	0.8	1.4	1.6	1.3	1.3	...
7	4.7	...	2.6	10.8	3.6
8	5.2	4.0	1.1	2.2	10.0	1.7	1.7	1.4	1.4	3.6

Long-Range Couplings. Long-range interactions of appreciable magnitude across four saturated bonds have been observed for a number of bicycloheptane⁹, bicyclohexane^{10,11} derivatives. These long-range interactions appear to depend primarily upon the spatial arrangements of the interacting protons, although other factors such as electronegativity and steric effects of substituents appear also to be of importance. Recent studies have shown, both theoretically and experimentally, that a near-planar zigzag arrangement of the protons is necessary for detectable interactions. With the recently available techniques this amounts to about 0.3 Å. On this basis, for the structure below, proton pairs, 1-3-exo, 2-exo-4, 6-exo-4, 5-endo-7(b), 3-endo-7(a), 2-exo-6-exo are expected to exhibit long-range couplings. For similar systems, couplings of 3-4 cps⁸



have been reported between protons of the C_3 -endo-7(a), and C_5 -endo-7(b) type, 0.7-1.8 cps for protons of the C_2 -exo- C_6 -exo variety,¹² and 0.8-1.4 cps for protons of the 1-4 type.¹² A weak coupling between protons C_3 -exo- C_1 and C_6 -exo- C_4 has been postulated,¹³ but no values were reported.

In the present work values of $J_{7(a)-3-endo}$ and $J_{7(b)-5-endo}$ ranging from 1.3 to 3.2 and 1.7 to 2.6 cps, respectively, were observed. These results are similar to those reported by Musher,⁹ but smaller than the values found by Meinwald and Meinwald⁸ for related compounds. The published data^{8,9} seem to indicate that there is a fairly large substituent effect upon these interactions particularly for compounds of the type 1-4. However, in the system under investigation in this study, the substitution of a methyl group in the C_2 -exo position (5-6) appears to increase $J_{7(a)-3-endo}$ while decreasing $J_{7(b)-5-endo}$. Furthermore, a change in the oxygenated bridge spanning the 2-6 positions produces a smaller value of $J_{7(b)-5-endo}$ than that of $J_{7(a)-3-endo}$. This seems to indicate that the long-range couplings are sensitive to changes in the planarity of the zigzag arrangement of the interacting atoms. The relatively small values of J_{1-4} and $J_{2-exo-6-exo}$ for which the interacting protons conform to a more strictly planar arrangement than other cases, as

judged by inspection of scale models, indicate that planarity of the systems may not be the dominant factor in determining the magnitude of coupling over four bonds. Furthermore, a direct relationship does not appear to exist between the size of the coupling constant and the 1,3 proton internuclear distance. Thus, inspection of scale models reveals that the C_1 - C_3 -exo proton distance in 2 is 4 Å while the C_5 -endo- C_7 (b) and C_2 -exo- C_6 -exo distances are 4.4 Å. Yet, the latter gives rise to considerably larger long-range couplings.

As shown in Table IV, a number of small long-range couplings were observed involving C_6 -exo-4, C_1 -3-exo, and C_2 -exo-4 for compounds 1-8. These interactions were usually less than 1 cps and were generally difficult to detect in normal spectra. Under the condition of our decoupling experiments at 60 and 100 Mc/sec, it was possible to detect long-range couplings as small as 0.5 cps.

Solvent Effects

The effect of solvent upon proton chemical shifts is well documented.^{14,15} Solvent-solute interactions be-

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9. I. Musher, *Mol. Phys.*, **6**, 93 (1963).

10. J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, **83**, 2769 (1961).

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(14) J. S. Waugh and R. W. Fessenden, *J. Am. Chem. Soc.*, **79**, 846 (1957).

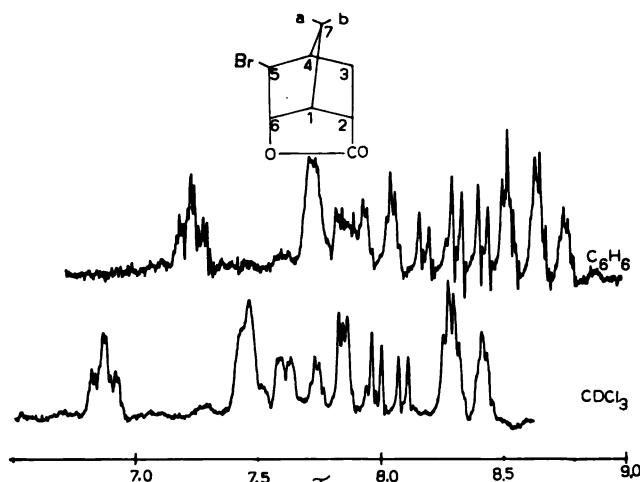
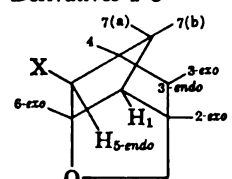


Figure 6. Upfield portion of the spectrum of compound 2 in solution in CDCl_3 and C_6H_6 .

tween aromatic solvents and polar solutes have been used widely to identify conformational isomers of N-methyl amides¹⁶ and N-methyl lactams.¹⁷

Table IV. Long-Range Coupling Constants for Bicyclo[2.2.1]heptane Derivatives 1-8



Compd	Coupling constants, J , cps						
	6- <i>exo</i> -4	3- <i>exo</i> -1	7(b)- 5- <i>endo</i>	7(a)-3- <i>endo</i>	2-6- <i>exo</i>	2-4	1-4
1	1.0	0.5	2.6	1.3	1.2	0.6	1.4
2	1.0	0.3	2.4	2.0	1.0	...	1.6
3	1.2	0.3	1.7	...	1.2	...	1.2
4	1.1	...	1.7	...	1.1	...	1.0
5		0.8	2.1	2.1	1.4
6	1.0		2.1	1.9	1.4
7				2.2			
8			1.8	2.2	1.0		

Structural information from these studies derives from the formation of a weakly associated solvent-solute collisional complex of definite stereochemical composition.¹⁸ A consequence of the nonrandom orientation of the aromatic ring with respect to the polar solute is that nuclei near the disk-like ring are shielded relative to nuclei either remote from the aromatic ring or coplanar with it. The structure of the collisional complex is governed by a weak polar attrac-

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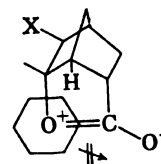
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(18) For an excellent discussion of the solvent effect of benzene upon the chemical shifts of protons of polar solutes see, J. Ronayne and D. H. White, *Chem. Commun.*, 712 (1966).

tion of the aromatic ring for the partially positively charged amide or lactam nitrogen. A comparable interaction is conceivable for *cis* lactones of the type under study.



Connolly and McCrindle¹⁹ have studied benzene-induced chemical shifts for a series of lactones. Table V lists dilution shifts for compounds 1, 5, and 7. The shifts observed for the two lactones 1 and 5 are large, while those for the oxido compound 7 are small. Based upon the model for the benzene-lactone complex proposed above, one might predict that the C_1 proton would experience the largest upfield shift and the C_2 -*exo* proton should experience a relatively smaller upfield shift. These predictions are realized and they may be further rationalized on the basis of the tendency of the benzene molecule to avoid the partially negatively charged carbonyl oxygen atom and residue closer to C_1 . On the average, the C_1 proton is the more highly shielded. Also, in the assumed model, the benzene ring and the front face of the molecule, which contains the lactone ring, lie in parallel planes. The C_1 proton, therefore, is axial and lies closer to the shield portion of the aromatic. This last point offers additional proof for the correctness of the C_1 proton assignment. The simplified cation of the spectrum observed in benzene solution for compound 2 (Figure 6) relative to the *d*-chloroform solution enables a more definitive analysis of the C_3 -*endo*- $\text{C}_7(\text{b})$, C_3 -*exo*- $\text{C}_7(\text{a})$, and C_2 -*exo*- C_4 protons. Finally, note should be made of the advantage of combining spin-spin decoupling with dilution shifts observed for solutions of polar solutes such as *cis* lactones with aromatic solvents such as benzene.

Experimental Section

The spectra were obtained using Varian HA-100 and A-60 spectrometers. Samples were run as 10% (w/v) solutions in CDCl_3 and C_6H_6 with tetramethylsilane as an internal reference. Decoupling was carried out with the HA-100 spectrometer utilizing the frequency sweep technique and the V-6058-1 spin decoupler at 60 Mc/sec, which utilizes the field-sweep technique. A Hewlett-Packard audiofrequency oscillator 201C in conjunction with a Hewlett-Packard audiofrequency counter 5512A was used for frequency sweep decoupling and for the calibration of both instruments.

5-*exo*-Iodo-6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (1) was prepared according to the method of Ver Nooy, *et al.*,²⁰ and had mp 59–60° (lit.²⁰ 58–59°), $\nu_{\text{C=O}}$ 1783 cm^{-1} .

5-*exo*-Bromo-6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (2) was prepared according to the method of Roberts, *et al.*,²¹ and had mp 65–66° (lit.²¹ 64.8–65.9°), $\nu_{\text{C=O}}$ 1779 cm^{-1} .

5-*exo*-Acetoxy-6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (3) was prepared according to the method of Henbest and Nichols²² and had mp 95–96° (lit.²² 95–96°), λ_{CHCl_3} (C=O) 5.60 and 5.75 μ (1786 and 1739 cm^{-1}).

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V. Solvent Shifts for Bicyclo[2.2.1] Derivatives upon Dilution with Benzene

ipd	$\Delta(\delta C_6H_6 - \delta CCl_3), \text{ppm}^{a,b}$										
	1	2- <i>exo</i>	3- <i>exo</i>	3- <i>endo</i>	4	5- <i>endo</i>	6- <i>exo</i>	7(a)	7(b)	8(a)	8(b)
	0.47	0.30	0.49	0.12	0.38	0.25	0.22	0.27	0.30
	0.59	0.28(CH ₃)	0.51	0.44	0.46	0.36	0.32	0.32	0.51
	0.18	0.29	0.19	0.11	0.10	0.04	0.02	0.17	0.18	0.11	0.08

^a % (w/v) solutions with TMS internal reference. ^b The changes are taken as positive when the resonances move upfield in going from C₆H₆ to CCl₄.

5-*exo*-Tosyloxy-6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid Lactone (4). To a solution of 1.2 g of alcohol 9 lived in the minimum amount of dry pyridine, 2.0 g of *p*-nesulfonyl chloride was added. The mixture was warmed on steam bath until solution was complete, and then the reaction was allowed to stand at room temperature overnight. Ice water were added, and the mixture was extracted thoroughly ether. The ether solution was washed with water, a dilute solution of hydrochloric acid, and then with a saturated solution of sodium bicarbonate. The solution was dried with magnesium sulfate and then concentrated to dryness *in vacuo*. The residue was recrystallized from ether-pentane to yield 2.07 g (87.5%), mp 84–95°. *Anal.* Calcd for C₁₅H₁₈O₄S: C, 58.58; H, 5.21. Found: C, 58.72; H, 5.21.

5-*exo*,6-*endo*-Dihydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (9) was prepared according to the method of Henbest and Nichols and had mp 155–157° (lit.²² 160°).

5-Keto-6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (10). A solution of 400 mg of ruthenium dioxide in carbon tetrachloride was prepared according to the procedure of Ito.²³ This solution was added dropwise to a suspension in carbon tetrachloride of 5-*exo*,6-*endo*-dihydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (9), 5 g, 0.033 mole, with stirring and cooling. Then, 7.0 g (0.033 mole) of sodium metaperiodate solution was added dropwise over a 1-hr period. The reaction system was stirred at ice temperature for 4 hr, then at room temperature for 18 hr. The excess oxidizing agent was removed by addition of isopropyl alcohol. The layers were separated and the aqueous layer was thoroughly extracted with ether. The chloroform and carbon tetrachloride solutions combined, dried over magnesium sulfate, and concentrated to dryness *in vacuo*. The resulting thick oil, 1.5 g, was sublimed at 175° (0.5 mm). The resulting sublimate, 1.2 g, showed five spots on tlc. The sublimate was chromatographed upon silica using a column (35 × 3.5 cm) of 100 g of silica gel prepared with benzene. The column was first eluted with benzene-chloroform (1:1), then with chloroform, and finally with chloroform-methanol (97:3). The first eight fractions were oils and were put aside. Fraction 9 gave five spots in thin layer chromatography and infrared spectrum showed a strong carbonyl absorption at 1790, cm⁻¹, doublet with a weak absorption band at 1705 cm⁻¹. Fractions 10–14, the eluates of chloroform, showed mainly one spot in layer chromatography and the infrared spectrum of each showed strong carbonyl absorption at 1800, 1770 cm⁻¹, doublet, and a weak absorption band at 1705 cm⁻¹. Fractions 15–17, eluates of chloroform-methanol (97:3), showed strong carbonyl absorption at 1735 cm⁻¹ and relatively weak absorption in the above-mentioned region. Fractions 18 and 19, chloroform-methanol (97:3) eluates, were identified as unreacted starting material by infrared comparison of authentic sample.

Fraction 11 (100 mg) deposited some crystalline material on keeping in chloroform solution for a few days. Filtration of crystals and washing with ether afforded 30 mg of compound. Recrystallization with chloroform gave quite pure crystalline sample, mp 196°, showing strong carbonyl absorption in the infrared at 1770 cm⁻¹, doublet with no hydroxyl absorption band. This showed a single spot in thin layer chromatogram using a chloroform-methanol (97:3) system as given before. The molecular weight of 152 was confirmed by a high-resolution mass spectrum. **5-*exo*-Iodo-6-*endo*,2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (5)** was prepared according to the method of Meek and Trapp²⁴ and had mp 85–86° (lit.²⁴ 83–86°), $\nu_{C=O}$ 1780

5-*exo*-Bromo-6-*endo*,2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone (6) was prepared according to the method of Meek and Trapp²⁴ and had mp 74–75° (lit.²⁴ 74–75°), $\nu_{C=O}$ 1790 cm⁻¹.

4-*exo*-Tosyloxy-6-oxatricyclo[3.2.1.1^{3,5}]nonane (7). A solution of 4.5 g of 4-*exo*-hydroxy-6-oxatricyclo[3.2.1.1^{3,5}]nonane and 9 g of *p*-toluenesulfonyl chloride in 12 ml of very dry pyridine was stored overnight at room temperature. After processing the reaction mixture in the usual way, the crude product was recrystallized from ether-pentane giving 7.6 g (77%), mp 86–87°. *Anal.* Calcd for C₁₅H₁₈O₄S: C, 61.20; H, 6.16. Found: C, 61.50; H, 6.27.

4-*exo*-Acetoxy-6-oxatricyclo[3.2.1.1^{3,5}]nonane (8) was prepared according to the method of Henbest and Nichols²² and had mp 52–53° (lit.²² 50–52°).

7(a),6-*endo*-Dihydroxybicyclo[2.2.1]-2-*endo*-carboxylic acid lactone (11). A three-necked, 300-ml, round-bottomed flask was equipped with an efficient stirrer and a condenser to which was attached a calcium chloride drying tube. Dried lead tetraacetate (20 g, 0.044 mole), dry CaCO₃ (12 g), and 200 ml of dry benzene were introduced into the flask, and the mixture was stirred at reflux for approximately 30 min. *exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid²⁵ (3 g, 0.022 mole) was then added after which refluxing was maintained for an additional 48 hr.

The solution was allowed to cool to room temperature and was then filtered through Celite. The filtrate was diluted with ether, washed with a small amount of saturated aqueous NaHCO₃, dried over MgSO₄, and concentrated *in vacuo*. Chromatography of the resulting yellow oil (2.5 g) on 100 g of silica gel (Baker) [elution with ether-benzene (1:4)] afforded 1.5 g (35%) of 7(a)-acetoxy-6-*endo*-hydroxybicyclo[2.2.1]-2-*endo*-carboxylic acid lactone. Two recrystallizations from acetone-pentane gave an analytical sample, mp 113–114°, $\nu_{C=O}$ 1735 and 1775 cm⁻¹. *Anal.* Calcd for C₁₀H₁₂O₄: C, 61.21; H, 6.17. Found: C, 61.07; H, 6.17.

The acetoxy lactone (2.09 g) and 4.5 g of potassium carbonate were refluxed in a mixture of 40 ml of water and 60 ml of methanol for 4 hr. At the end of this time, the water and methanol were removed using a rotary evaporator. The residue was dissolved in 30 ml of water and extracted twice with ethyl acetate to remove any of the unreacted acetate. The aqueous layer was acidified by dropwise addition of 50% H₂SO₄, after which the solution was continuously extracted with ethyl acetate for 36 hr.

The ethyl acetate solution was washed with three portions of saturated aqueous NaHCO₃ solution, dried over MgSO₄, and concentrated to yield 0.914 g of crude 9(a),6-*endo*-dihydroxybicyclo[2.2.1]-2-*endo*-carboxylic acid lactone. Continuous extraction of the NaHCO₃ combined washings for 24 hr afforded an additional 0.30 g of crude product, total yield 74%. Two recrystallizations from acetone-ligroin gave an analytical sample, mp 203–204°, ν_{O-H} 3600 and 3440 cm⁻¹; $\nu_{C=O}$ 1775 cm⁻¹. *Anal.* Calcd for C₈H₁₀O₄: C, 62.32; H, 6.54. Found: C, 62.13; H, 6.60.

7-Keto-6-*endo*-hydroxybicyclo[2.2.1]-2-*endo*-carboxylic acid lactone (12). A solution of 2.4 g of 7(a),6-*endo*-dihydroxybicyclo[2.2.1]-2-*endo*-carboxylic acid lactone in 8.2 ml of water was maintained at 20° for a period of 45 min while 7.4 ml of 6 *N* chromic acid was added dropwise with stirring. After an additional 10 hr of stirring, 0.3 ml of 2-propanol was introduced to decompose any excess chromic acid and the solution was extracted several times with ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated at room temperature on a rotary evaporator. Elution chromatography of the crude product mixture (2.4 g) on 140 g of silica gel (Baker) with ether-benzene (1:4) afforded initially 0.67 g (27%) of crude 7-keto-6-*endo*-hydroxybicyclo[2.2.1]-2-*endo*-carboxylic acid lactone followed immediately by approximately 0.5 g of unreacted starting alcohol. A pure

¹ H. Nakata, *Tetrahedron*, **19**, 1959 (1963).

² J. S. Meek and W. B. Trapp, *J. Am. Chem. Soc.*, **79**, 3909 (1957).

(25) J. Berson and D. Ben-Effraim, *ibid.*, **81**, 4083 (1959).

sample of the ketone was obtained after three recrystallizations from acetone-ligroin, mp 194–196°, $\nu_{C=O}$ 1775 cm^{-1} .

Treatment of the ketone with 2,4-dinitrophenylhydrazine dissolved in a mixture of phosphoric acid and ethanol afforded the corresponding hydrazone derivative, mp 262–263° dec, $\nu_{C=O}$ 1775 cm^{-1} . *Anal.* Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_6$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.37; H, 3.61; N, 16.81.

A thioketal derivative was prepared by the method of Fieser,²⁴ mp 134°. *Anal.* Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{S}_2$: C, 52.60; H, 5.30. Found: C, 52.46; H, 5.18.

4-*exo*-Tosyloxy-6-oxatricyclo[3.2.1.1^{3,5}]nonane (7). 4-*exo*-Hydroxy-6-oxatricyclo[3.2.1.1^{3,5}]nonane,²² 4.5 g, and *p*-toluenesulfonyl chloride, 9.0 g, were dissolved in 12 ml of dry pyridine. The reac-

tion mixture was allowed to stand at room temperature overnight. At the end of this time, ice was added, and the precipitate which deposited was collected and washed thoroughly with water. After drying at room temperature, the crude crystalline product was recrystallized from ether-pentane, 7.6 g (76%), mp 86–87°. *Anal.* Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{S}$: C, 61.20; H, 6.16. Found: C, 61.50; H, 6.27.

Acknowledgment. Discussions of the spectra of the compounds reported in this paper with Dr. B. Franzus of Esso Co., Linden, N. J., and with D. Dreyer of the U. S. Department of Agriculture, Pasadena, Calif., are gratefully acknowledged. P. von R. Schleyer, Princeton University, also contributed critical discussion of much value.

(26) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

New Heteroaromatic Compounds. XXV.¹ Studies of Salt Formation in Boron Oxyacids by ¹¹B Nuclear Magnetic Resonance

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Contribution from the Department of Chemistry, The University of Texas, Austin, Texas 78712. Received December 22, 1966

Abstract: The ¹¹B nmr spectra of several compounds containing the group BOH have been measured in neutral and alkaline solution. Salt formation shifts the ¹¹B resonance far upfield (> 13 ppm) in the case of boric acid and simple arylboronic acids, the line width remaining unchanged or becoming narrower; this indicates that such compounds behave as Lewis acids toward base. The B–OH derivatives of several borazaro³ compounds are quite different in this respect, salt formation leading to small downfield shifts (3–7 ppm) in the ¹¹B resonance, and also to extreme broadening of the lines. Here salt formation must involve proton transfer, in agreement with earlier conclusions³ and implying that compounds of this type are indeed aromatic.

Trivalent boron compounds are well known to behave as Lewis acids, combining with base to form coordination compounds (e.g., $\text{H}_3\text{N} \rightarrow \text{BF}_3$); an ambiguity therefore exists in the case of compounds which contain the grouping BOH and so could act either as protic acids, or as Lewis acids, toward base. Thus hydroxide ion could either deprotonate such a compound to give a planar ion, R_2BO^- (eq 1), or it could add to boron to form an ion in which boron is now quadricovalent and tetrahedral (eq 2).



The Raman spectrum of boric acid in alkali indicates that it behaves as a Lewis acid,⁴ forming the ion $\text{B}(\text{OH})_4^-$, and the available evidence, while scanty, seems to suggest⁵ that arylboronic acids act likewise. On the other hand, B–OH derivatives of borazaro compounds³ seem to behave as protic acids, judging by comparisons of their ultraviolet spectra in neutral and alkaline solu-

tion; this difference has been attributed to the aromaticity of the boron-containing rings in compounds of this kind, the boron being consequently reluctant to adopt a tetrahedral geometry.

It seemed to us that ¹¹B nmr spectroscopy could provide a definite distinction between the two possible modes of salt formation. Conversion of trivalent planar boron to quadricovalent tetrahedral boron would be expected⁶ to produce a large upfield shift in the ¹¹B resonance, due to the greater shielding of boron in compounds where four pairs of valence electrons surround the boron atom; the available evidence supports this conclusion. Thus the ¹¹B chemical shifts (relative to trimethyl borate) of quadricovalent boron compounds almost all lie above 7 ppm, while compounds with lower chemical shifts contain planar trivalent boron.⁷ Salt formation according to eq 2 should therefore lead to a large upfield shift of the ¹¹B resonance, while salt formation according to eq 1 should produce a much smaller change.

Conversion of boric acid to borate ion is indeed accompanied⁷ by a large upfield shift (17.5 ppm) in the ¹¹B resonance, as would be expected if the ion has the tetra-

(1) Part XXIV: M. J. S. Dewar and J. L. Von Rosenberg, Jr., *J. Am. Chem. Soc.*, **88**, 358 (1966).

(2) Robert A. Welch Postdoctoral Fellow.

(3) See M. J. S. Dewar, *Progr. Boron Chem.*, **1**, 235 (1964).

(4) J. O. Edwards, G. C. Morrison, V. F. Ross, and J. W. Shultz, *J. Am. Chem. Soc.*, **77**, 266 (1955).

(5) (a) M. J. S. Dewar and R. Dietz, *Tetrahedron*, **15**, 26 (1961);

(b) D. H. McDaniel and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 3757, (1955); (c) J. P. Lovard and J. O. Edwards, *J. Org. Chem.*, **24**, 769, (1959).

(6) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nmr Spectroscopy," Vol. II, Pergamon Press, Oxford, England, 1966, p 971.

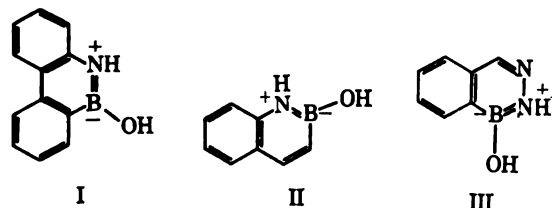
(7) P. C. Lauterbur in "Determination of Organic Structures by Physical Methods," Vol. II, F. C. Nachod and W. D. Phillips, Ed., Academic Press Inc., New York, N. Y., 1962, p 476.

Table I. ^{11}B Chemical Shifts for Boron Compounds in Neutral and Basic Solutions

Compd	Ref	Solvent	δ_{TMB}^a	δ_{EBT}^b	$\Delta\delta^c$	Line width at half-height, Hz
Boric acid (IV)	...	DMF	...	-19.9		370
		H_2O	...	-19.6		411
		1% NaOH- H_2O	...	-18.6		115
		5% NaOH- H_2O	...	-9.1		170
		10% NaOH- H_2O	...	-5.7	13.5	139
Phenylboronic acid (V)	<i>d</i>	EtOH	...	-28.4		272
		10% NaOH- H_2O	15.0	-3.15	25.3	74
<i>o</i> -Tolylboronic acid (VI)	<i>e</i>	EtOH	...	-32.2		191
		20% KOH-EtOH	...	-12.6	19.6	166
Boraphthalide (VII)	<i>f</i>	EtOH	...	-29.1		228
		20% KOH-EtOH	12.5	-5.6	23.5	291
10-Hydroxy-10,9-borazarophenanthrene (I)	<i>g</i>	EtOH	...	-36.8		623
		20% KOH-EtOH	...	-43.9	-7.1	>2500
2-Hydroxy-2,1-borazonaphthalene (II)	<i>h</i>	EtOH	...	-29.7		223
		20% KOH-EtOH	...	-33.0	-3.3	>2500
4-Hydroxy-4,3-borazaroisoquinoline (III)	<i>e</i>	EtOH	...	-29.8		265
		20% KOH-EtOH	...	-33.2	-3.4	>1500
4-Hydroxy-4,3-boroxaroisoquinoline (VIII)	<i>i</i>	EtOH	...	-30.0		290
		20% KOH-EtOH	13.1	-5.0	25.0	210
4-Methyl-4,3-borazaroisoquinoline (IX)	<i>e</i>	Benzene	...	-36.5		140
		EtOH	...	-38.5		247
		(None)	...	-18.1		37
Trimethyl borate	...	10% NaOMe-MeOH	15.3	-2.8		54
		20% NaOMe-MeOH	15.6	-2.5	15.6	32
		(None)	18.1

^a Chemical shift (ppm) relative to trimethyl borate. ^b Chemical shift (ppm) relative to diethyl ether-boron trifluoride complex. ^c Change in chemical shift on passing from neutral to alkaline solution. ^d R. M. Washburn, E. Levers, C. F. Albright, and F. A. Billig, *Org. Syn.*, **39**, 3 (1959). ^e M. J. S. Dewar and R. C. Dougherty, *J. Am. Chem. Soc.*, **86**, 433 (1964). ^f K. Torsell, *Arkiv Kemi*, **10**, 507 (1957). ^g M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3073 (1958). ^h M. J. S. Dewar and R. Dietz, *ibid.*, 2728 (1959). ⁱ H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Am. Chem. Soc.*, **80**, 835 (1958).

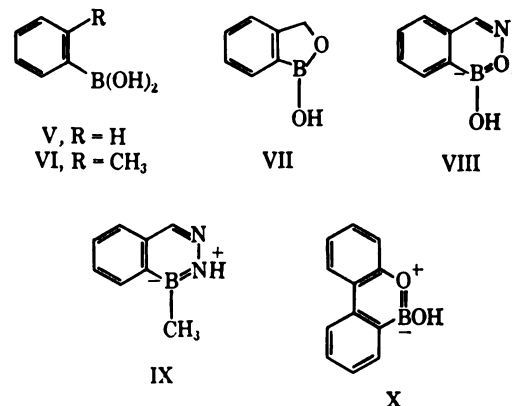
hedral structure $\text{B}(\text{OH})_4^-$. However this observation cannot in itself be taken as evidence for such a structure since one cannot estimate *a priori* what the chemical shift would be for a planar ion such as $(\text{HO})_2\text{BO}^-$. In other words, one needs for comparison a reference compound R_2BOH in which salt formation involves loss of a proton (eq 1) rather than addition to boron (eq 2). Now independent evidence had suggested³ that this is the case for B-OH derivatives of several borazaro compounds, in particular 10-hydroxy-10,9-borazarophenanthrene (I), 2-hydroxy-2,1-borazonaphthalene (II), and 4-hydroxy-4,3-borazaroisoquinoline (III). It seemed to us that by comparing the



^{11}B nmr spectra of such compounds in neutral and alkaline solution with corresponding spectra for conventional boron oxyacids, we might kill two birds with one stone. Not only might the comparison provide a definite and general criterion between the two modes of salt formation, but it could also provide unambiguous evidence that compounds such as I-III do indeed act as protic acids. This is an important point, since the reluctance of boron to undergo addition provides one of the strongest lines of evidence that compounds of this type are indeed aromatic.³

We have, therefore, measured the ^{11}B nmr spectra of I-III in neutral and alkaline solution, and also the corre-

sponding spectra of boric acid (IV), phenylboronic acid (V), *o*-tolylboronic acid (VI), boraphthalide (VII), and 4-hydroxy-4,3-boroxaroisoquinoline (VIII). For comparison, we also measured the spectrum of 4-methyl-4,3-borazaroisoquinoline (IX) and that of trimethyl borate in methanol and in methanolic sodium methoxide; in the latter case salt formation can take place only by addition to boron, giving the tetrahedral ion $\text{B}(\text{OMe})_4^-$.



Results

The nmr spectra were measured with a Varian DP-60 spectrometer, using trimethyl borate, or the diethyl ether-boron trifluoride complex, as external standards. The results are listed in Table I. The chemical shifts are believed to be accurate to ± 0.5 ppm. The various compounds were prepared by the methods described in the references quoted and their physical properties agreed with those previously reported. The chemical

shifts for trimethyl borate and the tetramethoxyboride ion, $\text{B}(\text{OCH}_3)_4^-$, are in good agreement with values reported by Phillips, *et al.*⁸

Discussion

It is immediately obvious that the compounds listed in Table I fall into two distinct categories. One group shows a large upfield shift (>13 ppm) on passing from neutral to alkaline solution, comparable with the difference between trimethyl borate and the ion $\text{B}(\text{OCH}_3)_4^-$, while the other group shows a small downfield shift (3–7 ppm). The arguments given above seem to suggest unequivocally that compounds of the first group are acting as Lewis acids, those of the second group as protic acids.

This conclusion is further supported by the changes in line width accompanying salt formation. Resonances due to ^{11}B are usually broad, due to quadrupole relaxation; two factors can influence the relative importance of this in a boron oxyacid and in its conjugate base. In the first place, there is a contribution due to unsymmetrical field gradients about boron inside the molecule or ion; these should be less important in an ion formed by addition to boron than in one formed by loss of a proton, since the electron distribution about a quadrivalent tetrahedral boron atom must, in general, be more symmetrical than that about a planar trivalent one. An effect of this kind is well known in the case of nitrogen, ^{14}N nmr lines being much sharper for ammonium ions than for the corresponding amines.⁹ A second source of quadrupole relaxation is provided by fluctuating electric potentials due to surrounding molecules; these should be much more important in the case of an ion than a neutral molecule, since ions in solution tend to be surrounded by ionic atmospheres (Debye-Hückel effect). Now when a typical boron oxyacid forms a salt by addition of base, these two factors will act in opposition; the change in covalency of boron should tend to decrease quadrupole relaxation and so reduce the line width, whereas the acquisition of negative charge should tend to increase it. If, on the other hand, salt formation involves loss of a proton so that the boron atom remains planar and trivalent, one might expect the line-broadening effect of the charge to operate unopposed. One might therefore expect the change in line width on passing from neutral to alkaline solution to serve as an additional criterion of acid type; boron protic acids should show a much greater increase. Examination of Table I shows that this prediction holds rather spectacularly. The line widths for Lewis acids are usually less in

alkaline than in neutral solution and certainly show no significant increase with salt formation, whereas the line widths for the protic acids increase enormously on addition of alkali.

We can therefore conclude with some assurance that boric acid, the arylboronic acids V and VI, and boraphthalide (VII) behave as Lewis acids to hydroxide ion, while the hydroxyborazaro compounds I–III behave as protic acids. This difference can of course be attributed⁸ to the aromatic nature of the latter compounds; addition of base to boron would destroy cyclic conjugation in the boron-containing ring.

The last of our hydroxy acids, 4-hydroxy-4,3-boroxarisoquinoline (VIII), is particularly interesting in this respect. Boroxaro compounds should be less aromatic than their nitrogen counterparts and this is known to be the case for the oxygen analog of I,¹⁰ 10-hydroxy-10,9-boroxarophenanthrene (X). Nevertheless ultraviolet spectral data seemed to suggest unambiguously that X behaves as a protic acid, the aromaticity of the central ring still being sufficient to inhibit addition to boron; it is therefore of interest to see if the same is true of VIII. The ultraviolet spectrum of VIII is almost the same in alkali as in neutral solution, suggesting that VIII also behaves as a protic acid;¹¹ however, the results in Table I show that this tentative conclusion was incorrect, VIII behaving as a Lewis acid toward hydroxide ion. This is indicated both by the large upfield shift (25 ppm), and by the decrease in line width (290 \rightarrow 210 Hz), on passing from neutral to alkaline solution.

The chemical shifts listed in Table I are also of some general interest in connection with the problem of relating chemical shifts to structure. It will be noticed that the resonances for arylboronic acids appear downfield by *ca.* 10 ppm relative to boric acid, implying that replacement of hydroxyl by phenyl has a deshielding effect. Phillips, *et al.*,⁸ have drawn attention to this surprising circumstance and have pointed out that it cannot be attributed to any effect of ring current or unsaturation, for the ^{11}B chemical shifts of phenylboronic acid and *n*-butylboronic acid differ by less than 1 ppm. The effect seems to be related in some way to the presence of boron-carbon bonds, for replacing the B–OH group in III by methyl (to form VIII) leads to a further downfield shift of 6.7 ppm. The most likely explanation seems to lie in a strong magnetic anisotropy of the C–B bond, resulting in a net deshielding effect on the boron atom.

Acknowledgment. This work was supported by a grant from the Robert A. Welch Foundation. We also wish to thank Dr. B. A. Shoulders for advice.

(8) W. D. Phillips, H. C. Miller, and E. L. Muetterties, *J. Am. Chem. Soc.*, **81**, 4496 (1959).

(9) See, *e.g.*, R. A. Ogg and J. D. Ray, *J. Chem. Phys.*, **26**, 1339 (1957).

(10) M. J. S. Dewar and R. Dietz, *J. Chem. Soc.*, 1344 (1960).

(11) Unpublished work by Dr. R. C. Dougherty; see M. J. S. Dewar and R. C. Dougherty, *J. Am. Chem. Soc.*, **86**, 433 (1964).

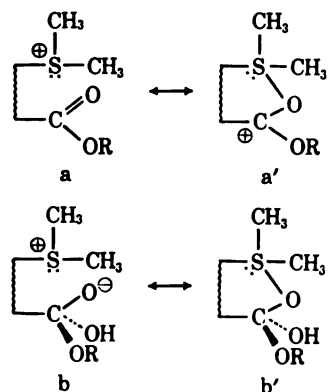
The Neighboring Sulfonium Group in Ester Hydrolysis

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Contribution from the Department of Chemistry, California State College at Los Angeles, Los Angeles, California 90032. Received December 16, 1966

Abstract: The alkaline hydrolysis of methyl 2-dimethylsulfoniophenylacetate *p*-toluenesulfonate (*o*-5) proceeds 5.2 times faster than that of the 4 isomer (*p*-5). With a correction for steric effects, the ratio is 14. The 2-dimethylsulfonio ester is hydrolyzed 356 times faster than the 2-isopropyl ester, and the 4-dimethylsulfonio ester is hydrolyzed 25 times faster than the 4-isopropyl ester. From these data and proton resonance spectra, it is concluded that the neighboring sulfonium group in these compounds exhibits a small rate-enhancing effect on ester hydrolysis, probably *via* a field effect rather than by covalent bonding between sulfur and oxygen.

The role of neighboring functional groups in intramolecular nucleophilic catalysis of ester hydrolysis is clearly established and has been the topic of extensive researches.¹ The intervention of intramolecular electrophilic catalysis in alkaline ester hydrolysis has been advanced in the case of hydroxylic hydrogen,² and is thought to be of the general acid type. Such electrophilic catalysis has not been reported for other electrophiles, perhaps due to the paucity of functional groups which are potentially capable of serving in this capacity. The extensive distribution of sulfonium compounds in biological systems³ and the well-documented propensity of sulfur for d orbital resonance⁴ suggested that a neighboring sulfonium group might function as such an electrophilic group, capable of the intramolecular catalysis of alkaline ester hydrolysis, either by bonding with, or inducing polarization in the carbonyl group (a, a') or by stabilizing the tetrahedral intermediate (b, b') in ester hydrolysis, or both. Either effect should lead to a rate increase. The object of the work described in this paper was to prepare esters containing



(1) (a) B. Capon, *Quart. Rev.* (London), 18, 45 (1964); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1966; (c) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).

(2) (a) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957); (b) H. G. Zachan and W. Karau, *Ber.*, 93, 1830 (1960); (c) H. Morawetz and I. Oreskes, *J. Am. Chem. Soc.*, 80, 2591 (1958); (d) H. Morawetz and J. Shaffer, *ibid.*, 84, 3783 (1962); (e) B. Capon, *Tetrahedron Letters*, 911 (1963).

(3) F. Schlenk, "Progress in the Chemistry of Organic Natural Products," Vol. XXIII, L. Zechmeister, Ed., Springer-Verlag, Berlin, 1965, pp 61-104.

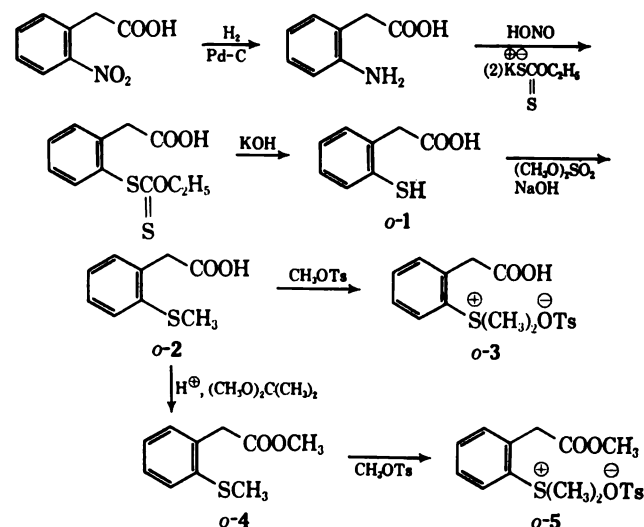
(4) (a) G. Cilento, *Chem. Rev.*, 60, 147 (1960); (b) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press Co., New York, N. Y., 1962; (c) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 77, 521 (1955); (d) L. Goodman, A. H. Konstam, and L. H. Sommer, *ibid.*, 87, 1012 (1965); (e) P. Haake, W. B. Miller, and D. B. Tyssee, *ibid.*, 86, 3255 (1964).

sulfonium groups disposed in space so as to favor the incursion of such an effect and to examine the hydrolysis rates of these esters when compared to isomeric systems incapable of intramolecular catalysis.

Results and Discussion

The substrates selected for this study were methyl 2-dimethylsulfoniophenylacetate *p*-toluenesulfonate (*o*-5) and the 4-substituted isomer (*p*-5). Their preparation is shown in Charts I and II. Their selection

Chart I



was predicated on the well-defined rigid geometry imparted by the aromatic ring and by the insulating effect of the α -methylene group, which would operate so as to minimize direct resonance interaction between the sulfur and carbonyl carbon. Inductive effect differences between the *ortho* and *para* isomers should also be small, since the effect is already attenuated by four bonds in the *ortho* isomer.

In order to assess the magnitude of *ortho* steric effects, which are substantial in the case of substituted benzoates,⁵ methyl 2- and 4-isopropyl phenylacetates were prepared and their hydrolytic behavior was examined under the same conditions as employed for the sulfonio esters. The assumption was made that an isopropyl group simulates a dimethylsulfonio group in steric requirement. The preparation of the isopropyl substituted esters is shown in Chart III.

(5) (a) M. Hojo, M. Utaka, and Z. Yoskida, *Tetrahedron Letters*, 19 (1966); (b) *ibid.*, 25 (1966).

Chart II

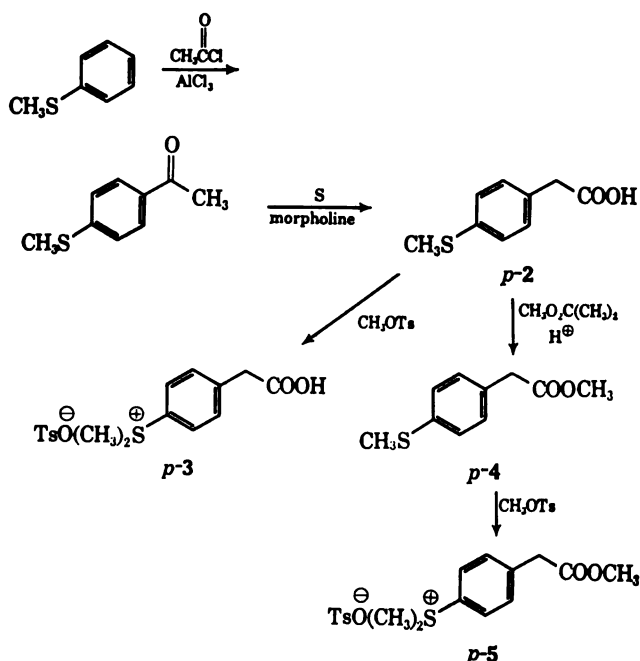
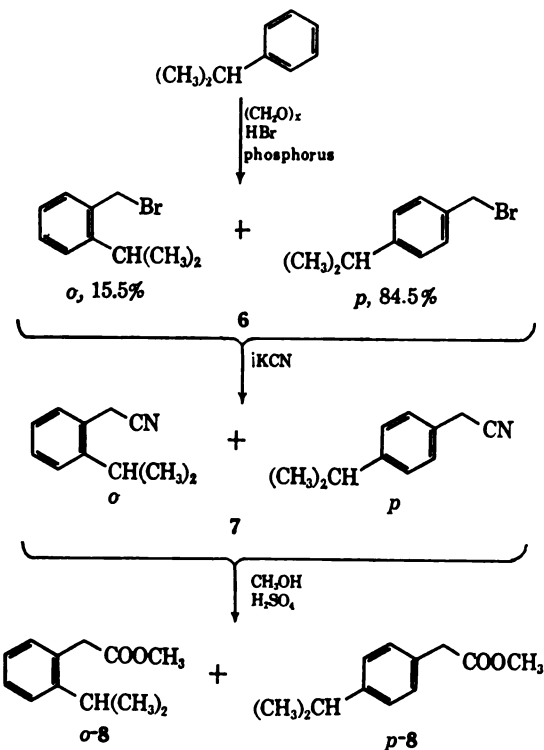


Chart III



Hydrolysis rates were measured titrimetrically at constant pH using 50% v/v aqueous dioxane as solvent. A plot of $\log C_0/C_t$ vs. time gave a straight line for several half-lives. Rate constants were measured under conditions of similar ionic strength, although the effect of added salt was very small. A sample run is shown in Figure 1. The pseudo-first-order rate constants were calculated by the method of least squares using a simple computer program⁶ and are shown in Table I. A graph of $\log k$ vs. pH for the two sulfonio esters gave good parallel straight lines over the pH range 7.2–10.3 with a slope of 1.0 (Figure 2). Thus, both esters follow the simple

(6) J. Casanova, Jr., and E. R. Weaver, *J. Chem. Educ.*, **42**, 137 (1965).

Table I. The Hydrolysis Rates of Methyl 4-Dimethylsulfonylphenylacetate *p*-Toluenesulfonate, Methyl 2-Dimethylsulfonylphenylacetate *p*-Toluenesulfonate, Methyl 4-Isopropylphenylacetate, and Methyl 2-Isopropylphenylacetate in 50% Aqueous Dioxane at Constant pH

Compd	Temp, °C	pH _{app}	$10^4 k_1$, sec ⁻¹	$10^4 k_1$, av, sec ⁻¹	
o-5	69.5	10.33	16,800	17,000	± 200
			17,200		
			17,000		
p-5			3,450	3,619	± 133
			3,810		
			3,580		
o-5		8.84	665	651	± 14
			638		
			121		
p-5			131	126	± 5
			295		
			344		
o-5		8.56	351	330	± 23
			65.5		
			67.0		
p-5			12.9	13.1	± 0.2
			13.2		
			1.95		
o-5		10.33	2.49	2.22	± 0.29
			7,530		
			2,200		
p-5			7,000	66.2	± 0.8
			1,570		
			1,553		
o-5		10.33	4,950	4,970	± 20
			4,990		
			929		
p-5			884	907	± 22
			3,190		
			2,910		
o-5		10.33	2,620	2,830	± 220
			2,600		
			500		
p-5			501	524	± 32
			572		
			12.9		
o-8		9.68	10.6	11.8	± 1.1
			32.9		
			29.9		
p-8			35.2	32.8	± 1.4
			33.1		

rate expression $-d(\text{ester})/dt = k(\text{ester})(\text{OH}^-)$. A summary of the calculated second-order rate constants for hydrolysis of the four esters at 69.5° is given in Table II. It can be seen that the *o*-sulfonio ester (*o*-5) is hydrolyzed 5.2 times faster than its *para* isomer (*p*-5). This rate order is reversed for the isopropyl esters (*o*-8 and *p*-8).

Table II. Second-Order Rate Constants for the Alkaline Hydrolysis of Methyl 4-Dimethylsulfonylphenylacetate *p*-Toluenesulfonate, Methyl 2-Dimethylsulfonylphenylacetate *p*-Toluenesulfonate, Methyl 4-Isopropylphenylacetate, and Methyl 2-Isopropylphenylacetate at 69.5° in 50% Aqueous Dioxane

Ester	k_2 , l. mole ⁻¹ sec ⁻¹	k_{ortho}/k_{para}	k_8/k_{Pr-i}
o-5	88.3 ± 4.8	5.2	356
p-5	17.1 ± 1.2		
o-8	0.248 ± 0.002	0.36	25
p-8	0.687 ± 0.003		

When the *ortho:para* rate ratio for sulfonium ester hydrolysis is corrected for steric rate retardation, which would operate in the hindered *ortho* ester but not in the

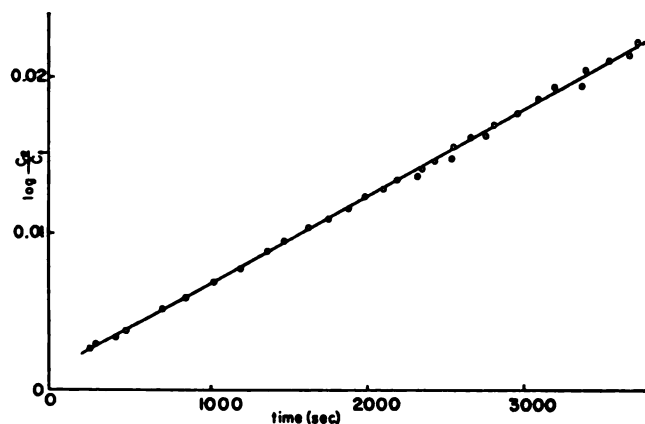


Figure 1. $\log C_0/C_t$ vs. time for the hydrolysis of methyl 2-dimethylsulfoniophenylacetate *p*-toluenesulfonate in 50% aqueous dioxane at pH 7.17 and 69.5° (run 026).

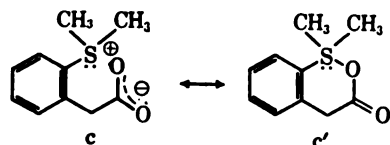
para, by dividing by the *ortho:para* rate ratio obtained for the isopropyl esters (*o*-8 and *p*-8), the ratio becomes 14. Contrasted with the magnitude of rate acceleration values which have been observed for systems in which nucleophilic neighboring group assistance is thought to occur efficiently⁷ (10^2 – 10^6), the enhanced reactivity in the present case is hardly significant.

To assess the importance of a neighboring sulfonium ion in stabilizing a negatively charged carboxyl derivative, the pK_a was measured for 2- and 4-dimethylsulfoniophenylacetic acids (*o*-3 and *p*-3). These values are shown in Table III. Although the resonance-stabilized car-

Table III. Acidity Constants of Carboxylic Acids Prepared in This Study, Measured in 45.0% w/w Dioxane–Water at 29°

Compd	pK_a
<i>o</i> -2	6.16
<i>p</i> -2	5.95
<i>o</i> -3	4.07
<i>p</i> -3	4.82

boxylate anion with a delocalized negative charge must be a poor model for the anticipated tetrahedral intermediate with a full negative charge localized on one oxygen atom, both effects operate in the same direction and the difference in acidity between the two acids should give an indication of the importance of stabilization of the tetrahedral intermediate during ester hydrolysis. The *o*-sulfonium acid (*o*-3) is seen to be more than 100 times stronger an acid than the corresponding methylthio acid (*o*-2), whereas the ratio between the *para* acids (*p*-3 and *p*-2) is close to 10. However, the difference in acidity between *o*-3 and *p*-3 is only 0.75 pK unit, which does not suggest considerable stabilization of the carboxylate anion by the neighboring sulfonium ion. In its ultimate form, stabilization could take the form of covalent bonding between the carboxylate anion and the sulfonium sulfur atom (*c'*).



(7) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 104–126.

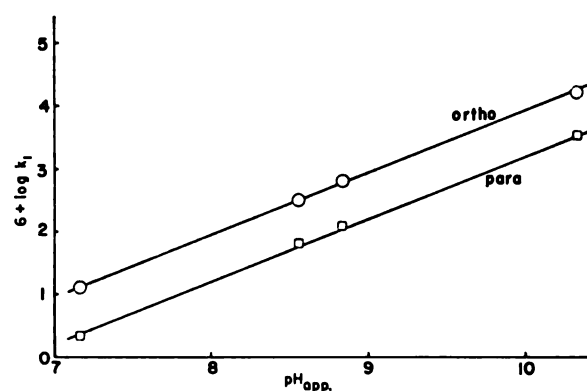


Figure 2. The pH-rate profile for the alkaline hydrolysis of methyl 4-dimethylsulfoniophenylacetate *p*-toluenesulfonate (*p*-5) and methyl 2-dimethylsulfoniophenylacetate *p*-toluenesulfonate (*o*-5).

The proton resonance spectra of the sulfonio acids (*o*- and *p*-3) in 2 *N* DCl and 2 *N* NaOD in D_2O were determined, and the chemical shift of the dimethylsulfonio protons was measured with respect to the chemical shift of the same protons in pure D_2O . If the covalent form (*c'*) made a significant contribution to the structure of the anion, then the methyl protons should show a substantial increase in shielding as the medium was changed from acidic to basic, and the species present became the carboxylate anion. The results of these measurements are shown in Table IV. Although the *ortho* zwitterion shows a slightly greater shielding than the *para*, the magnitude of the difference does not warrant invoking structure *c'* as a significant contributing form.

Table IV. The Chemical Shift of the Dimethylsulfonio Protons of 4-Dimethylsulfoniophenylacetic Acid and 2-Dimethylsulfoniophenylacetic Acid Measured in 2 *N* HCl and 2 *N* NaOH

Compd	Chemical shift, cps ^a	
	2 <i>N</i> HCl	2 <i>N</i> NaOH
<i>o</i> -3	+6.5 ^b	–17.0
<i>p</i> -3	+7.5	–4.5

^a Relative to the chemical shift of the dimethylsulfonio group in pure D_2O . ^b A positive number designated a shift downfield from the standard.

It might be anticipated that if the transition state for hydrolysis of *ortho* ester (*o*-5) involved covalent bonding to sulfur (*b'*) this difference would be reflected in a more negative ΔS^\ddagger for the *ortho* than for the *para* ester because of greater constraint in such a transition state. The activation parameters for the sulfonium esters were determined from the second-order rate constants for hydrolysis at pH 10.33 using rate measurements at four temperatures. The calculated values of E_a and ΔS^\ddagger are shown in Table V. The near coincidence of both the activation energy and the activation entropy for the two sulfonio esters suggests again that the rate differences between the esters should not be attributed to any fundamental differences in the mode of reaction.

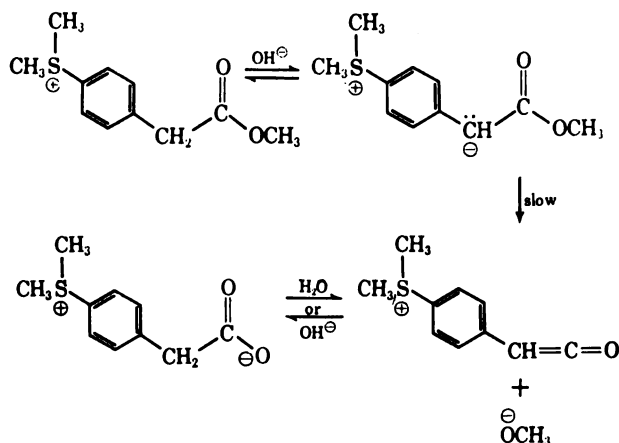
The magnitude and sign of the entropy of activation is itself very unusual and warrants comment. Most reactions which are bimolecular in the rate-controlling

Table V. Activation Parameters for the Hydrolysis of Methyl 2-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate and Methyl 4-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate at pH 10.33

Compd	E_a , kcal/mole ^a	ΔS^\ddagger , eu ^b
<i>o</i> -5	20.0 ± 1.0	$+6.4 \pm 2.9$
<i>p</i> -5	21.6 ± 1.0	$+7.9 \pm 2.9$

^a Calculated graphically from a plot of $\log k_2$ vs. $1/T$. These values are, within experimental error, the same as the values obtained from the expression $E_a = RT_1T_2 \ln (k_2/k_1)/(T_2T_1)$. ^b Calculated from the expression $k_2 = (ek_B T/h) \exp(\Delta S^\ddagger/R) \exp(-E_a/RT)$. L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

step exhibit an entropy of activation of about -20 eu.⁸ Although the magnitude of the activation energy observed here is similar to that reported for many ester hydrolysis reactions, the entropy of activation is 15–30 eu greater than anticipated.⁹ One interpretation of this result is that ester hydrolysis in the present case (both *ortho* and *para*) is not bimolecular in the rate-controlling step. A reasonable mechanism involving a ketene intermediate can be devised to accommodate that interpretation.¹⁰



Inductive and resonance stabilization of the enolate anion renders this mechanism an attractive possibility. Suggestions of the operation of this mechanism in the literature are rare.¹¹ A necessary condition for the intervention of this novel pathway is that the rate of exchange of α -hydrogen be at least as fast as the over-all hydrolysis rate. This has been determined to be the case for the *para* ester *p*-3, for which k_2 (exchange per hydrogen)/ k_2 (hydrolysis) is 8. Other experiments designed to test the interpretation stated above are in progress.

A recent report¹² of the kinetics of alkaline hydrolysis of several substituted ethyl acetates included the bro-

(8) K. B. Wilberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 387.

(9) M. L. Bender, R. D. Ginger, and J. P. Unik, *J. Am. Chem. Soc.*, **80**, 1044 (1958); A. Fischer, W. J. Mitchell, G. S. Ogilvie, J. Packer, J. E. Packer, and J. Vaughn, *J. Chem. Soc.*, 1426 (1958); E. Tommila, A. Nurro, R. Muren, S. Merenheimo, and E. Vuorinen, *Suomen Kemistilehti*, **32B**, 115 (1959); K. J. Laidler and D. Cheu, *Trans. Faraday Soc.*, **5b**, 1026 (1958); J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Am. Chem. Soc.*, **80**, 3458 (1958); A. Moffat and H. Hunt, *ibid.*, **81**, 2082 (1959); S. Sarel, L. Tsai, and M. S. Newman, *ibid.*, **78**, 5420 (1956); T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957); G. L. Nolan and E. S. Amis, *J. Phys. Chem.*, **65**, 1556 (1961); ref 1c, p 11.

(10) The authors are indebted to E. Cordes for pointing out this possibility.

(11) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 2901 (1965); ref 1c, p 8.

(12) R. P. Bell and B. A. W. Collier, *Trans. Faraday Soc.*, **61**, 1445 (1965).

mid salt of ethyl dimethylsulfonium acetate. The rate differences observed were attributed largely to electrostatic effects of substituent charges and dipoles, rather than to inductive effects. The possibility of covalent bonding between sulfur and the carbonyl group of the ester was not discussed. Inductive effects were dismissed as small in the sulfur-substituted series, based on the questionable assumption that electronegativity differences should be small in the series $RS^+(CH_3)_2$, $RSCH_3$, and RS^- . In addition, the data presented by these authors gives a straight line when plotted as $\log k_2$ vs. σ^* . Under the circumstances we feel that it would be premature to dismiss an inductive effect as unimportant in the sulfonium salts.

The magnitude of the *ortho:para* ratio for the sulfonio esters is small enough so that it could be interpreted in terms of an inductive effect alone. This is contrary to our assumption at the onset of this study. To the extent that the hydrolysis of sulfonium esters *o*-5 and *p*-5 follows a normal hydrolytic sequence, a supposition to which some doubt has been raised here, it is evident that neighboring sulfonium sulfur exerts a surprisingly small electrophilic enhancement of the rate of ester hydrolysis.

Experimental Section

***o*-Mercaptophenylacetic Acid (1).** This compound was prepared by the method of Pascal and Tarbell.¹³ The acid did not crystallize and was used directly in the preparation of the sulfide. The yield was 22%.

2-(Methylthio)phenylacetic Acid (*o*-2). A solution of 4.0 g of *o*-mercaptophenylacetic acid in 15 ml of absolute ethanol was added slowly to a warm solution of 3.01 g (0.024 mole) of dimethyl sulfate in 15 ml of 33% aqueous sodium hydroxide and heated at reflux for 0.5 hr. The ethanol was removed *in vacuo*, and approximately 10 ml of water was added. The solution was acidified with 6 *N* HCl and solid appeared. The solid recrystallized from chloroform, 1.31 g (30%), mp 127–129°. An infrared spectrum in chloroform showed strong absorption at 1715 cm^{-1} (s), 3600–2500 cm^{-1} (m). An nmr spectrum in $CDCl_3$ with tetramethylsilane as an internal standard showed a complex multiplet, centered at 7.32 ppm, a singlet at 3.86 ppm, and a singlet at 2.44 ppm with the area ratio 4:2:3, respectively.

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 58.91; H, 5.55; S, 17.59.

2-Dimethylsulfoniophenylacetic Acid *p*-Toluenesulfonate (*o*-3). 2-(Methylthio)phenylacetic acid (0.5 g, 2.7 mmoles), 1.0 g (5.4 mmoles) of methyl *p*-toluenesulfonate (Eastman, distilled), and 5 ml of toluene (reagent grade, dried over sodium) were heated overnight. An oil separated and the toluene was decanted. The oil was crystallized by trituration with methanol. The white solid was twice recrystallized by dissolving it in acetone containing a few milliliters of ethanol and then adding ethyl acetate to give 0.28 g (27%) of white solid, mp 153.0–153.5°.

Anal. Calcd for $C_{17}H_{20}O_5S_2$: C, 55.41; H, 5.47; S, 17.40. Found: C, 55.38; H, 5.55; S, 17.22.

4-(Methylthio)phenylacetic Acid (*p*-2). This compound was prepared in 45% yield by the method of Elderfield and Burgess,¹⁴ mp 93–95° (lit.¹⁴ 94–95°).

4-Dimethylsulfoniophenylacetic Acid *p*-Toluenesulfonate (*p*-3). 4-(Methylthio)phenylacetic acid (1 g, 5.4 mmoles), 2.0 g (10.8 mmoles) of methyl *p*-toluenesulfonate (Eastman, distilled), and 10 ml of anhydrous toluene were refluxed for 6 hr. The solid which had formed was collected on a filter and washed with benzene. The solid was twice recrystallized from ethanol–ethyl acetate to give 0.80 g (41%) of white solid, mp 180–182°.

Anal. Calcd for $C_{17}H_{20}O_5S_2$: C, 55.41; H, 5.47; S, 17.40. Found: C, 55.47; H, 5.56; S, 17.08.

pK_a Determinations. A standard solution of sodium hydroxide (0.0498 *N*) in 55.0% (by weight) of distilled water and 45.0% (by

(13) I. I. Pascal and D. S. Tarbell, *J. Am. Chem. Soc.*, **79**, 6015 (1957).

(14) R. C. Elderfield and K. L. Burgess, *ibid.*, **82**, 1975 (1960).

weight) of dioxane (purified by the Hess and Frahm method¹⁵) was the titrant. The general method of Albert and Serjeant¹⁶ was used to determine the pK_a values. The sample was dissolved in 55.0% (by weight) of water and 45.0% (by weight) of dioxane. A Leeds and Northrup pH meter was used, and the meter was standardized with both phthalate buffer (pH 4.00) and phosphate buffer (pH 6.86) before and after the measurements. During the measurement of pH, prepurified nitrogen gas was bubbled through Fieser's solution,¹⁷ reaction solvent, and into the cell. The calculation of the pK_a values was carried out as described elsewhere.¹⁸ Corrections for the hydrogen ion concentration were applied.

Methyl 4-(Methylthio)phenylacetate (p-4). A solution of 5.5 g (20 mmoles) of 4-(methylthio)phenylacetic acid, 10 ml of methanol (reagent grade), 10 ml of 2,2-dimethoxypropane (Dow Chemical Co.), and a few milligrams of *p*-toluenesulfonic acid monohydrate was stirred overnight at room temperature. The solution was concentrated *in vacuo* and then taken up in chloroform and washed in sodium bicarbonate and saturated aqueous sodium chloride. The dried chloroform solution was concentrated to give a tan liquid. Distillation of this liquid gave 3.0 g (51%), bp 178–180° (0.5 mm) [lit.¹⁹ 179–181° (3 mm)]. An infrared spectrum in chloroform showed no absorption between 3600 and 3200 cm^{-1} and strong absorption at 1735 cm^{-1} .

Methyl 4-Dimethylsulfonylphenylacetate *p*-Toluenesulfonate (p-5). Methyl ester *p*-4 (3 g, 0.015 mole) and methyl *p*-toluenesulfonate (3.6 g, 0.019 mole) (Eastman, distilled) were heated at 100° for 3 hr. After cooling to room temperature the reaction mixture solidified. The solid was first washed with ethyl ether and then collected on a filter. Recrystallization from dioxane-methanol gave 5.0 g (87%) of a white solid, mp 145–147°.

Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_6\text{S}_2$: C, 56.52; H, 5.80; S, 16.77. Found: C, 56.35; H, 5.80; S, 16.40.

Methyl 2-(Methylthio)phenylacetate (o-4). A solution of 3.7 g (0.020 mole) of 2-(methylthio)phenylacetic acid, 15 ml of absolute methanol, 10 ml of 2,2-dimethoxypropane (Dow Chemical Co.), and a few milligrams of *p*-toluenesulfonic acid monohydrate was heated at reflux for 4 hr. The dark solution was concentrated *in vacuo*, taken up in chloroform, and washed with sodium bicarbonate solution and saturated aqueous sodium chloride solution. The chloroform solution was dried and distilled to give 2.8 g (72%) bp 99–100° (0.75 mm); n_D^{20} 1.5632. An infrared spectrum in chloroform showed no absorption between 3600 and 3200 cm^{-1} and strong absorption at 1730 cm^{-1} .

Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{S}$: C, 61.20; H, 6.16; S, 16.34. Found: C, 61.14; H, 6.08; S, 16.13.

Methyl 2-Dimethylsulfonylphenylacetate *p*-Toluenesulfonate (o-5). A solution of 2.8 g (0.014 mole) of methyl ester *o*-4 and 3.2 g (0.017 mole) of methyl *p*-toluenesulfonate (Eastman, distilled) was heated at 100° for 3 hr. The reaction mixture was cooled to room temperature and a solid formed which was washed with ethyl ether and collected on a filter. The white solid was recrystallized from 2-butanol to give 2.5 g (46%) of a white solid, mp 156–158°. A second crop of 1.2 g (22%) was obtained.

Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_6\text{S}_2$: C, 56.52; H, 5.80; S, 16.77. Found: C, 56.15; H, 5.74; S, 16.54.

2- and 4-Isopropylbenzyl Bromides (o- and p-6). Into a solution of 120 ml of (48%) HBr, 93 g of cumene, 39 g of paraformaldehyde, and 200 mg of red phosphorus, gaseous HBr was bubbled for 6 hr while the mixture was stirred vigorously. After 20 min the reaction mixture became hot and was cooled for 30 min in an ice bath until all paraformaldehyde was dissolved and no further exothermic reaction was observed. It was then held at 55° for 18 hr. The organic layer was separated, washed with water, and dried over MgSO_4 .

Distillation at 64° (0.5 mm) yielded 141.8 g (77%) [lit.¹⁹ bp 126–130° (20 mm)].

2- and 4-Isopropylbenzyl Cyanides (o- and p-7). Potassium cyanide (60 g) was dissolved with stirring in 70 ml of water. After addition of 60 ml of ethanol, the solution was cooled with ice and 140 g of the bromide (*o*- and *p*-6) in 60 ml of ethanol was added over a period of 30 min. The reaction mixture was then stirred at room temperature for 2 hr. The solid KBr was removed by filtra-

tion and the alcohol evaporated. The oily layer was washed with water and extracted with ether. The ether solution was dried over MgSO_4 and evaporated. Distillation on a Vigreux column, 92° (0.5 mm), yielded 96.5 g (93%) of product.

Methyl 2- and 4-Isopropylphenyl Acetates (o- and p-8). The mixed cyanides (*o*- and *p*-7), 96.5 g, in 180 ml of methanol and 80 ml of concentrated sulfuric acid were refluxed for 20 hr. Water was added, and the resulting oil was extracted into ether, washed with 10% NaHCO_3 and water, dried, and distilled, bp 68–83° (0.5 mm), 77 g (66%). This material was distilled on a spinning-band column and collected in three fractions (see Table VI). The first distillation fraction was separated by preparative glpc on a 10-ft Carbowax 20M column, 185°, and the esters (8) collected were redistilled.

Table VI

Bp, °C (0.5 mm)	Glpc, %		Wt, g
	<i>ortho</i>	<i>para</i>	
86–90	27.5	72.5	15
96	15	85	40
96–98	6	94	15

Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$ [*ortho*: bp 78° (1 mm)]: C, 74.96; H, 8.39. Found: C, 74.94; H, 8.43. Found [*para*: bp 80° (0.2 mm)]: C, 75.39; H, 8.51.

Kinetics Procedure. The dioxane used was commercial grade, purified by the method of Hess and Frahm.¹⁵ Standard sodium hydroxide solutions were prepared in the reaction solvent so that the composition of the solvent would not be changed during the reaction. The concentration of the sodium hydroxide solution was between 10^{-3} and 10^{-2} *N*, so as to give about 2 ml volume change, depending on the rate of the hydrolysis reaction.

A solution (50 ml) of 50.0% (by volume) dioxane and 50.0% (by volume) water was pipetted into a jacketed reaction cell which was equipped with a Beckman amber glass electrode and a Beckman silver chloride reference electrode, an automatic buret, the tip of which was immersed in the reaction solution, and a water condenser. The reaction solution was stirred magnetically under an atmosphere of prepurified nitrogen. The solvent was allowed to equilibrate thermally for 1 hr in the cell. During the equilibration period, the pH of the solution was adjusted to the desired regulation point by the addition of a very small amount of either acid or base. Either 100 or 50 mg of sample was added to the reaction cell.

Base was added automatically in small increments to maintain the pH constant to ± 0.04 unit. The buret was driven by a relay which was activated by imbalance in a 1:10 scale-expanded pH meter. The results were recorded automatically on a chart. First-order rate constants were calculated by the method of least squares using an IBM 1620 computer.⁶

The nature of the hydrolysis products was confirmed by carrying out several reactions in nmr tubes and identifying methanol and the carboxylic acids which formed by their characteristic spectra.

α -Methylene Exchange and Hydrolysis Rates by Nmr. A sample of *p*-5 (54.7 mg, 0.143 mmole) was dissolved in 0.50 ml of $\text{K}_2\text{BO}_3\text{--H}_3\text{BO}_3$ buffer in D_2O (pH 10.69), and the sample was immediately frozen to -78° . The proton resonance spectrum was followed at 36.5° as a function of time. The α -methylene exchange rate was calculated by comparing one-half of the methylene peak integral to an internal standard (3 H from the *p*-toluenesulfonate anion). A plot of $\log [0.5(\text{area CH}_2)/(\text{area CH}_3(\text{tosyl}))]$ vs. time gave a straight line, from which a pseudo-first-order rate constant for α -hydrogen exchange was obtained. The result is shown below. By determining the area under the ester CH_3 peak, relative to that under the tosyl CH_3 peak during the reaction, or by plotting a graph of $\log [\text{area CH}_3(\text{ester})/(\text{area CH}_3(\text{ester}) + \text{area CH}_3(\text{methanol}))]$ vs. time, a straight line could be obtained which measured the over-all hy-

Table VII

	$10^4 k_1$, sec^{-1}	k_2 , l. mole^{-1} sec^{-1}
Exchange, per H	18	3.7
Hydrolysis	2.3	0.47

(15) K. Hess and H. Frahm, *Ber.*, **71B**, 2627 (1938).

(16) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co., Ltd., London, England, 1962.

(17) L. Fieser, *J. Am. Chem. Soc.*, **46**, 2639 (1924).

(18) J. W. Corse, R. G. Jones, Q. F. Soper, C. W. Whitehead, and O. K. Behrens, *ibid.*, **70**, 2837 (1948).

(19) I. N. Nazarova and A. V. Semenovskii, *Otd. Khim. Nauk*, **840** (1957).

hydrolysis rate constant. The values are shown below, and compare quite favorably with those obtained by the titrimetric method shown in Table VII.

Acknowledgment. The work described in this paper was supported financially by a grant from the National Institutes of Health (CA-6369), for which the authors

are grateful. J. C. is particularly indebted to the Chemistry Department of Indiana University for an appointment during the academic year 1965-1966, during which period this manuscript was prepared. The authors further acknowledge helpful discussions with Professor Eugene Cordes of that department.

Dimethyl Sulfoxide-Acid Anhydride Mixtures for the Oxidation of Alcohols

J. Donald Albright and Leon Goldman

Contribution from the Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965. Received December 22, 1966

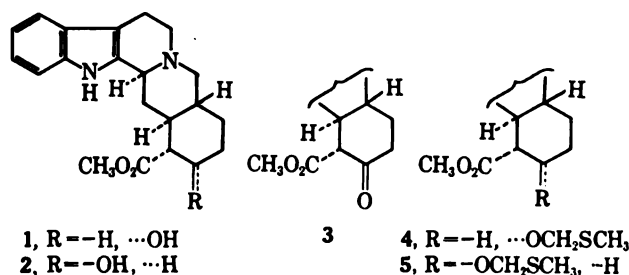
Abstract: Oxidation of alcohols with dimethyl sulfoxide and acetic anhydride is reported. The conversion of secondary hydroxyl functions to ketones in a variety of alkaloids and steroids occurs in moderate to excellent yields. The dimethyl sulfoxide-acetic anhydride oxidation procedure is particularly useful for oxidation of sterically hindered hydroxyl groups and for oxidation of hydroxyl functions in sensitive molecules such as indole alkaloids. The mechanism of oxidation is discussed. By-products often formed are methylthiomethyl ethers of the starting alcohols.

Our continued interest in improved methods for the oxidation of secondary hydroxyl groups of indole alkaloids¹ to ketones led to the discovery of a novel method of oxidation of alcohols to their corresponding carbonyl derivatives with dimethyl sulfoxide (DMSO) and acetic anhydride.² Oxidation of alcohols with acetic anhydride-DMSO is a mild oxidative method and is particularly useful with indole alkaloids which are sensitive to nonselective oxidizing reagents. In addition this procedure gives good yields with sterically hindered hydroxyl groups and has been applied to a number of steroids. However, it is obvious that this method will fail in cases where alcohols are rapidly acetylated under the conditions of the reaction, for O-acetylation will then effectively compete with oxidation.

In general, the procedure consists of stirring a solution of the alcohol in a mixture of DMSO and acetic anhydride for 15-24 hr at room temperature. Dimethyl sulfoxide has been used as both solvent and reagent, although there is no reason to believe that an inert diluent is deleterious. In our original experiments a ratio of 20 moles of acetic anhydride to 1 mole of alcohol was employed; however, such a large excess of acetic anhydride is not necessary. Successful oxidations have been carried out with 3-5 moles of anhydride per mole of alcohol.

Optimal conditions for the reaction and variations which could be employed were determined using yohimbine (1) as substrate. The reaction of 1 (1 mmole), 3 ml of DMSO, and 2 ml (*ca.* 20 mmoles) of acetic anhydride was followed by periodically removing aliquots

and determining the extent of reaction by thin layer chromatography (tlc) on silica gel. In 4-5 hr the reaction was approximately 50% complete and in 12 hr no more starting material remained. Yohimbine³ (3) was isolated in 80% yield at the end of this time. No reduction in the yield was observed on decreasing the molar ratio of alcohol 1 to acetic anhydride to 1:5.



Certain other acid anhydrides can be used in place of acetic anhydride. Benzoic anhydride (17 moles) and yohimbine (1 mole) in DMSO at room temperature for 22 hr afforded 82% of β -keto ester 3. However trifluoroacetic anhydride and *p*-toluenesulfonic anhydride were not effective. Based on plausible mechanistic considerations (*vide infra*) anhydrides unreactive to DMSO should be unsatisfactory as should overly reactive ones. Phosphorus pentoxide⁴ and polyphosphoric acid were studied briefly with the following results. Yohimbine (1) (1 mole) and phosphorus pentoxide (1 mole) in DMSO at 65° for 18 hr gave yohimbine-3-one (3) in 45% yield. Polyphosphoric acid and 1 at room temperature for 41 hr afforded 3 in 51%

(1) For a previous study of oxidation of alcohols see J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965).

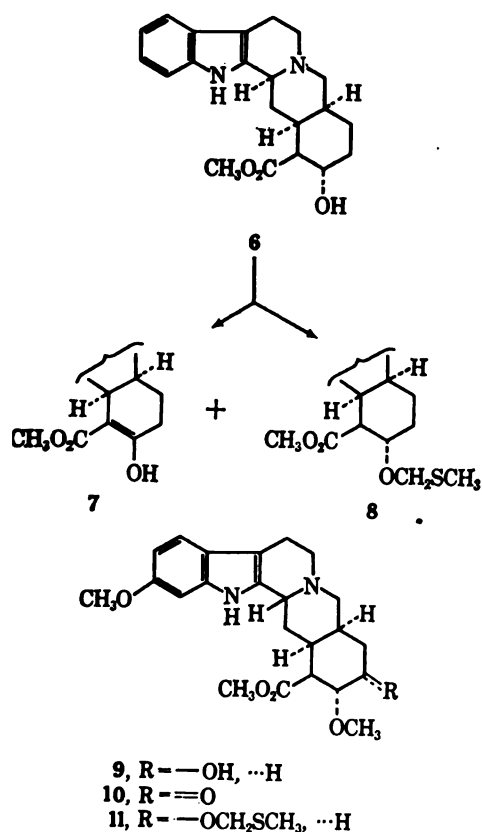
(2) See J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965), for preliminary communication of this work; for application of this method in the carbohydrate field see W. Sowa and G. H. S. Thomas, *Can. J. Chem.*, **44**, 836 (1966).

(3) M.-M. Janot, R. Goutarel, E. W. Warnhoff, and A. Le Hir, *Bull. Soc. Chim. France*, 637 (1961).

(4) The oxidation of alcohols to ketones in the carbohydrate field with DMSO-phosphorus pentoxide has been described recently: K. Onodera, S. Hirano, and N. Kashimura, *J. Am. Chem. Soc.*, **87**, 4651 (1965).

Oxidation of testosterone with polyphosphoric acid in DMSO at room temperature was unsatisfactory. Oxidation of ajmaline with phosphorus pentoxide at 65° (multiplicity of products on tlc). Use of sulfoxides other than DMSO was briefly investigated. For example, with tetramethylene sulfoxide, ajmaline (1) (1 mole) and acetic anhydride (21 moles) gave ajmalinone (3) in 80% yield, while diphenyl sulfoxide gave no oxidation. These limited results showed that sulfoxides reactive to acid anhydrides will give oxidation as anticipated from mechanistic considerations.

Yohimbine (1) undergoes oxidation with acetic anhydride to give yohimbine (3) in 70% yields, this method constitutes a superior procedure for the preparation of 3.^{6,7} In the oxidation of 1 to 3 a small amount of a second product was isolated. From a large-scale oxidation of 1 the minor product was isolated and identified as methyl 17 α -(methylthio)methoxy]yohimban-16 α -carboxylate (4). The NMR spectrum (in δ) of 4, with singlets at 2.10 (OCH₃) and 3.73 (OCH₂S) and an AB quartet centered at 4.5 (OCH₂S), demonstrated the presence of the methylthiomethoxy group and established the structure. The application of the DMSO-acetic anhydride oxidation procedure to a variety of substrates was undertaken to further define the utility of the method and to obtain information bearing on the mechanism of the oxidation. β -Yohimbine (2), which differs from 1 only in the configuration of the C-17 hydroxyl group (equatorial),



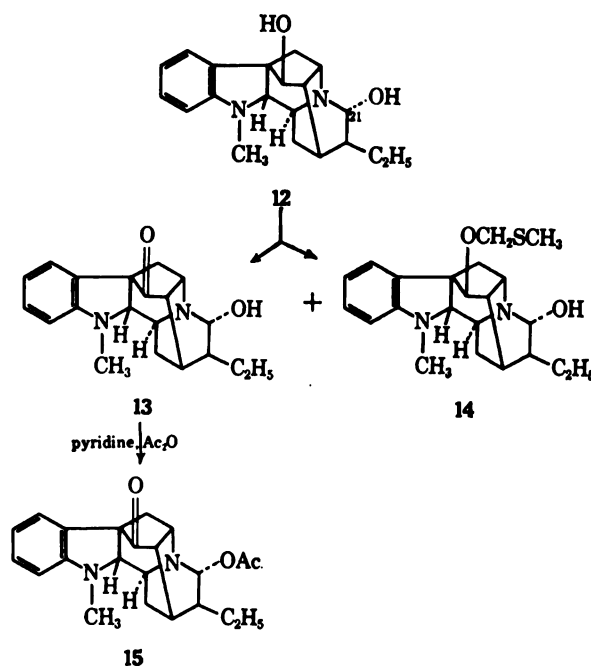
* reactivity of sulfoxides to anhydrides (Pummerer rearrangement, R. Pummerer, *Ber.*, 43, 1401 (1910); L. Horner and P. Kaiser, *ibid.*, 19 (1959)).

himbine (1) was oxidized to 3 (80%) with dicyclohexylcarbodiimide and phosphoric acid.¹

torial in 2 *vs.* axial in 1), was completely converted to a 50:50 mixture (determined by tlc and integration of pmr signals) of ketone 3 and methylthiomethoxy derivative 5. Chromatography on silica gel afforded 25% of 3 and 18% of 5. In a similar manner α -yohimbine (6) (equatorial hydroxyl) afforded equal amounts of two components which were separated by chromatography to give 40% of crude methyl 17-hydroxyalloyohimb-16-ene-16-carboxylate¹ (7) and 10% of methylthio-methyl ether 8.

Methyl reserpate (9) (equatorial hydroxyl) afforded 33% of methyl ketoreserpate⁸ (10) and 11% of methyl reserpate methylthiomethyl ether (11).

Ajmaline (12) has two possible sites for oxidation, the C-17 hydroxyl and the C-21 carbinolamine hydroxyl. However, oxidation with DMSO-acetic anhydride, followed by treatment of the product with methanolic sodium hydroxide to hydrolyze O-acetates, gave ajmalidine⁹ (13) (52% as a glass) and methylthiomethoxy derivative 14 (10%). Difficulties were encountered in crystallizing ajmalidine. From the glass crystalline 13 (4% from 12) was obtained with the expected spectral

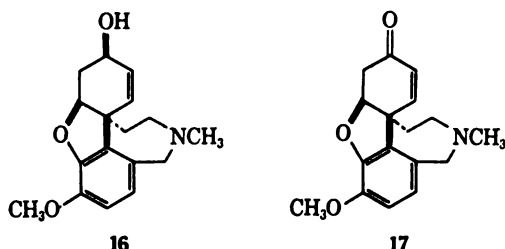


(infrared, ultraviolet, pmr) properties. Thin layer chromatography and pmr spectral data indicated that both the glass and the crystalline material were identical. Furthermore, treatment of the glass with acetic anhydride-pyridine gave, in 68% yield, the same O-acetate **15** as was obtained from crystalline **13**. That ajmalidine O-acetate (**15**) is one of the original products of the oxidation was shown by isolation of **15** when the methanolic base treatment was eliminated from the product work-up. On a larger scale (0.04 mole) oxidation of ajmaline (**12**), crystalline ajmalidine (**13**) was obtained in 25% yield along with 18% of methylthiomethoxy derivative **14**.

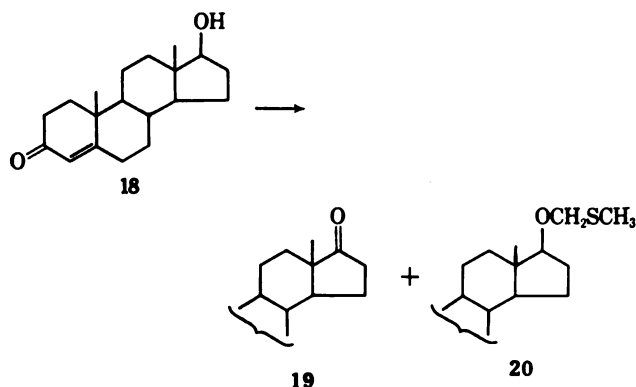
(8) M. M. Robison, W. G. Pierson, R. A. Lucas, I. Hsu, and R. L. Dziemian, *J. Org. Chem.*, **28**, 768 (1963).

(9) (a) M. Gorman, N. Neuss, C. Djerassi, J. P. Kutney, and P. J. Scheuer, *Tetrahedron*, **1**, 328 (1957); (b) C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakrashi, *J. Am. Chem. Soc.*, **79**, 1217 (1957); (c) C. Djerassi, M. Gorman, S. C. Pakrashi, and R. B. Woodward, *ibid.*, **78**, 1259 (1956); (d) S. C. Pakrashi, C. Djerassi, R. Wasicky, and N. Neuss, *ibid.*, **77**, 6687 (1955).

Oxidation¹⁰ of galanthamine (16), an allylic alcohol, with DMSO and acetic anhydride gave narwedine¹¹ (17) in moderate yield, while oxidation of codeine to codeinone was unsuccessful.

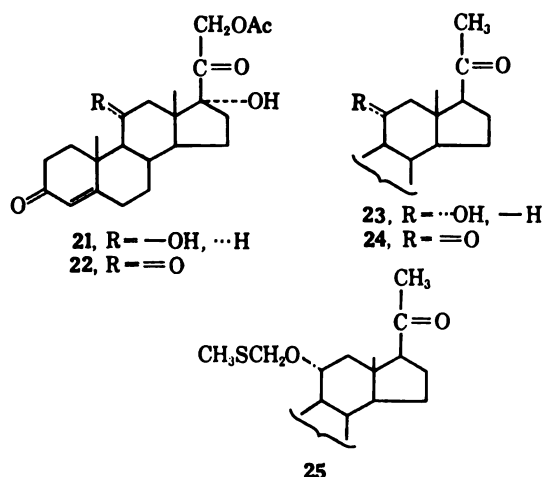


The oxidation of a number of steroidal alcohols was studied. Tlc showed that testosterone (18) is oxidized with DMSO-acetic anhydride to give approximately 70% of 4-androstene-3,17-dione¹² (19) and 30% of

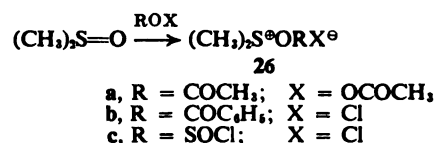


17β-[(methylthio)methoxy]-4-androsten-3-one¹³ (20). Chromatography afforded 34% of 19 and 8% of 20. The effect of the configuration of the hydroxyl group on the product composition was vividly demonstrated by comparison of the oxidation of hydrocortisone 21-acetate (21) (axial 11β-hydroxyl) and 11α-hydroxyprogesterone (23) (equatorial hydroxyl). The sterically hindered 11β-hydroxyl group of 21 was oxidized smoothly but slowly (92 hr at room temperature) to give cortisone 21-acetate¹⁴ (22) (53% by direct crystallization of the product). In contrast, 11α-hydroxyprogesterone (23) afforded, after partition chromatography, two major components, the larger of which was a gum (56%) identified by its pmr spectrum as methylthiomethoxy derivative 25. The second component (30% as glass) was crystallized to give 11-ketoprogesterone¹⁵ (24) in 13% yield. It is of interest that oxidation of 23 with dicyclohexylcarbodiimide (DCC), DMSO, and pyridinium trifluoroacetate has been reported by Pfitzner and Moffatt¹⁶ to proceed smoothly while no oxidation was observed with 21.

Some conclusions about the mechanism of oxidation of alcohols with DMSO and acid anhydrides can be



drawn. Carboxylic acid anhydrides are known to react with sulfoxides to give α-acyloxy sulfides^{5,17} and recently carboxylic acids have been shown to react with phosphorus pentoxide and DMSO to give α-acyloxy sulfides.¹⁸ The reaction of thionyl chloride and acid chlorides such as benzoyl chloride with sulfoxides has been shown¹⁹ to give α-chloro sulfides. All these reactions have one feature in common in that they are best visualized as proceeding by reaction of an electrophile on the electronegative oxygen atom of the sulfoxide to give intermediate oxysulfonium salts of type 26.

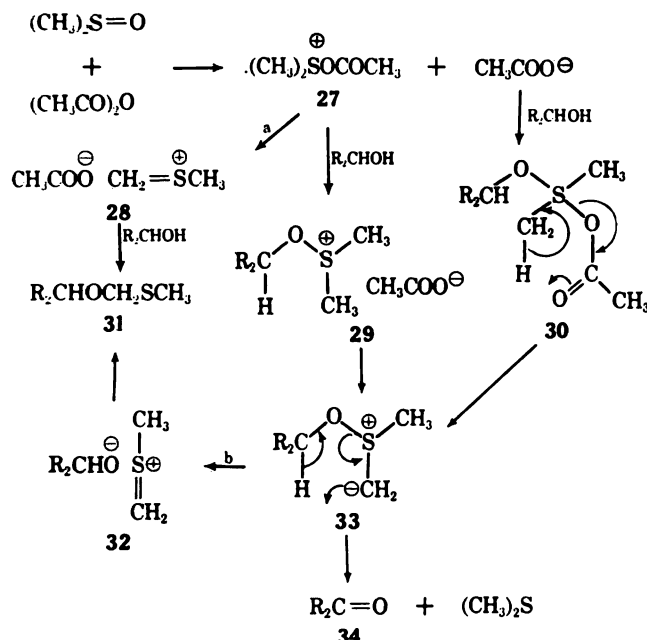


We were led to consider an oxidation sequence involving activation of DMSO to give an intermediate of type 26 by the evidence for such intermediates and by reasoning that they might react with an alcohol *in situ*. Such S_N2 displacements with alkoxysulfonium salts²⁰ have been demonstrated recently. Alkoxysulfonium salt 26 (wherein R = alkyl or cycloalkyl) could be reasonably expected to collapse in the presence of a base to give carbonyl products. The oxidation of α-bromoketones and alkyl tosylates with DMSO and base is based on similar mechanistic principles.²¹ The sequence of reactions in Chart I can be considered for the oxidation of alcohols with DMSO-acetic anhydride. The acyloxysulfonium salt 27 is first formed, and nucleophilic attack of an alcohol on the positively charged sulfur atom of 27 with back-side displacement of acetate ion occurs to give alkoxysulfonium salt 29. Base-promoted removal of a proton from the methyl group of 29²² then gives the sulfur stabilized ylid 33 which, through a cyclic transition state, collapses to give

- (10) Experiment carried out by E. Benz of these laboratories.
 (11) D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 806 (1962).
 (12) E. S. Wallis and E. Fernholz, *J. Am. Chem. Soc.*, 57, 1511 (1935).
 (13) Compound 20 has also been isolated in the oxidation of 19 with dicyclohexylcarbodiimide, DMSO, and phosphoric acid: K. E. Pfitzner and J. G. Moffatt, *ibid.*, 87, 5670 (1965); J. B. Jones and D. C. Wigfield, *Tetrahedron Letters*, 4103 (1965), have also isolated methylthiomethoxy derivatives in oxidations with DCC and DMSO.
 (14) T. Reichstein, *Helv. Chim. Acta*, 20, 978 (1937).
 (15) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, *J. Am. Chem. Soc.*, 74, 5933 (1952).
 (16) K. E. Pfitzner and J. G. Moffatt, *ibid.*, 85, 3027 (1963); 87, 5670 (1965).

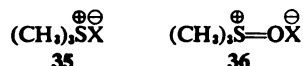
- (17) S. Oak, T. Kitao, S. Kawamura, and Y. Kitaoka, *Tetrahedron*, 19, 317 (1963); W. E. Parham and M. D. Bhavsar, *J. Org. Chem.*, 28, 2686 (1963); W. E. Parham and S. H. Groen, *ibid.*, 30, 728 (1965).
 (18) K. Onodera, S. Hirano, N. Kashimura, and T. Yajima, *Tetrahedron Letters*, 4327 (1965).
 (19) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, 77, 572 (1955).
 (20) C. R. Johnson, *ibid.*, 85, 1020 (1963); C. R. Johnson and W. G. Phillips, *Tetrahedron Letters*, 2101 (1965).
 (21) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Am. Chem. Soc.*, 81, 4113 (1959); N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Zevand, and W. M. Weaver, *ibid.*, 79, 6562 (1957).
 (22) See ref 20 for the reactions of alkoxysulfonium salts with alkoxides.

Chart I



carbonyl derivative **34** and dimethyl sulfide. Fenselau and Moffatt²³ have recently demonstrated that, in oxidations of alcohols with sulfoxides and carbodiimides, sulfur ylid **33** is an intermediate and showed that proton abstraction is intramolecular.

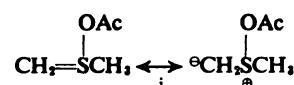
If an alkoxy-sulfonium salt **29** is an intermediate in oxidations with DMSO-acetic anhydride, acetate anion must be serving as the base to remove a proton from alkoxy-sulfonium salt **29** to give ylid **33**. That acetate is a strong enough base for this step is expected, since it is known that protons of methyl groups attached to sulfur in trimethylsulfonium and trimethyloxosulfonium salts **35** and **36** are readily exchanged²⁴ with D₂O.



The possibility that an alkoxy-sulfonium salt **29** is not an intermediate in oxidations with DMSO-acetic anhydride must be considered. Thus, nucleophilic attack of an alcohol on acyloxysulfonium salt **27** without displacement of acetate ion would give a neutral tetrasubstituted sulfur intermediate **30**. Collapse of **30** in a cyclic mechanism (loss of acetic acid) would give the ylid **33** directly without the intermediacy of alkoxy-sulfonium salt **29**. The recent report²⁵ that isobutoxydimethylsulfonium tetraphenylborate gave only traces of carbonyl compounds under DMSO-acetic anhydride oxidative conditions would appear to indicate that alkoxy-sulfonium salts **29** are not intermediates. However, these results do not definitively rule out intermediate **29**. In DMSO-acetic anhydride oxidations, 1 mole of acetate anion is produced for each mole of alkoxy-sulfonium ion formed. In the absence of an alcohol acetic anhydride and DMSO produce intermediate **27** which undergoes Pummerer rearrangement to acetoxymethyl methyl sulfide (**37**) and acetic acid. Thus acetate anion is not available for removal of

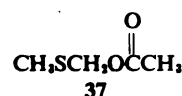
a proton from the preformed alkoxydimethylsulfonium tetraphenylborate to give ylid **33**. It would be instructive to know whether addition of potassium acetate would promote the conversion of alkoxy-sulfonium salts to carbonyl products.

Several pathways for formation of methylthiomethyl ethers are possible, either through an independent competitive reaction *via* intermediate **28** (path a) or by rearrangement of ylid **33** (path b). If methylthiomethyl ether **31** is, indeed, formed by rearrangement of ylid **33**, it is difficult to reconcile the greater yields of methylthiomethoxy derivative **31** in oxidations with DMSO and acetic anhydride than with carbodiimides and DMSO.¹⁶ With the same intermediate ylid **23** involved in both oxidations, similar amounts of rearranged product would be expected, and this is not observed. Therefore, it appears unlikely that rearrangement of ylid **33** is the sole source of methylthiomethoxy derivative. If, however, a competitive reaction is occurring involving intermediate **28**²⁶ a greater amount of ether



31 in oxidations involving DMSO-acetic anhydride than in oxidations with carbodiimides may be expected, for a solvated form of **28**, or more likely an ion pair with acetate anion, may be an intermediate in this reaction as well as in the Pummerer rearrangement⁵ reaction. With DMSO-acetic anhydride the Pummerer rearrangement and oxidation are occurring concurrently.

Another pathway for the formation of methylthiomethoxy derivatives was also considered. It is conceivable that under the mildly acidic conditions of the reaction, acetoxymethyl methyl sulfide (**37**) and an alcohol might give ether **31**, for acetoxymethyl methyl sulfide (**37**)⁵ is an acetylated hemithioacetal of formaldehyde. This possibility was eliminated when it was found that acetoxymethyl methyl sulfide (**37**) and alcohols such as



yohimbine and β -yohimbine do not give methylthiomethoxy derivatives under the conditions of the oxidation either in the presence or absence of acetic acid.

Some qualitative information about the rate of reaction of acetic anhydride and DMSO was obtained by the observation that a mixture of acetic anhydride and DMSO (slight excess) still contained unreacted acetic anhydride after standing at room temperature for 1 month. This aged mixture converted β -yohimbine (**2**) to yohimbine (**3**) and methylthiomethoxy derivative **5** very slowly at room temperature, but heating at 65–70° for 7 hr gave complete conversion to β -keto ester **3** (50%) and ether **5** (50%). Yohimbine, on heating with the 1 month aged DMSO-acetic anhydride mixture for 9 hr at 65–70° was converted to a 50:50 mixture of ketone **3** and ether **4**. The increase in methylthiomethoxy derivative from yohimbine on oxidation in aged DMSO-acetic anhydride is due to the presence of acetic acid. The use of acetic acid as solvent in the oxidation of testosterone with equimolar

(23) A. H. Fenselau and J. G. Moffatt, *J. Am. Chem. Soc.*, **88**, 1762 (1966).

(24) W. von E. Doering and A. H. Hoffman, *ibid.*, **77**, 521 (1955); G. S. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958).

(25) K. Torssell, *Tetrahedron Letters*, 4445 (1966).

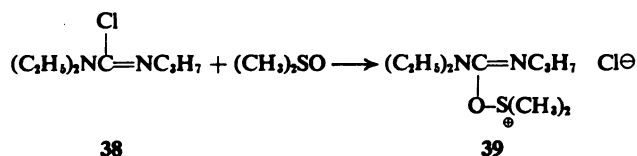
(26) It is conceivable that ylid **i** is the reactive intermediate in formation of ether **31** although this possibility appears unlikely.

amounts of acetic anhydride and DMSO leads to ca. 65% of methylthiomethoxy derivative 20 after 6 days at room temperature. In addition, testosterone O-acetate and 4-androstene-3,17-dione (19) were formed as evidenced by tlc.

The difference in product composition observed between compounds with an axial or equatorial hydroxyl group deserves further comment. The increased amounts of methylthiomethoxy derivative with compounds having an equatorial hydroxyl group may be explained on the basis of two independent pathways, one for oxidation (*via* intermediates 29 or 30 and ylid 33) and one for methyl thiomethyl ether formation (*via* ion pair 28). It is then necessary to postulate that the less hindered equatorial alcohol reacts sufficiently faster with ion pair 28 than an axial alcohol due to steric factors. If ylid 33 is the intermediate for both oxidation and ether formation and the rate-determining steps are collapse of ylid with abstraction of the hydrogen on the carbinol carbon and rearrangement, a faster rate of oxidation of sterically hindered hydroxyl groups (steric assistance) would explain the fact that axial alcohols give more ketone and less ether derivative. A faster rate of oxidation of sterically hindered hydroxyl groups has been observed in chromic acid oxidations of steroidal alcohols²⁷ and these results were rationalized in terms of steric assistance.²⁷

Without definitive rate data no conclusive choice between alternative mechanisms can be made. However, we believe methylthiomethoxy derivatives 31 are formed in a pathway independent of the oxidative sequence rather than by rearrangement of ylid 33 (*via* ion pair 32). This belief rests mainly on the fact that little rearrangement of ylids of type 33 is observed in oxidations with DMSO, DCC, and phosphoric acid.^{1,13,16,23}

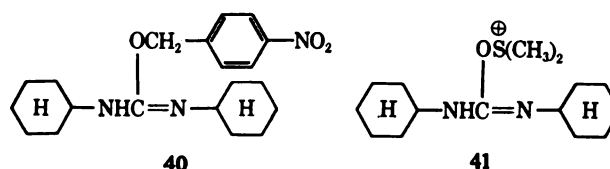
The fact that trifluoroacetic anhydride and *p*-toluenesulfonic anhydride were unsatisfactory was mentioned previously and is readily understood on the basis of mechanistic considerations. For successful oxidations the intermediate acyloxysulfonium salt must be stable enough and present in sufficient concentration to allow nucleophilic attack by an alcohol to occur. With a very reactive anhydride, the acyloxysulfonium salt will rearrange (Pummerer reaction) too rapidly to allow subsequent reactions with it. Experimentally trifluoroacetic anhydride reacts violently with DMSO at room temperature. Probably for similar reasons a mixture of 1-chloro-N,N-diethyl-N'-propylformamidine²⁸ (39) and DMSO failed to oxidize testosterone. Alcohols react rapidly with chloroformamidine 38 and, therefore, intermediate 39 must be preformed. However, 39 may go on to other products too rapidly for subsequent reaction with an alcohol.



(27) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955); E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 289.

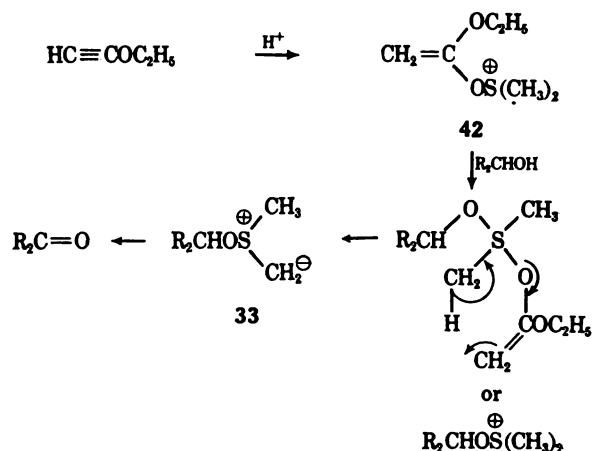
(28) Prepared by R. B. Conrow of these laboratories from N,N-diethyl-N'-propylurea and phosgene.

Further evidence that oxidations of alcohols by reagents prepared from mixtures of DMSO and suitable electrophiles proceeds *via* oxy-sulfonium salts, and that this is a general phenomenon was provided by experiments with ¹⁸O-labeled alcohols. Oxidation of benzhydrol-¹⁸O (4.8% ¹⁸O) with DCC, DMSO, and phosphoric acid gave unlabeled N,N'-dicyclohexylurea and 42% of the ¹⁸O was found in the benzophenone isolated.²⁹ Oxidation of ethanol-¹⁸O (1.9% ¹⁸O) afforded N,N'-dicyclohexylurea with only 16% of ¹⁸O label.³⁰ In addition pseudourea 40³¹ was unaffected by the oxidizing reagent. These results indicate that DCC and DMSO interact to give sulfonium salt 41 which reacts



with alcohols to give alkoxy-sulfonium salts. Similar conclusions have been reached by Fenselau and Moffatt.²³

Testosterone was found to be oxidized to 4-androstene-3,17-dione by a mixture of ethoxyacetylene, DMSO, pyridine, and phosphoric acid. Mechanistically the reaction may be illustrated as follows.



Protonation of ethoxyacetylene followed by reaction with DMSO gives intermediate 42 which then reacts with an alcohol. Tlc demonstrated that no testosterone O-acetate was formed in the reaction.

Experimental Section

All melting points were taken on a Mel-Temp apparatus and are uncorrected. Samples for analysis were dried *in vacuo* over phosphorus pentoxide at 100° for 18–24 hr. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Pmr spectra were determined with a Varian Model A-60 spectrometer in deuterated chloroform or deuterated dimethyl sulfoxide; chemical shifts (δ) are in parts per million

(29) Per cent ¹⁸O was determined by mass spectral analysis. Partial loss of label in the benzophenone probably resulted from exchange with solvent during aqueous acidic work-up.

(30) If ethanol were added to the DCC the N,N'-dicyclohexylurea should have been extensively labeled with ¹⁸O. The small incorporation of label may have occurred from reaction of DCC with water-¹⁸O produced by aldol condensation of the acetaldehyde-¹⁸O formed in the oxidation.

(31) Prepared by the method of E. Schmidt and F. Moosmüller, *Ann.*, **597**, 235 (1955); E. Schmidt and W. Carl, *ibid.*, **639**, 24 (1961).

relative to internal tetramethylsilane. Concentrations were carried out *in vacuo*. Dimethyl sulfoxide was dried over Molecular Sieves (Type 4A, Fisher). Per cent ^{18}O in labeled compounds was determined by mass spectral analysis. The ^{18}O labeled water was purchased from Yeda Research and Development Co., Ltd. (affiliated with Weizmann Institute of Science), Rehovoth, Israel.

Oxidation of Yohimbine (1) to Yohimbine (3). A. With DMSO and Acetic Anhydride. To a mixture of 886 g of yohimbine (1) and 7.55 l. of dry dimethyl sulfoxide was added 5.05 l. of acetic anhydride. The mixture was stirred at room temperature for 18 hr. The mixture was diluted with 16.8 l. of ethanol, stirred for 1 hr, and diluted with 4.2 l. of water. Concentrated ammonium hydroxide (11 l.) was added while maintaining the temperature at 15–30° by cooling and the mixture was then diluted with 16.8 l. of water. Filtration gave a solid which was washed with water and dried to give 818 g (93%) of tan crystals, mp 248–250° dec. This was slurried twice with 4 l. of ethanol and filtered to give 742 g (84%) of 3, mp 253–254° dec; lit.³ mp 243–249°.

The filtrate from the first slurry with 4 l. of ethanol was concentrated to give a dark colored gum. The gum was dissolved in chloroform–acetone–ethanol (6:3:1) and filtered through synthetic magnesia silica gel, the filter cake was washed with acetone, and the combined filtrates were concentrated to give 40 g of dark gum. The gum (20 g) was chromatographed on a column of 300 g of silica gel using chloroform–ethanol (99.3:0.7) as eluting solvent and 250-ml cuts were collected. Evaporation of cuts 5–11 gave the product as a glass. The combined glass from two column purifications was crystallized from methanol to give 6.95 g (0.7%) of methyl 17 α -(methylthio)methoxy]yohimban-16 α -carboxylate (4) as tan crystals, mp 195–198°. On standing the mother liquors gave a second crop (2.7 g, 0.3%) of yellow crystals, mp 195–198°. Recrystallization of 2.0 g from 20 ml of methanol gave 1.2 g of off-white crystals of 4, mp 198–200°; $[\alpha]^{25}_{\text{D}} -164^\circ$ (c 1.03, pyridine); pmr (CDCl₃) singlets at δ 2.10 (SCH₃) and 3.73 (OCH₃); AB quartet centered at δ 4.62 ($J_{\text{AB}} = 12$ cps) (OCH₂S); $\nu_{\text{max}}^{\text{KBr}}$ 1724 (s), 1156 (s), 1041 cm⁻¹ (s).

Anal. Calcd for C₂₃H₃₀N₂O₅S: C, 66.6; H, 7.30; N, 6.76; S, 7.74. Found: C, 66.8; H, 6.99; N, 6.89; S, 7.74.

B. With DMSO and Benzoic Anhydride. A mixture of 2.12 g (0.0060 mole) of 1, 22.6 g (0.10 mole) of benzoic anhydride, and 20 ml of dry dimethyl sulfoxide was allowed to stand at room temperature for 22 hr. The mixture was diluted with 10 ml of water and 50 ml of ethanol and allowed to stand 30 min. The mixture was chilled by means of an ice bath and made basic with concentrated ammonium hydroxide. After diluting with 75 ml of water, the solid was collected by filtration and washed with water and with ether to give 1.73 g (82%) of 3 as light tan needles, mp 253–256° dec.

C. With Tetramethylene Sulfoxide and Acetic Anhydride. A mixture of 0.708 g (0.0020 mole) of 1, 10 ml of tetramethylene sulfoxide, and 4 ml of acetic anhydride was allowed to stand at room temperature for 21 hr. The solution was poured into 20 ml of ethanol, chilled, and made basic with concentrated ammonium hydroxide. The mixture was diluted with 25 ml of water and filtered to give 0.57 g (80%) of 3 as tan crystals, mp 250–253° dec.

D. With DMSO and Polyphosphoric Acid. A mixture of 1.8 g of polyphosphoric acid (Matheson Coleman and Bell, 82–84% P₂O₅), 0.708 g of 1, and 6 ml of dry dimethyl sulfoxide was warmed on a steam bath until the solid dissolved, and the solution was then stirred at room temperature for 41 hr. The resulting solution was diluted with 25 ml of ethanol and 5 ml of water, chilled, and made basic with concentrated ammonium hydroxide. The chilled mixture was diluted with 30 ml of water and filtered, and the precipitate was washed twice with 25-ml portions of water. The solid was then washed with ether to give 0.36 g (51%) of 3 as tan crystals, mp 239–243° dec. Recrystallization from ethanol–chloroform gave the product as tan crystals, mp 250–253° dec.

E. With DMSO and Phosphorus Pentoxide. To a solution of 1.06 g (0.0030 mole) of 1 in 10 ml of dry dimethyl sulfoxide was added 0.425 g (0.0030 mole) of phosphorus pentoxide. The solution was heated at 65° for 18 hr under nitrogen. The mixture was poured onto ice and made basic with concentrated ammonium hydroxide, and the resulting solid was removed by filtration and washed with water. The partially dried solid was dissolved in chloroform–ethanol (6:4) and filtered through Florisil. The filter cake was washed with chloroform–ethanol (9:1), and the filtrate was concentrated. The residue was triturated with ethanol, and the crystals were removed by filtration and washed with ether to give 0.48 g (45%) of 3 as yellow crystals, mp 240–243° dec.

Oxidation of β -Yohimbine (2) to Yohimbine (3). A mixture of 5.30 g of 2, 45 ml of dry dimethyl sulfoxide, and 30 ml of acetic anhydride was allowed to stand at room temperature for 19.5 hr under an atmosphere of nitrogen. The solution was diluted with 100 ml of ethanol and 10 ml of water, chilled, and made basic with concentrated ammonium hydroxide. The chilled mixture was diluted with 125 ml of water and filtered; the precipitate was washed with water to give 4.35 g of tan crystals. Chromatography of the product over silica gel gave, on elution with chloroform–methanol (99.5:0.5), a glass which was crystallized from methanol to yield 1.1 g (18%) of methyl 17 β -(methylthio)methoxy]yohimban-16 α -carboxylate (5) as colorless crystals, mp 167–169°. Recrystallization from methanol gave 0.7 g of 5, mp 189–190°; $[\alpha]^{25}_{\text{D}} -80^\circ$ (c 1.0, pyridine); pmr (CDCl₃) singlets at δ 2.10 (SCH₃), 3.78 (OCH₃), and 4.62 (OCH₂S); $\nu_{\text{max}}^{\text{KBr}}$ 1736 (s), 1064 (s), and 1047 cm⁻¹ (s) (sh).

Anal. Calcd for C₂₃H₃₀N₂O₅S: C, 66.6; H, 7.30; N, 6.76; S, 7.74. Found: C, 66.5; H, 7.47; N, 6.71; S, 7.36.

Further elution of the column with chloroform–methanol (99.5:0.5) afforded, after recrystallization from acetone–chloroform (80:20), 1.4 g (25%) of 3, mp 255–258°.

Oxidation of α -Yohimbine (6) to Methyl 17-Hydroxyallooyohimban-16-ene-16-carboxylate (7). A mixture of 2.12 g of 6, 25 ml of dry dimethyl sulfoxide, and 4.0 ml of acetic anhydride was stirred at room temperature for 21 hr. The mixture was poured onto 60 g of ice and 10 ml of water and made basic with concentrated ammonium hydroxide. The solid which separated was removed by filtration and washed with water. The dry solid was dissolved in ether and filtered through 10 g of synthetic magnesia silica gel. The filter cake was washed with ether and the combined filtrates were concentrated to give 2.10 g of a pale orange glass. Chromatography of 4.1 g of the glass over 200 g of silica gel gave in the first fractions, on elution with chloroform–ethanol (99.5:0.5), a glass which was crystallized from methanol to yield 0.48 g (10%) of methyl 17 α -(methylthio)methoxy]allooyohimban-16 β -carboxylate (8) as tan crystals; melting point changes above 92° to a viscous mass which slowly liquifies. Recrystallization from methanol gave colorless crystals of 8 hemihydrate, melting point changes to viscous mass above 100° which slowly liquifies; $[\alpha]^{25}_{\text{D}} +25^\circ$ (c 1.0, pyridine); pmr (CDCl₃) singlets at δ 2.10 (SCH₃), 3.76 (C(=O)-OCH₃), and 4.62 (OCH₂S); $\nu_{\text{max}}^{\text{KBr}}$ 1724 (s) and 1064 cm⁻¹ (s).

Anal. Calcd for C₂₃H₃₀N₂O₅S·0.5H₂O: C, 65.2; H, 7.38; N, 6.61; S, 7.57. Found: C, 65.5, 65.0; H, 7.76, 7.05; N, 6.74; S, 7.62.

Further elution of the column with chloroform–ethanol (99.5:0.5) afforded 1.8 g (40%) of 7 as a glass which was crystallized from methanol to give 0.67 g of tan crystals, mp 176–179° dec; lit.¹ mp 185–188° dec.

Oxidation of Methyl Reserpate (9) to Methyl Ketoreserpate (10). A mixture of 8.29 g of 9, 60 ml of dry dimethyl sulfoxide, and 40 ml of acetic anhydride was stirred at room temperature for 20 hr. The mixture was poured onto 350 g of ice and made basic with 10 N sodium hydroxide. The mixture was extracted with 250 ml and with two 100-ml portions of dichloromethane. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated. The residue was suspended in ethanol and concentrated nearly to dryness. The residue was triturated with ether and filtered to give 5.17 g of off-white crystals. The ether filtrate was concentrated, and the residue was triturated with ether and filtered to give 2.2 g of solid. Trituration with 15 ml of hot ethanol and filtration afforded 1.81 g (22%) of 10 as tan crystals, mp 229–231° dec; lit.⁸ mp 241–242° dec.

The 5.17 g of solid from above was chromatographed over 250 g of silica gel with chloroform–ethanol (96:4). The first fractions afforded 1.45 g (15%) of methyl reserpate methylthiomethyl ether (11) which was recrystallized from methanol to give 1.0 g (11%) as off-white crystals, mp 248–252° dec; $[\alpha]^{25}_{\text{D}} -81^\circ$ (c 1.1, pyridine); pmr (CDCl₃–DMSO-*d*₆) singlets at δ 2.15 (SCH₃), 3.53 (OCH₃), 3.78 (two OCH₃), and 4.73 (OCH₂S); $\nu_{\text{max}}^{\text{KBr}}$ 1736 (s), 1151 (s), 1058 cm⁻¹ (s).

Anal. Calcd for C₂₃H₃₄N₂O₅S: C, 63.3; H, 7.22; N, 5.90; S, 6.76. Found: C, 63.1; H, 7.28; N, 6.18; S, 6.74.

The latter fractions from the column afforded an additional 0.65 g (11%) of 10 as off-white crystals, mp 229–231° dec.

Oxidation of Ajmaline (12) to Ajmalidine (13). A mixture of 7.17 g of 12, 60 ml of dry dimethyl sulfoxide, and 40 ml of acetic anhydride was allowed to stand at room temperature for 18 hr. The solution was poured onto 250 g of ice, and the chilled mixture was made basic with concentrated ammonium hydroxide and extracted with dichloromethane. The extract was washed with water,

dried over magnesium sulfate, and concentrated to give a gum. The gum was dissolved in 50 ml of hot ethanol, and the solution was diluted with 10 ml of water and 2.5 ml of 10 *N* sodium hydroxide. The solution was heated on a steam bath for 45 min, and the solvent was then removed under reduced pressure. Ethanol was added, and the solvent was again removed. The residue was triturated with water and filtered to give 6.1 g of solid. Chromatography of the solid over silica gel with chloroform-methanol (98:2) as eluent gave 3.4 g (52%) of 13 as a colorless glass which was crystallized from acetone to give 0.26 g (4%) of colorless crystals, mp 240–243°; lit.¹⁴ mp 241–242°; $[\alpha]^{25}_D -80^\circ$ (c 1.0, acetic acid); $\nu_{\text{max}}^{\text{KBr}}$ 1742 (s) and 1616 cm^{-1} (m).

Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$: C, 74.0; H, 7.46; N, 8.64. Found: C, 73.7; H, 7.76; N, 8.63.

The mother liquors from crystalline 13 were evaporated to a glass which was acetylated in the next experiment.

Further elution of the column with chloroform-methanol (98:2) gave 0.80 g (10%) of 17 β -[(methylthio)methoxy]-21 α -ajmalaninol (14) as colorless crystals, mp 145–147°. Recrystallization from methanol afforded 0.45 g of colorless crystals, mp 148–150°; $[\alpha]^{25}_D -9.8^\circ$ (c 1.0, pyridine); pmr (CDCl_3) singlets at δ 2.20 (SCH_3) and 2.77 (NCH_3); AB quartet at δ 4.73 ($J_{AB} = 12$ cps) (OCH_2S); $\nu_{\text{max}}^{\text{KBr}}$ 1605 (m) and 1047 cm^{-1} (s).

Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2\text{S} \cdot 0.25\text{H}_2\text{O}$: C, 67.6; H, 7.86; N, 7.16; S, 8.20. Found: C, 67.3; H, 8.04; N, 7.00; S, 7.97.

B. In a similar manner 14.34 g (0.040 mole) of 12 was oxidized and the product chromatographed over 350 g of silica gel (200-ml cuts) with the eluents chloroform-ethanol (99.3:0.7) (5.2 l.), chloroform-ethanol (98.3:1.7) (1 l.), and chloroform-ethanol (97:3) (3 l.). The solid from fractions 13–33 was crystallized from methanol to give 3.5 g (25%) of 13 as colorless crystals, mp 240–243°. The solid from fractions 40–50 were crystallized from methanol to give 2.3 g (15%) of 14, mp 147–150°.

In another oxidation of 12 the crude product, extracted with dichloromethane from the basified (with ammonium hydroxide) reaction mixture, gave crystals of ajmalidine O-acetate (15), mp 209–211°.

Ajmalidine O-Acetate (15). Ajmalidine (13) (1.8 g of glass obtained from mother liquors of crystalline 13; see part A of preceding experiment) was dissolved in 5 ml of dry pyridine and 2 ml of acetic anhydride. The solution was allowed to stand for 19 hr at room temperature and then poured onto 35 g of ice. After standing 2 hr the mixture was made slightly basic with concentrated ammonium hydroxide and filtered. The solid was washed thoroughly with water and dried to give 1.4 g (68%) of 15 as off-white crystals, mp 208–213°. Recrystallization from ethanol gave 0.80 g of 15 as colorless needles, mp 218–220°; $[\alpha]^{25}_D +242^\circ$ (c 1.0, pyridine); pmr (CDCl_3) singlets at δ 2.12 (OCOCH_3), 2.78 (NCH_3), and 5.35 ($>\text{CHOCO}$), one proton doublet at 3.77 (C-2 H), and one proton multiplet at 3.23 (C-16 H); $\nu_{\text{max}}^{\text{KBr}}$ 1739 (s), 1613 (m), and 1244 cm^{-1} (s).

Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4$: C, 72.1; H, 7.15; N, 7.65. Found: C, 72.1; H, 6.96; N, 7.81.

In a similar experiment crystalline ajmalidine afforded the same O-acetate as colorless crystals, mp 218–219°.

Oxidation of (–)-Galanthamine (16) to Narwedine (17). A mixture of 1.00 g of 16, 10.5 ml of dimethyl sulfoxide, and 6.98 ml of acetic anhydride was stirred at room temperature for 18 hr. The solution was poured into 200 ml of ice-water and made alkaline with concentrated ammonium hydroxide. The mixture was extracted with dichloromethane and the extract was washed with water, dried over magnesium sulfate, and concentrated. Trituration of the residual yellow gum with ether and filtration gave 0.38 g (38%) of 17 as a yellow solid, mp 167–180° dec. Recrystallization from acetone gave 0.20 g of colorless crystals, mp 184–188°; lit.¹¹ mp 187–190°.

Oxidation of Testosterone (18) to 4-Androstene-3,17-dione (19).
A. With DMSO and Acetic Anhydride. To a solution of 1.15 g of 18 in 12 ml of dry dimethyl sulfoxide was added 8 ml of acetic anhydride. The solution was stirred for 13 hr at room temperature and poured onto 125 g of ice. The mixture was made basic with 10 *N* sodium hydroxide, and the resulting precipitate was removed by filtration and washed thoroughly with water to give 1.10 g of white crystals. Recrystallization from ether gave 0.70 g (60%) of 19 as white crystals, mp 160–162°. Concentration of the mother liquors gave 0.25 g of crystals which were partitioned on a column of 640 g of Celite diatomaceous earth (stationary phase: 2-methoxy-ethanol saturated with heptane). The column was developed with heptane and the fraction which was collected at 3.8–5.8 hold-back

volumes (HBV) gave, on evaporation, 0.090 g (8%) of 19, mp 168–170°; lit.¹² mp 170°.

The fraction collected at 1.0–1.5 HBV was concentrated and the solid was recrystallized from petroleum ether (bp 30–60°) to give 0.117 g (8%) of 17 β -[(methylthio)methoxy]-4-androsten-3-one (20) as colorless needles, mp 123–124°; lit.¹³ mp 128–129°; $[\alpha]^{25}_D +113^\circ$ (c 1.1, CHCl_3); pmr (CDCl_3) singlets at δ 0.82 (CH_3), 1.20 (CH_2), 2.12 (SCH_3), 4.60 (OCH_2S), 5.70 ($>\text{C}=\text{C}(\text{CO})\text{H}$); $\nu_{\text{max}}^{\text{KBr}}$ 1675 (s), 1626 (m), 1075 (s), and 1062 cm^{-1} (s).

Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_2\text{S}$: C, 72.4; H, 9.26; S, 9.20. Found: C, 71.9; H, 9.37; S, 9.07.

B. With DMSO, Phosphoric Acid, Pyridine, and Ethoxyacetyl-ene. To a chilled mixture of 4.0 ml of dry dimethyl sulfoxide, 0.98 g (0.010 mole) of crystalline phosphoric acid, 0.577 g (0.0020 mole) of 18, and 0.95 ml (0.012 mole) of dry pyridine was added 1.0 ml of redistilled ethoxyacetylene. The mixture was allowed to warm to room temperature and stand at room temperature for 23 hr. The mixture was poured into 25 ml of ice-water and ten drops of acetic acid was added. The mixture was extracted with four 25-ml portions of dichloromethane; the combined extracts were washed with two 25-ml portions of water, dried over magnesium sulfate, and concentrated to a gum. Ether was added several times, and the solvent was removed *in vacuo* after each addition. Ether and heptane were added, and the solvent was evaporated to give 0.5 g of off-white crystals. Tlc on silica gel [solvent: cyclohexane-ethyl acetate (7:3)] showed the presence of three components: ca. 25% 4-androstene-3,17-dione, ca. 70% testosterone, and ca. 5% of a fast moving component [probably 17 β -(methylthiomethoxy)-4-androsten-3-one]; the infrared spectrum showed a ketone band at 1747 cm^{-1} . No testosterone O-acetate was present as determined by tlc comparison with an authentic sample.

17 β -(Methylthiomethoxy)-4-androsten-3-one (20). To a mixture of 11.5 g (0.040 mole) of testosterone, 35 ml of dimethyl sulfoxide, and 40 ml of acetic anhydride was added 40 ml of glacial acetic acid. The mixture was chilled briefly and then allowed to stand at room temperature for 6 days. The solution was poured onto 500 g of ice and, after standing for 2 hr, was made basic with concentrated ammonium hydroxide. A gummy solid separated, and the liquid was decanted. The gummy solid was triturated with methanol and filtered to give 9.2 g of colorless crystals. Recrystallization from hot methanol gave 6.9 g (49%) of 20 as colorless crystals, mp 126–127°. Recrystallization from methanol afforded 5.35 g (38%) of colorless crystals, mp 127–128°; lit.¹³ mp 128–129°.

Oxidation of Hydrocortisone 21-Acetate (21) to Cortisone 21-Acetate (22). A mixture of 0.404 g (0.0010 mole) of 21, 3 ml of dry dimethyl sulfoxide, and 2 ml of acetic anhydride was allowed to stand at room temperature for 56 hr. The mixture was poured into a mixture of 50 g of ice and 10 ml of water, and the resulting gummy precipitate was triturated while the pH of the mixture was adjusted to 7 by addition of concentrated ammonium hydroxide. Filtration gave 0.400 g of white crystals. Recrystallization from acetone gave 0.15 g (37%) of 22, mp 237–239°; $[\alpha]^{25}_D +236^\circ$ (c 0.63, CHCl_3); lit.¹⁴ mp 239–241°.

Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{O}_4$: C, 68.6; H, 7.51. Found: C, 69.0; H, 7.45.

In a similar run with 0.606 g (0.0015 mole) of 21 carried out for 92 hr, 0.57 g (94%) of product was obtained. Recrystallization from acetone-petroleum ether (bp 30–60°) afforded 0.31 g (53%) of 22 as colorless crystals, mp 236–239°.

Oxidation of 11 α -Hydroxyprogesterone (23) to 11-Ketoprogesterone (24). A mixture of 0.330 g of 23, 3 ml of dry dimethyl sulfoxide, and 2 ml of acetic anhydride was allowed to stand at room temperature for 25 hr. The solution was poured onto a mixture of 20 g of ice and 10 ml of water, made basic with concentrated ammonium hydroxide, and diluted with 25 ml of water. The mixture was extracted with chloroform, and the extracts were dried over magnesium sulfate and concentrated to give 300 mg of a gum. This material was chromatographed on a column of 440 g of Celite diatomaceous earth (stationary phase: methanol saturated with heptane) with a hold-back volume (HBV) of 600 ml, using heptane saturated with methanol as solvent. The fraction collected from 6.0–7.6 HBV was concentrated under reduced pressure to yield 0.100 g (30%) of 24 as a colorless glass. Crystallization from acetone-petroleum ether (bp 30–60°) gave 0.044 g (13%) of 24 as colorless crystals, mp 171–172°; lit.¹⁵ mp 172–175°; $\nu_{\text{max}}^{\text{KBr}}$ 1709 (s), 1667 (s), and 1613 cm^{-1} (m).

The fraction collected at 2.77–4.1 HBV was concentrated to give 0.220 g (56%) of methylthiomethoxy derivative 25 as a pale yellow gum which could not be induced to crystallize; pmr (CDCl_3) singlets at δ 0.72 (CH_3), 1.35 (CH_2), 2.15 and 2.23 (COCH_3 , SCH_3), 4.72

(OCH₃S), 5.77 (>C=C(CO)H); $\nu_{\text{max}}^{\text{KBr}}$ 1709 (s), 1667 (s), 1613 (m), and 1042 cm⁻¹ (s).

Oxidation of *p*-Nitrobenzyl Alcohol to *p*-Nitrobenzaldehyde. A mixture of 1.53 g of *p*-nitrobenzyl alcohol, 30 ml of dry dimethyl sulfoxide, and 10 ml of acetic anhydride was allowed to stand at room temperature for 20 hr. The solution was poured onto 75 g of ice and allowed to stand for 1 hr. The chilled mixture was made basic with cold 10 *N* sodium hydroxide and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and concentrated. The residue was triturated with ether and filtered, and the precipitate was recrystallized from ether to give 0.47 g (31%) of *p*-nitrobenzaldehyde as pale yellow crystals, mp 102–103° (infrared spectrum identical with an authentic sample).

The mother liquors were combined and concentrated to give 0.95 g of crystals which were recrystallized from ether to yield 0.55 g of crystals. The pmr spectrum (CDCl₃) showed the latter crystals were a mixture composed of two-thirds *p*-nitrobenzaldehyde and one-third *p*-nitrobenzyl alcohol *O*-acetate: singlets at δ 2.13 (C(=O)CH₃), 5.20 (CH₂O), and 10.1 (CHO) with intensities of 1.5:1:1.

Oxidation of Ethanol-¹⁸O with DMSO, Phosphoric Acid, and DCC. To a mixture of 4.09 g (0.020 mole) of DCC and 5 ml of dry DMSO under nitrogen was added 0.300 g of crystalline phosphoric acid. The mixture became warm and was cooled. After standing for 15 min, 0.39 ml (0.0067 mole) of ethanol (containing 1.9% ¹⁸O) was added. The temperature was kept below 20° by cooling and, after stirring for 1.33 hr, 10 ml of dry dichloromethane was added, and the mixture was filtered. The solid was washed with 200 ml of dichloromethane, two 20-ml portions of dry acetone, and finally with ethanol and water to give, after drying, 1.83 g of *N,N'*-dicyclohexylurea, mp 228–229°. Analysis by mass spectral measurements for ¹⁸O content showed a maximum of 0.3% ¹⁸O. In a similar run the solid which precipitated during the reaction was removed by filtration and washed with dichloromethane and ethanol. The solid was extracted with 250 ml of hot acetone, and the acetone extract was chilled and filtered to give 0.30 g of *N,N'*-dicyclohexylurea, mp 231–232°. Mass spectral analysis showed a maximum of 0.26% ¹⁸O.

Benzhydrol-¹⁸O. A mixture of 4.04 g (0.020 mole) of benzhydrol chloride, 25 ml of dry acetone, and 5.0 ml of water labeled with 10% ¹⁸O was allowed to stand at room temperature for 7 days. The solution was concentrated and filtered to give 3.3 g of colorless crystals. These crystals were washed with 10 ml of ethanol, and the ethanol wash was diluted with water. The resulting crystals were removed by filtration. The filtrate was concentrated, chilled, and filtered to give colorless crystals which were recrystallized from petroleum ether (bp 60–90°) to yield 0.53 g of benzhydrol as white needles, mp 64–65°. Mass spectral analysis showed the benzhydrol to contain 4.8% ¹⁸O.

Oxidation of Benzhydrol-¹⁸O with DMSO, Phosphoric Acid, and DCC. A mixture of 0.184 g (0.001 mole) of benzhydrol-¹⁸O (4.8% ¹⁸O), 0.613 g (0.003 mole) of DCC, 0.050 g of phosphoric acid, and 1 ml of DMSO was allowed to stand at room temperature for 16 hr.

The mixture was diluted with 8 ml of dry ether and filtered to remove solid A. To the filtrate was added 5 ml of water and several drops of acetic acid. After standing 6 hr, the mixture was filtered, and the solid was washed with ether. The ether was separated from the aqueous layer of the filtrate, and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate and concentrated. The residue was extracted with petroleum ether (bp 60–90°) and the petroleum ether extract was concentrated to a gum. Mass spectral analysis of the crude benzophenone showed the presence of 2.0% ¹⁸O (42% of the original label).

Solid A was washed with ether and with water to yield 0.39 g of white crystals. Recrystallization from acetone gave 0.31 g (0.00138 mole) of *N,N'*-dicyclohexylurea, mp 227°; no ¹⁸O above natural abundance was found by mass spectral analysis.

1,3-Dicyclohexyl-2-*p*-nitrobenzylpseudourea (40). To a solution of 7.66 g (0.050 mole) of *p*-nitrobenzyl alcohol and 10.2 g (0.050 mole) of DCC in 150 ml of acetone was added 10 mg of anhydrous cupric chloride. The mixture was stirred at room temperature for 70 hr, and the solvent was then removed. The oil was dissolved in 30 ml of petroleum ether (bp 30–60°) and 30 ml of acetone and 1.0 g of *p*-nitrobenzyl alcohol and 10 mg of cupric chloride were added. After 70 hr the solvent was removed and a solution of the residual oil in ether was filtered through neutral alumina (Woelm, activity I). The first 250 ml of filtrate was concentrated to a pale yellow oil which crystallized on chilling [12.2 g (66%), mp 48–52°]. A portion (8.6 g) was recrystallized from petroleum ether (bp 30–60°) to give 7.1 g (38%) of 40 as nearly colorless crystals, mp 55–57°.

Anal. Calcd for C₂₀H₂₉N₃O₂: C, 66.8; H, 8.13; N, 11.7. Found: C, 66.3; H, 8.32; N, 11.9.

Reaction of 1,3-Dicyclohexyl-2-*p*-nitrobenzylpseudourea (40) with DMSO and Phosphoric Acid. A mixture of 3.61 g (0.010 mole) of 40, 0.40 g of crystalline phosphoric acid, and 12 ml of dry dimethyl sulfoxide was stirred at room temperature for 18 hr. The mixture was poured onto 50 g of ice and allowed to stand. The mixture was made basic with 10 *N* sodium hydroxide and extracted with ether. The ether extracts were concentrated, and the residue was diluted with water and extracted with petroleum ether (bp 30–60°). Concentration of the extract gave a pale yellow oil which crystallized. Chilling and filtering gave 2.2 g (61%) of starting material, mp 48–50°.

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Studies on the Reaction between Peroxydisulfate Ions and Aromatic Amines. The Boyland-Sims Oxidation

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Abstract: Aromatic amines and persulfate ions react in aqueous base to give a 45–55% yield of *o*-aminoaryl sulfate, ammonia, and a polymeric material known as humic acid. The reaction is first order in neutral amine and initially first order in persulfate ion. The effect of substituents on the rate of the reaction, the activation parameters, and the lack of effect of a radical trap suggest a nucleophilic displacement by the amine nitrogen on peroxide oxygen to give the corresponding arylhydroxylamine O-sulfonate. This postulated intermediate may then rearrange to the *o*-aminoaryl sulfate or be oxidized by persulfate to humic acid and ammonia.

The reaction between aromatic amines and peroxydisulfate (persulfate, peroxodisulfate) ions in aqueous base to form *o*-aminoaryl sulfates was first reported in 1953.¹ The preparative aspects of this reaction were explored in a series of further papers which established the scope of the reaction.^{2–4} The reaction might appropriately be named the Boyland-Sims oxidation. Primary, secondary, and tertiary aromatic amines are all successfully converted to the *o*-sulfate esters, although the yields of isolated material are frequently poor. The range is generally between 10 and 40%. If both *ortho* positions are blocked, *para* substitution takes place. Otherwise, *ortho* substitution is exclusive except for the case of the persulfate oxidation of anthranilic acid⁵ in which a small proportion of the *para* isomer was detected. Much starting material is generally recoverable, even though an excess of persulfate is used. The reaction mixtures are highly colored^{2,6} and a number of products in addition to the sulfate esters have been reported. Azo and azoxy compounds have been isolated⁴ and a substituted quinone imine has been found as a product of the oxidation of 2-naphthylamine.¹ The formation of insoluble, brown, amorphous material, frequently in substantial amounts, has been noted in a number of these oxidations.^{1,3,4} The scope of the reaction has been extended to include indoles and aminopyrimidines.^{7,8} The results of a preliminary mechanistic study of this reaction⁹ suggested that it proceeds *via* a nucleophilic displacement on peroxide oxygen¹⁰ rather than by a radical mechanism, and that it is, therefore, closely allied to the Elbs persulfate oxidation of phenols¹¹ with the notable exception of the orientation of the sulfate group. This investigation was undertaken with the hope of defining those

differences between the phenol and the amine oxidations which for the latter case lead to preferential *ortho* substitution.

Materials and Methods

2-Amino-3-hydroxypyridine and 2-amino-3-pyridyl hydrogen sulfate were prepared by the persulfate oxidation of 2-aminopyridine according to Boyland and Sims.⁴ 2,2'-Azopyridine and 2-nitropyridine were prepared according to Kirpal and Böhm.¹² 2-Amino-3,5-dideuteriopyridine was prepared by heating 20 g of D₂O, 4.7 g of 2-aminopyridine, and 2.45 g of sulfuric acid in a sealed tube at 180° (refluxing 2-octanol) for 90 hr. At the end of this period, the tube was cooled, the contents removed, and the volatile material removed *in vacuo*. An additional 20 g of D₂O was then added and the heating repeated. A third run was then completed following which the reaction mixture was made basic with sodium hydroxide and extracted continuously with ether. The ether was removed and the material crystallized from *n*-hexane-ether. The yield was 2.7 g. The calculated isotopic purity is 99.8%. Examination of the nmr spectrum of the product in D₂O showed no trace of the multiplet attributable to the 3 and 5 protons centered at τ 3.4, and the collapse of the 4-proton triplet to a singlet at τ 2.4. Other amines were obtained from Eastman or Aldrich and were either redistilled or recrystallized before use. Inorganic compounds were reagent grade and were used without further purification.

Kinetic runs were carried out in a water bath held to within 0.1° of the indicated temperature. The kinetics of the reactions were followed by measurement of persulfate concentration as a function of time using the iodometric method of Kolthoff and Carr¹³ with the modification that the reaction aliquots were quenched in acetic acid which was consequently present during the 15-min incubation. The blank value was 0.1 ml of 0.01 *M* thiosulfate. Kinetics were run under pseudo-first-order conditions with the amine present in at least tenfold excess. The formation of 2-amino-3-hydroxypyridine was followed by assay with the Folin phenol reagent, essentially according to the method already described.¹¹ Hydrolysis of the sulfate ester was complete within 5 min at 100° in 3 *N* HCl. The blue color produced by the reduction of the Folin phenol reagent

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was measured in a Klett-Summerson photoelectric colorimeter using the 660-m μ filter. 2-Aminopyridine does not interfere. 2-Amino-3-hydroxypyridine (0.1 μ mole) gave a Klett reading of 90. Beer's law was obeyed up to at least a Klett reading of 400. 2-Amino-3-hydroxypyridine is stable to heating in acid but is rapidly destroyed under these conditions in the presence of persulfate.

The formation of 2-amino-5-nitrophenol from *p*-nitroaniline was measured similarly. The formation of *o*-aminophenol from aniline was measured by use of the Folin uric acid reagent.¹⁴ Ammonia was determined by direct Nesslerization.

Results

2-Aminopyridine was chosen as the model amine for these studies because of the ease of product determination.

1. Yield and Stoichiometry. Yield of material capable of reducing the Folin phenol reagent was examined as a function of the ratio of the reactants, of temperature, and of hydroxyl ion concentration. These results are summarized in Table I. All reactions were run for a sufficiently long time to consume at least 99% of the smaller component. The yield appears to be independent of temperature, but dependent on both the hydroxyl ion concentration and the ratio of the reactants.

Table I. Yield of 2-Amino-3-hydroxypyridine from the Reaction of Persulfate and 2-Aminopyridine

[2-AP] ^a	[S ₂ O ₈ ²⁻]	Ratio	[KOH]	Temp, °C	Yield, ^b %
0.0475	0.00250	19	0.5	40	56
0.0450	0.0050	9	0.5	40	52
0.0400	0.0100	4	0.5	40	45
0.0250	0.0250	1	0.5	40	29
0.0100	0.0400	0.25	0.5	40	4
0.200	0.0245	8.15	0.475	40	40.5
0.400	0.0387	10.2	0.475	30	41
0.400	0.0400	10	0.475	50	42.5
0.10	0.01	10	1.8	40	31
0.10	0.01	10	0.9	40	36
0.10	0.01	10	0.45	40	44
0.10	0.01	10	0.09	40	46
0.10	0.01	10	0.018	40	50

^a 2-AP is 2-aminopyridine. ^b Yield determinations are the averages of two runs.

The ultraviolet spectra of ether extracts of reaction mixtures were examined for the presence of 2-nitrosopyridine, 2-nitropyridine, 2,2'-azopyridine, and 2,2'-azoxypyridine. None of these materials was detected. Paper chromatography of reaction mixtures following acid hydrolysis revealed only one Folin-positive spot corresponding to 2-amino-3-hydroxypyridine, although a number of other unidentified ultraviolet-absorbing spots were present.

2. Order in Persulfate. At an amine:persulfate ratio of 10, the disappearance of persulfate followed apparent first-order kinetics for about 75% of the reaction, when the kinetics were examined as plots of the logarithm of persulfate concentrations *vs.* time; a negative deviation was evident thereafter. A typical plot is shown in Figure 1. If, however, successive *k*

(14) E. J. Behrman and M. N. D. Goswami, *Anal. Chem.*, **36**, 2189 (1964).

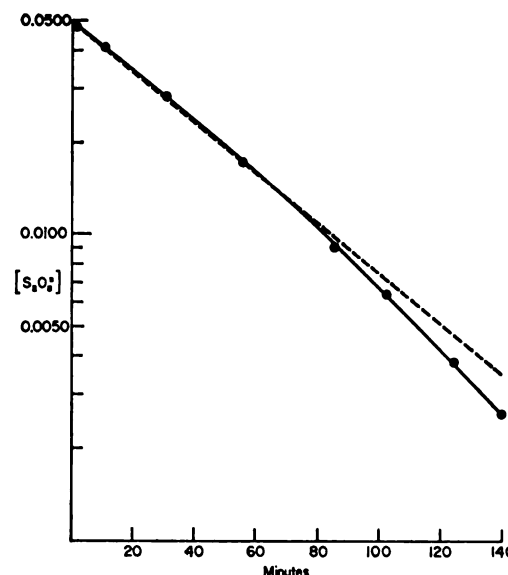


Figure 1. Rate plot for the oxidation of 2-aminopyridine by persulfate. Conditions were: 0.450 *N* KOH, 0.5 *M* 2-aminopyridine, 0.0501 *M* K₂S₂O₈, 40.0°. The solid line represents the experimental findings; the dotted line is straight.

values are computed, a steady drift to more negative values is evident. The drift during the first half of the reaction is less than 5%.

3. Order in Amine. Table II shows that the reaction is likewise first order in amine. We may thus write the rate law, $v = k[S_2O_8^{2-}][ArNH_2]$, at least for the major part of the reaction.

Table II. Order in 2-Aminopyridine^a

[2-AP]	[S ₂ O ₈ ²⁻]	<i>k</i> , l./mole min
0.040	0.0038	0.0403
0.100	0.010	0.0392
0.1062	0.010	(0.0402)
0.200	0.024	0.0404
0.300	0.0295	(0.0397)
0.400	0.030	0.0405

^a General conditions: 0.475 *M* KOH, 40.0°. 2-AP is 2-aminopyridine. *k* values were calculated by measurement of the pseudo-first-order rate constant during the first half-time of the reaction and division of this constant by 2-aminopyridine concentration. The values given are the averages of duplicate determinations with the exception of the values marked with parentheses, which are the result of single runs. The average *k* value is 0.0401.

4. pH Dependency. The variation of rate with pH is shown in Figure 2 and demonstrates that it is the unprotonated amine which is the reactive species. 2-Aminopyridine has a *pK_a* of 6.9. The ionic strength was constant within this series of experiments.

5. Salt Effects. Table III shows that there is a general and positive salt effect of rather small magnitude, as expected for a reaction between an ion and an uncharged molecule.

6. Activation Parameters. The variation of the rate constant with temperature is given in Table IV. The derived activation parameters are as follows: *E_a* = 15.7 ± 0.3 kcal/mole; Δ*S*[‡] = -25.5 ± 1 eu. These values are of the magnitude expected for nucleophilic displacement on peroxide oxygen.¹⁰

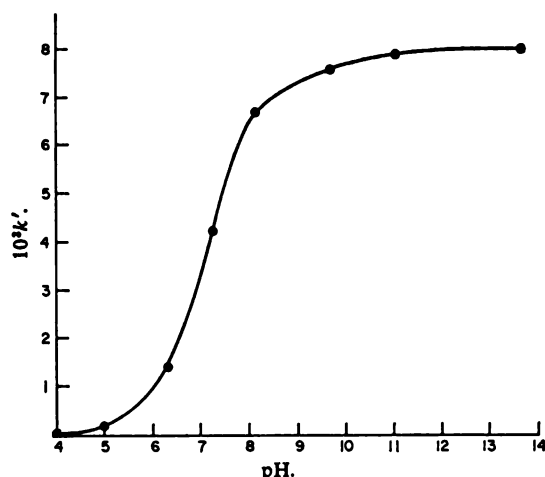


Figure 2. The effect of pH on the rate of oxidation of 2-aminopyridine by persulfate. General conditions were: 0.200 *M* 2-aminopyridine, 0.020 *M* persulfate, 40.0°. Buffers were added such that the ionic strength increment was equal to 0.475. The specific pH values and additions were: pH 13.7, KOH; pH 11.1, phosphate; pH 9.7, carbonate; pH 8.1, phosphate; pH 7.3, phosphate; pH 6.3, phosphate; pH 5.0, acetate; pH 4.0, acetate.

7. Effect of Radical Traps. Allyl acetate, an effective sulfate radical trap,¹⁶ had no effect on the rate of disappearance of persulfate in the presence of 2-aminopyridine at pH 7. The final yield of 2-amino-3-hydroxypyridine was likewise unaffected. The rate of

Table III. Salt Effects^a

Additions	<i>k</i> , l./mole min
No additions	0.0401
0.2 <i>M</i> NaCl	0.0415
0.5 <i>M</i> NaCl	0.0457
1.0 <i>M</i> NaCl	0.0535
2.0 <i>M</i> NaCl	0.0782
1/2 <i>M</i> Na ₂ SO ₄	0.0471
1/2 <i>M</i> Na ₂ SO ₄	0.0725
1 <i>M</i> KCl	0.0507
1 <i>M</i> NaClO ₄ ^b	0.0498

^a General conditions: 0.475 *M* KOH, 0.200 *M* 2-aminopyridine, 0.02 *M* persulfate, 40.0°. ^b For the reaction in the presence of sodium perchlorate, NaOH was substituted for KOH.

Table IV. Rate Dependence on Temperature^a

Temp, °C	<i>k</i> , l./mole min
50.0	0.0822
40.0	0.0401
30.0	0.0178
19.3	0.00665

^a General conditions: 0.475 *M* KOH, 0.400 *M* 2-aminopyridine, and 0.04 *M* persulfate.

disappearance of persulfate in the presence of *p*-nitroaniline at pH 7 was also unaffected by the presence of allyl acetate.

8. Effect of Substituents. Second-order constants for the reaction of persulfate with aniline, *p*-toluidine, and *p*-nitroaniline are presented in Table V. It is clear

Table V. The Effect of Substituents on the Rate of Oxidation of Anilines

Compound	Concn, <i>M</i>	Solv ^a	Temp, °C	<i>k</i> ', min ⁻¹	<i>k</i> , l./mole min
<i>p</i> -Nitroaniline	0.029	A	40.0	0.00326 ^b	0.113
<i>p</i> -Nitroaniline	0.029	B	40.0	0.00062 ^b	0.0215
Aniline	0.0302	B	40.0	0.0344	1.14
Aniline	0.0302	C	40.0	0.0764	2.53
Aniline	0.0121	C	40.0	0.0298	2.47
Aniline	0.0121	D	40.0	0.0297	2.46
Aniline	0.0302	C	30.0	0.0399	1.32
<i>p</i> -Toluidine	0.0300	C	30.0	0.101	3.36

^a Solvents: A, 0.475 *M* KOH in 24% 2-propanol; B, 0.04 *M* phosphate buffer, pH 7.0 in 24% 2-propanol; C, 0.04 *M* phosphate buffer, pH 7.0 in water; D, 0.1 *M* KOH in water. ^b These values have been corrected for the rate of oxidation of 2-propanol by subtracting 0.00018 from the pseudo-first-order rate constants.

that the reaction is accelerated by electron-releasing substituents. A Hammett plot of these data suggests a ρ value in the vicinity of -1.3 . This may be compared with the value of -1.86 reported for the reaction of aromatic amines with peroxyacetic acid,¹⁶ and of -1.58 for the reaction of nitrosobenzenes with peroxyacetic acid.¹⁷ The rate of oxidation of aniline is decreased by about a factor of two in 24% 2-propanol as compared with water as solvent. In accordance with the evidence that the reactive species of 2-aminopyridine is the unprotonated amine, the rate of oxidation of aniline ($pK_a = 4.6$) is the same at pH 7 and in 0.1 *M* KOH. *p*-Nitroaniline is oxidized more rapidly in 0.475 *M* KOH than at pH 7, but this is perhaps attributable to ionization to the anion.¹⁸

9. Site of Attack. Since aromatic amines are ambident nucleophiles, either attack at carbon or attack at nitrogen followed by rearrangement is *a priori* conceivable. Table VI compares the rates of oxidation of three sets of aromatic amines in which one *ortho* position is blocked and a common substituent is placed either *meta* to the amino group (*para* to the final position of the sulfate group) or *para* to the amino group (*meta* to the final position of the sulfate group). One isomer will react with persulfate faster on the hypothesis of rate-limiting electrophilic attack at nitrogen, the other on the assumption of rate-limiting electrophilic attack at carbon. For each set, the order of reactivity is that to be expected on the basis of rate-limiting attack at nitrogen, as shown by the values of the σ constants.

10. Rate of Oxidation of 2-Amino-3,5-dideuterio-pyridine. The rate of oxidation of this material by persulfate was identical with that of the undeuterated material. The yield of product at hydroxyl ion concentrations from 0.1 to 3 *M* as measured by the quantity of Folin-reactive material present following acid hydrolysis was likewise unaffected by deuteration.

11. Formation of Ammonia from 2-Aminopyridine and 2-Amino-3-hydroxypyridine. Considerable quantities of ammonia are produced during the oxidation of 2-aminopyridine by persulfate. At 2-aminopyridine: persulfate ratios between 100 and 10, in 0.9 *M* KOH

(16) K. M. Ibne-Rasa and J. O. Edwards, *ibid.*, **84**, 763 (1962).

(17) K. M. Ibne-Rasa, C. G. Lauro, and J. O. Edwards, *ibid.*, **85**, 1165 (1963).

(18) C. H. Rochester, *Trans. Faraday Soc.*, **59**, 2820 (1963).

(15) I. M. Kolthoff, E. J. Meehan, and E. M. Carr, *J. Am. Chem. Soc.*, **75**, 1439 (1953).

VI. Comparison of the Rate of Oxidation of 2,3- and Disubstituted Aromatic Amines by Persulfate Ions^a

Compound	Concn, M	k , min ⁻¹	k , l./mole min
I. 2-Aminopyridine Series (0.475 M KOH in water)			
2-Amino-5-methylpyridine	0.1001	0.0184	0.183
2-Amino-5-methylpyridine	0.200	0.0380	0.190
2-Amino-6-methylpyridine	0.1001	0.00935	0.0934
2-Amino-6-methylpyridine	0.2023	0.0189	0.0935
Values for the methyl σ constants are: $\sigma_m = -0.069$, $\sigma_p^+ = -0.311$			
II. 2-Chloroaniline Series (0.04 M phosphate buffer, pH 7.0 in 24% 2-propanol)			
2-Dichloroaniline	0.0401	0.00276	0.0690
4-Dichloroaniline	0.0401	0.00538	0.134
Values for the chloro σ constants are: $\sigma_m = 0.373$, $\sigma_p^+ = 0.114$			
III. 2-Methylaniline Series (0.04 M phosphate buffer, pH 7.3 in 24% 2-propanol)			
Methyl-4-nitroaniline	0.01505	0.000790	0.0525
Methyl-3-nitroaniline	0.01502	0.00350	0.233
Values for the nitro σ constants are: $\sigma_m = 0.710$, $\sigma_p^- = 1.27$			

all runs were conducted at 40.0°. The initial amine:persulfate was 10 in all cases. Values for the σ constants are from J. "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., New York, N. Y., 1962, pp 87-90.

°, the molar ratio between ammonia produced and persulfate added is between 0.34 and 0.21. Thus only 30% of the persulfate added in these experiments, where the yield of 2-amino-3-pyridyl hydrogen sulfate is in the 45-55% range (see Table I), is consumed in reactions resulting in deamination. 2-Aminoloxypyridine reacts with persulfate at least 1000 times faster than 2-aminopyridine to give a quantitative yield of ammonia and oxidation products (see below). *o*-Aminophenol likewise gives a quantitative yield of ammonia, while aniline, like 2-aminopyridine, gives a yield of about 30%. 2-Amino-3-pyridyl hydrogen sulfate reacts with persulfate, but only at a rate about one-half that of 2-aminopyridine.

Formation of Material with the Properties of Synthetic Humic Acid. When an alkaline mixture of aniline and persulfate is acidified, a dark brown polymeric material precipitates. The ultraviolet spectrum in alkaline solution shows no peaks at wavelengths longer than 220 m μ . The infrared spectrum is shown in Figure 3. Oxidation of *o*-aminophenol by persulfate under alkaline conditions produced a similar material whose infrared spectrum is shown for comparison in Figure 3. The spectra, although not identical, are closely similar. The oxidation of *o*-aminophenol by persulfate in alkali was described in 1925 by ¹⁹. The product is a member of the class of materials known as synthetic humic acid. In quantitative experiments, the oxidation of 1 mole of aniline by 0.1 mole of persulfate in 1 l. of 0.5 M KOH gave an isolated yield of 1 g of this polymer. These are conditions which give a 50-55% yield of *o*-aminoaryl sulfate so that the isolated yield of sulfate ester and polymer amounts to roughly 75-80% of starting material.

Discussion

The evidence suggests rate-limiting electrophilic attack of persulfate ion on nitrogen of the neutral amine (W. Eller, *Ann.*, **442**, 173 (1925)).

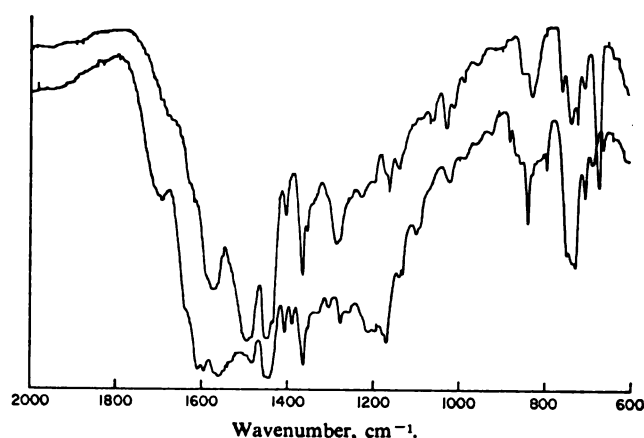


Figure 3. Infrared spectra of humic acids isolated from the persulfate oxidation of aniline (upper curve) and of *o*-aminophenol (lower curve). The spectra were taken in mineral oil mulls using a Perkin-Elmer Model 237B.

followed by rearrangement to the *o*-aminoaryl sulfate. Attack at nitrogen rather than at carbon is consistent with work in other systems.^{16, 17, 20-23} Haberfield and Paul have recently demonstrated the existence of an N-chloro intermediate in the chlorination of N-methylaniline.²⁴

The effect of substituents in the persulfate-aromatic amine reaction argues strongly for electrophilic attack at nitrogen. Initial attack at nitrogen also provides the rationale for the preferential *ortho* orientation. The absence of significant radical involvement is shown by the first-order dependence on both amine and persulfate and by the lack of effect of radical traps on either the rate of disappearance of persulfate or the yield of *o*-aminoaryl sulfate. The points of difficulty are the nature of the initial product resulting from attack of the peroxide on nitrogen and the fate of those molecules which do not appear as *o*-aminoaryl sulfate. If the attack were initially at nitrogen, a reasonable intermediate would be the arylhydroxylamine-O-sulfonate.

Salts of phenylhydroxylamine-O-sulfonate have been prepared by Boyland and Nery.²⁵ These authors report that phenylhydroxylamine O-sulfonate rearranges to *o*-aminophenyl sulfate on standing at room temperature in 2 N HCl. The paper states that salts of the various hydroxylaminesulfonic acids "are unchanged in 2% aqueous sodium hydrogen carbonate or 2 N ammonia after 16 hr at room temperature in the dark..." and that "In hot 2 N sodium hydroxide they give complex mixtures containing *o*- and *p*-aminophenol, aniline, azoxybenzene, and unidentified products." Our attempts to demonstrate the presence of alkali-labile material in aniline-persulfate reactions run at neutrality were unsuccessful. However, Professor Boyland has informed me that although the N-acyl derivatives are stable, phenylhydroxylamine-O-sulfonic acid itself is unstable in solution at all pH values, that the potassium salt shows signs of decom-

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(21) D. B. Denney and D. Z. Denney, *J. Am. Chem. Soc.*, **82**, 1389 (1960).

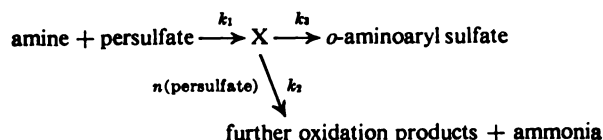
(22) D. M. Graham and R. B. Mesrobian, *Can. J. Chem.*, **41**, 2938 (1963).

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(25) E. Boyland and R. Nery, *J. Chem. Soc.*, 5217 (1962).

position in the solid state at 0° after a few days, and that considerable rearrangement occurs during chromatography of the compound in neutral solvent systems.²⁶ Although we cannot say how the rate of rearrangement of the arylhydroxylamine-O-sulfonates to the *o*-aminoaryl sulfates varies as a function of pH, it appears that the O-sulfonates are at least not unreasonable intermediates in the reaction between aromatic amines and persulfate ions. Boyland and Nery also report that phenylhydroxylaminesulfonic acids (both O- and N-substituted compounds are discussed) reduce ammoniacal silver nitrate and Fehling's solution. Aniline does not reduce either solution. Phenylhydroxylamine-O-sulfonate is thus a better reducing agent than the parent amine. This is reasonable since the hydroxylamines are members of the class of nucleophiles which exhibit an enhanced degree of nucleophilic reactivity which has been termed the α effect by Edwards and Pearson.²⁷ This aspect of their expected behavior is consistent with their role as intermediates in the persulfate oxidation of aromatic amines and with the low yields of *o*-sulfates obtainable in the reaction. The postulated intermediate is more readily oxidized than the starting material. The yield of *o*-aminoaryl sulfate falls in strong alkali, a fact perhaps attributable to even more ready attack by persulfate on the dianion of the arylhydroxylamine-O-sulfonate. We may write a general scheme for the course of the reaction



where X may be the arylhydroxylamine-O-sulfonate. On the steady-state assumption, the ratio of the rate of formation of *o*-aminoaryl sulfate to the rate of formation of further oxidation products will be equal to $k_2/k_3[\text{persulfate}]$.²⁸ This expression is then consistent with the dependence of the yield on the persulfate: amine ratio and also explains the deviation from first-order dependence on persulfate concentration.

(26) Letter from Professor Boyland.

(27) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

The major product of the reaction other than the *o*-aminoaryl sulfate is a polymer known as synthetic humic acid. Materials of this class were reported as products of the alkaline persulfate oxidation of dihydric phenols and aminophenols by Eller.^{19,28} Even monohydric phenols are oxidized to humic acids with persulfate: phenol ratios of 2 to 4.^{28b} These are conditions under which the phenol *p*-sulfate (the normal Elbs product) is formed in very low yield.¹¹ Ziechmann and Scholz²⁹ and Elofson³⁰ have reported spectroscopic characteristics of humic acids from a variety of sources which are thought to arise through condensation of hydroxyquinones.³¹ A substituted naphthoquinone imine of this oxidation level has been identified as a product of the persulfate oxidation of 2-naphthylamine.¹ Characterization of humic acids is difficult and we have not undertaken this task here. Recent reviews are available.^{32,33} It suffices for our purposes to have shown the close similarity between the polymeric material obtained from the oxidation of *o*-aminophenol, known to be oxidized to a humic acid by persulfate,¹⁹ and that obtained from aniline. A corresponding product is presumably obtained from 2-aminopyridine, but due to the ring nitrogen, it is soluble in acid and we have not isolated it.

The humic acid polymers should be distinguished from polymers of the aniline black-emeraldine type which result from homolytic coupling of aromatic amines in acid solution.³⁴

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Ozonolysis. Steric and Stereochemical Effects in the Olefin

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Abstract: Ozonolysis of a series of *cis* and *trans* olefins indicates that the ozonide *cis:trans* ratio produced in both normal ozonides and cross-ozonides is a function of both olefin stereochemistry and steric effects in the olefin. Isolation of an epoxide in which the olefin stereochemistry has been preserved has been observed in the case of one *trans* olefin. The mechanistic consequences of these results are discussed.

It has now been amply demonstrated²⁻⁹ that olefins can give both *cis* and *trans* ozonides. Of greater significance to the mechanism of ozonolysis are a few observations which indicate that the ozonide *cis:trans* ratio obtained can be a function of olefin stereochemistry. A different ozonide *cis:trans* ratio is obtained from the stereoisomers of di-*t*-butylethylene,² 1,4-dibromo-2,3-dimethylbutene-2,³ methyl *p*-methoxycinnamate,⁶ and a number of simple alkenes.⁷⁻⁹

Also of considerable importance to the study of the mechanism of ozonolysis are the reports by several groups^{5,8-10} that unsymmetrical olefins give, in addition to the expected unsymmetrical ozonide *cis:trans* pair, two symmetrical ozonide *cis:trans* pairs derived from the cleavage of the olefin unsaturation. We have recently shown that a combination of these two important pieces of information, that is, the formation of cross-ozonides and the observation of ozonide *cis:trans* pairs, can be used to provide results which raise serious questions about the general validity of the Criegee mechanism of ozonolysis.¹¹ Specifically, it was shown that the ozonide *cis:trans* ratios observed in cross-ozonides are also dependent upon olefin geometry.¹² In these cases the intervention of an intramolecular stereoselective pathway, such as was considered to explain similar results in the normal ozonide cases,^{8,9} is not possible. These results have led us to propose a new path to ozonide formation in which the molozonide assumes the role of a true intermediate in an exchange reaction with aldehydes, and, thus, exerts an influence on the ozonide *cis:trans* ratios produced.¹³

The observation that both ozonide and cross-ozonide *cis:trans* ratios can be dependent on olefin geometry provides a powerful new probe for studying the mechanism of ozonolysis. Effective use of this









probe requires that the ozonide stereoisomer designations be made on an unequivocal basis, however. Such an assignment has recently become available¹⁴ and is based on the fact that the *trans* isomer of a symmetrical ozonide must consist of a *dl* pair and, hence, be amenable to complete or partial resolution.

The establishment of a comprehensive mechanism of ozonolysis on a sound basis requires that a number of variables be studied in a systematic manner. We report here the results of such a study in which the major emphasis is on the effect of olefin steric factor and olefin stereochemistry.

Discussion of Results

We consider first the normal¹⁵ ozonides produced upon ozonolysis of a series of olefins. In the *cis* series there is a clear dependence of the ozonide *cis:trans* ratios on the substituent size in the olefin as shown in Table I. A similar, although less-pronounced, effect

Table I. Normal Ozonide Stereoisomers from *cis* Olefins

Olefins	<i>cis</i> , %	<i>trans</i> , %	Total yield ^a of ozonides, %
	67	33	84
	66	34	85
	54	46	81
	53	47	81
	49	51	86
	42	58	91
	41	59	72
	39	61	48

^a It should be noted that for unsymmetrical olefins this figure includes the yield of cross-ozonide.

(14) R. W. Murray, R. D. Youssefeyeh, and P. R. Story, *ibid.*, **88**, 3655 (1966).

(15) The term normal ozonide is here used to describe the parent ozonide obtained upon ozonolysis of an olefin. For a symmetrical olefin this is a symmetrical ozonide. For an unsymmetrical olefin it is the unsymmetrical ozonide. The two symmetrical ozonides obtained in the latter case are here referred to as cross-ozonides.

(1) (a) Bell Telephone Laboratories. (b) On leave of absence from the Weizmann Institute of Science, Rehovoth, Israel. (c) The University of Georgia, Athens, Ga.

(2) G. Schröder, *Chem. Ber.*, **95**, 733 (1962).

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







(11) R. Criegee, *Record Chem. Progr. (Kresge-Hooker Sci. Lib.)*, **18**, 111 (1957).

(12) R. W. Murray, R. D. Youssefeyeh, and P. R. Story, *J. Am. Chem. Soc.*, **88**, 3143 (1966).

(13) P. R. Story, R. W. Murray, and R. D. Youssefeyeh, *ibid.*, **88**, 3144 (1966).

is seen in the *trans* series for olefins below, and including, diisopropylethylene in steric requirements (Table II). In the *cis* series this effect is in the form

Table II. Normal Ozonide Stereoisomers from *trans* Olefins

Olefins	<i>cis</i> , %	<i>trans</i> , %	Total yield ^a of ozonides, %
	29	71	16 ^b
	30	70	32 ^b
	53	47	47
	53	47	49
	48	52	66
	40	60	53 ^b
	38	62	56
	38	62	36

^a It should be noted that for unsymmetrical olefins this figure includes the yields of cross-ozonide. ^b Yield of one or both cross-ozonides could not be determined.


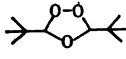

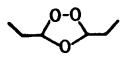

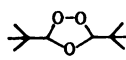

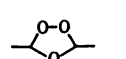

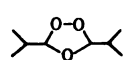

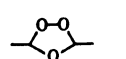

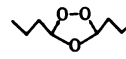

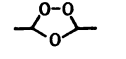

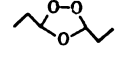

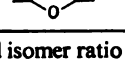
of a higher per cent *cis* ozonide accompanying higher steric requirements in the olefin. The same effect is noticed in the *trans* series for olefins below diisopropylethylene. The remaining two members of the *trans* series, both of which contain a *t*-butyl group, do not follow this trend but instead give a much higher per cent *trans* ozonide. The results reported earlier by Schröder also fit well into these two series. For *cis*-di-*t*-butylethylene Schröder obtained a 70:30 *cis:trans* ratio, placing it at the top of the *cis* series, consistent with its higher steric requirements. Likewise, for *trans*-di-*t*-butylethylene he reported obtaining 100% *trans* ozonide, which places this result in the group at the top of the *trans* series. Apparently, the presence of the *t*-butyl group in the *trans* olefins introduces a new factor which disrupts the trend in the ozonide *cis:trans* ratios. Our observations with two members of this group indicate that these same olefins are also most prone to give olefin-ozone adducts which undergo rearrangements. One of these rearrangements, that which gives *t*-butyl formate, involves migration of the *t*-butyl group. These processes are undoubtedly competing with ozonide formation and are probably responsible for the change in trend in the ozonide *cis:trans* ratios as well as the lower yields obtained in these cases.

The difference in the steric effect between the *cis* and *trans* series is seen to diminish with size of substituent until the diethylethylene case (hexene-3) is reached where the ozonide isomer distribution is the same for both series at 53:47 (*c:t*). In fact with all of the olefins below hexene-3 in steric requirements both olefin series

give approximately the same ozonide isomer distribution, and the steric effect on this ratio within either series is less pronounced than for those olefins having greater steric requirements than hexene-3.

Examination of the ozonide *cis:trans* ratios obtained in the cross-ozonides reveals a similar trend to that observed in the normal ozonides, although fewer examples are available to support this general observation (Tables III and IV). The effect is quite clear in the


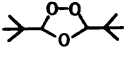

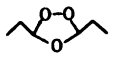

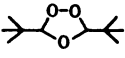

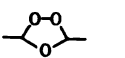

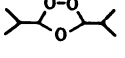

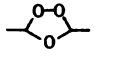

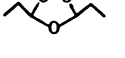

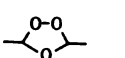

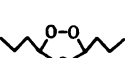

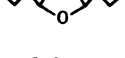
Table III. Cross-Ozonide Stereoisomers from *trans* Olefins

Olefins	Cross-ozonide obtained	Ozonide stereoisomer distributions, %		Yield of cross-ozonide, %
		<i>cis</i>	<i>trans</i>	
		<i>a</i>	<i>a</i>	<i>a</i>
		<i>a</i>	<i>a</i>	<i>a</i>
		<i>a</i>	<i>a</i>	<i>a</i>
		<i>a</i>	<i>a</i>	<i>a</i>
		50	50	11
		38	62	6
		<i>a</i>	<i>a</i>	<i>a</i>
		39	61	11
		41	59	8
		32	68	10

^a Yield and isomer ratio could not be obtained but ozonides were produced.

cis series where the larger of the two cross-ozonides obtained for each olefin is quite sensitive to the steric factor in the olefin. Thus, in the series, *cis*-4,4-dimethylpentene-2, *cis*-4-methylpentene-2, and *cis*-pentene-2 the *cis:trans* ratios in the cross-ozonides di-*t*-butylozonide, diisopropylozonide, and diethylozonide were 74:26, 66:34, and 56:44 (*c:t*), respectively. A similar trend is perhaps discernible in the *trans* series, but this conclusion must be regarded as tentative. One point is clear, however. As reported earlier,¹² the *cis:trans* ratios for cross-ozonides are dependent on olefin geometry for a number of olefins. To us this observation is inconsistent with the Criegee zwitterion mechanism, in which the zwitterion precursor to ozonide should give the same ozonide *cis:trans* ratios for both olefin stereoisomers in both normal and cross-ozonides. In considering alternatives to this mechanism¹³ we have considered several possible pathways as being in competition, with the Criegee zwitterion pathway retained as a possible contributing pathway.

Table IV. Cross-Ozonide Stereoisomers from *cis* Olefins

Olefins	Cross-ozonide obtained	Ozonide stereoisomer distributions, %		Yield of cross-ozonide, %
		<i>cis</i>	<i>trans</i>	
		82	18	11
		62	38	12
		74	26	3
		46	54	9
		66	34	19
		49	51	12
		56	44	14
		44	56	18
		<i>a</i>	<i>a</i>	<i>a</i>
		43	57	16

* Yield and isomer ratio could not be obtained but ozonides were produced.

An additional observation can be made relative to the *cis:trans* cross-ozonide ratios obtained in the *cis* series. In many cases this ratio for the larger of the two cross-ozonides obtained is almost identical with the ratio obtained from the symmetrical *cis* olefin which would give the same ozonide. In the *cis*-4,4-dimethylpentene-2 case, for example, the di-*t*-butyl-ozonide obtained has a 74:26 (*c:t*) ratio while Schröder² reported a 70:30 (*c:t*) ratio for the same ozonide from *cis*-di-*t*-butylethylene. Likewise, *cis*-4-methylpentene-2 gives a 66:34 (*c:t*) ratio for the diisopropyl-ozonide, which is exactly the same ratio obtained from the symmetrical olefin, *cis*-2,5-dimethylhexene-3. A similar situation exists for the hexene-3 ozonides from *cis*-pentene-2 and *cis*-hexene-3 where the ratios are 56:44 and 53:47 (*c:t*), respectively. In the case of *cis*-*t*-butylethylene, on the other hand, the di-*t*-butyl-ozonide produced has the remarkably high *cis:trans* ratio of 82:18. This result surely argues against a pure zwitterion mechanism for cross-ozonide formation. In fact, the cross-ozonides from the *cis* olefins taken as a whole suggest an intermediate for their production which is quite sensitive to steric factors in the olefin and, like the normal ozonides, the correlation is that higher steric requirements leads to a higher per cent *cis* ozonide being produced.

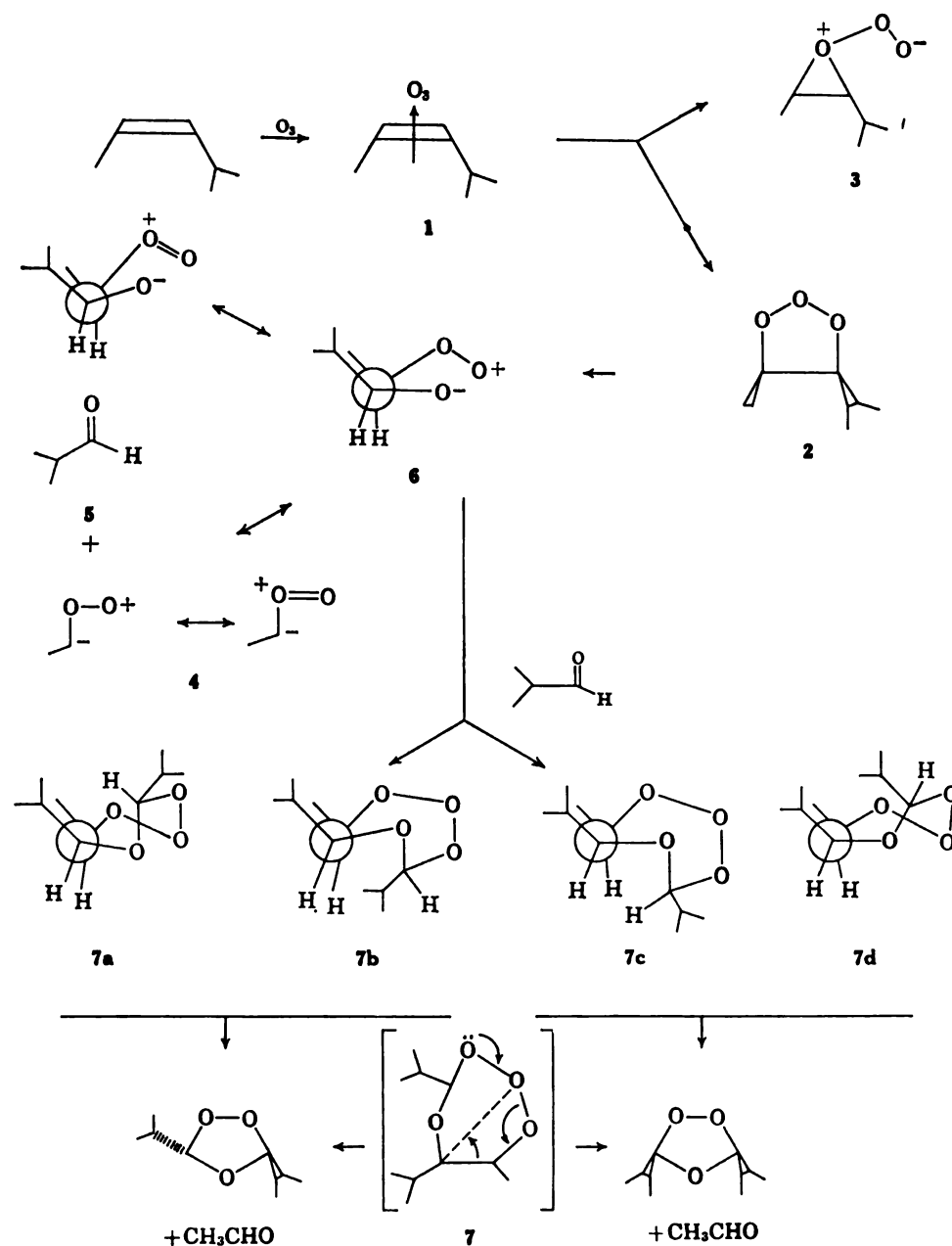
We have proposed a mechanism which we believe to be consistent with these observations¹³ (Scheme I). According to this proposal an olefin can give either a molozonide 2 or a σ complex 3 with either of these adducts perhaps, but not necessarily, preceded by a

π complex 1. The percentage of each pathway taken will depend on the stereochemistry and steric factors present in the olefin. In general *cis* olefins are more likely than *trans* to take the σ -complex pathway, and those which are badly sterically hindered proceed almost exclusively *via* this pathway, at least in producing normal ozonides. The molozonide pathway has several alternatives available to it, one of which is to cleave to give the Criegee zwitterion 4 and a carbonyl compound 5. The other alternative gives to the molozonide the role of a true intermediate which is visualized as cleaving to a zwitterionic form 6 either prior to or assisted by the approach of an aldehyde molecule, with which it will undergo an aldehyde exchange reaction. This latter reaction gives either normal ozonide or cross-ozonide, depending upon the nature of the aldehyde. The direction of cleavage of 2 shown here is contrary to that usually given¹⁶ in which the single oxygen carries the positive charge. It is our contention that a structure in which the positive charge can be delocalized over two oxygen atoms will be more stable. The adduct between the opened molozonide and the aldehyde is a transitory intermediate 7 which can exist in four possible conformations 7a-d. Two of these conformers are precursors to a *cis* ozonide and two to a *trans* ozonide.¹³ This process for the case of *cis*-4-methylpentene-2 and isobutyraldehyde is depicted in Scheme I. Examination of scale molecular models for this case reveals that one of these conformations is preferred (7c), since it contains only H-H non-bonded repulsions. Since this conformation leads to *cis* ozonide, the ozonide formed in this aldehyde interchange is expected to have a higher per cent *cis* configuration as observed. A similar analysis starting with the *trans* isomer is depicted in Scheme II. Here a consideration of the possible conformations of the molozonide-aldehyde adduct shows no over-all preference for *cis* or *trans* ozonide precursor. Again, the experimental results are in keeping with this analysis; e.g., see the cases of the diisopropyl ozonide formed from *trans*-4-methylpentene-2 and the hexene-3 ozonide formed from *trans*-pentene 2. It should be remembered that in all cases the observed *cis:trans* ratio is believed to be the net result of contributions from several pathways. In the cases just discussed, for example, these detailed pathways are seen as the dominant contributions to the observed ratio with other pathways making smaller contributions.

Another observation which seems to be generally true is that the *cis* olefins always give a higher yield of ozonide than the *trans*. This is true both for normal ozonides and cross-ozonides. Similar results with respect to normal ozonides have been reported by Schröder,² Greenwood and Haske,⁷ and Lorenz and Parks.⁸ We have also observed an increase in yields of free aldehyde in the *trans* series, as well as the production of acids which sometimes complicated isolation of the ozonides by glpc. Where the steric effect is especially pronounced as, for example, in *trans*-2,2-dimethylhexene-3, sufficient quantities of both ester and epoxide are produced to permit their isolation. The gas chromatograms also indicated that traces of these materials were formed in some of the other

(16) R. Criegee in "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p 32.

Scheme I

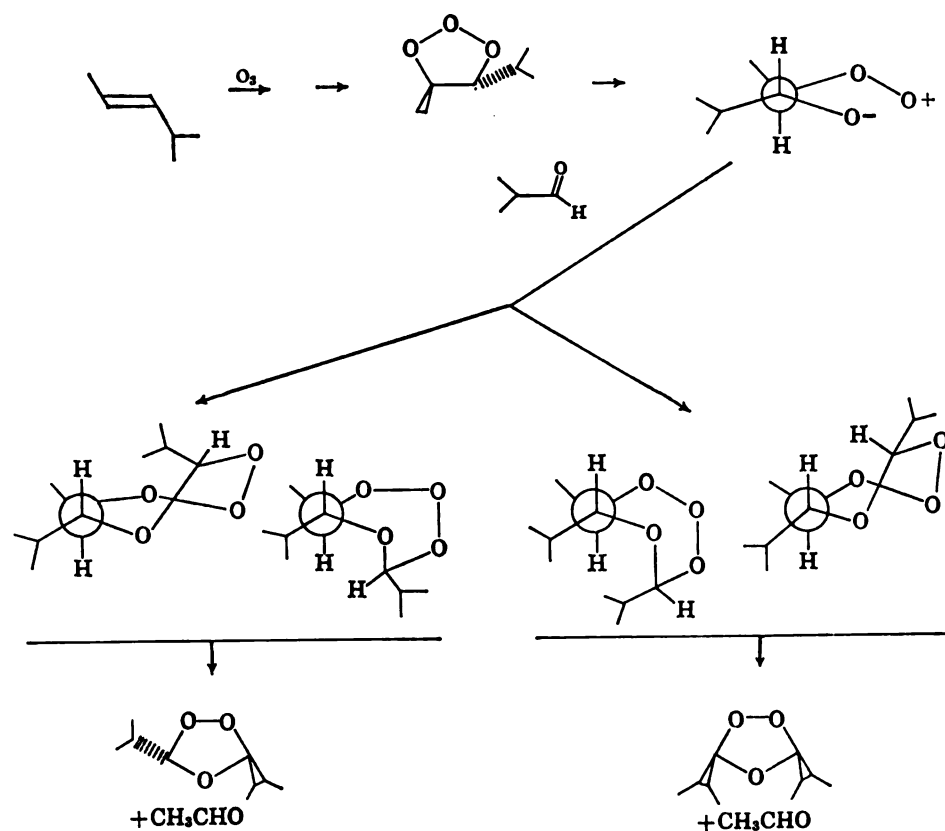


trans olefins. All of these observations seem to be consistent with the mechanistic scheme described above. That is, ozonolysis of a *trans* olefin is expected to involve a greater percentage of the pathways originating with molozonide. These pathways involve the polar intermediates 4 and 6, either of which can undergo rearrangements to give the acids and esters. These pathways might also be expected to give lower yields of ozonides since they involve a greater degree of separation of olefin fragments. The *cis* isomers, on the other hand, are more likely than the *trans* to proceed *via* the pathway involving the σ complex 3, which can proceed directly to normal ozonide without involving the molozonide or separation of olefin fragments. Important to this view is the reported¹⁷ absence of a molozonide upon ozonolysis of *cis*-di-*t*-butylethylene, whereas the *trans* isomer gives a molozonide which is stable at -75° . Greenwood⁷ has suggested that *cis* olefins in general may also give molozonides which are

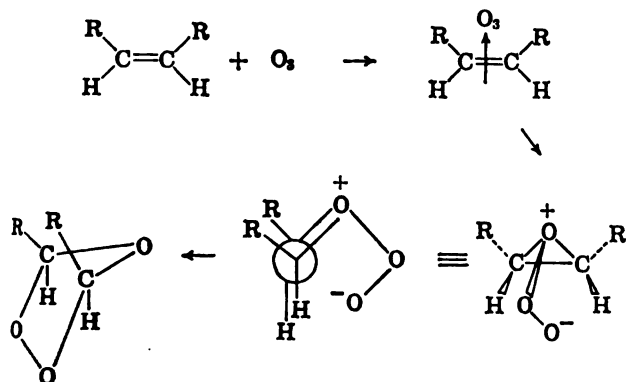
much less stable than those from the *trans* isomers. The conclusion was based in part upon the production of a white solid upon ozonolysis of *cis*-hexene-3, and the subsequent explosive decomposition of this material upon warm-up. While Greenwood's interpretation seems reasonable, it may be that the unstable species which is found in the *cis* case is not a molozonide at all, but a different species, perhaps the σ complex or something related to it. Besides explaining the higher yields the σ complex pathway may be the reason for the observed greater retention of configuration for hindered *cis* olefins.

The basic reason for *cis* olefins being more likely to involve the σ complex than the *trans* is perhaps seen from a critical examination of the steric requirements for its formation with the aid of scale models. The formation of the complex is depicted as involving approach of the ozone molecule so that the plane of the three oxygen atoms is perpendicular to the plane containing the olefinic carbon atoms. The complex itself is seen as having one end oxygen of the ozone

(17) R. Criegee and G. Schröder, *Chem. Ber.*, **93**, 689 (1960).



molecule above the olefinic carbon plane and the other end oxygen below this plane. It is this assembly which it is proposed can proceed stereospecifically and intramolecularly to ozonide. Formation of such an assembly and its subsequent internal rearrangement are both more difficult in a *trans* olefin than in the *cis* isomer.



Isolation of the epoxide in the case of *trans*-*t*-butylethylene provides further valuable information which may be highly pertinent to the mechanistic scheme described above. While the production of epoxides upon ozonolysis has been reported previously,¹⁸ this appears to be the first case of isolation of an epoxide where the olefin is capable of giving both *cis* and *trans* epoxides. The epoxide obtained from this *trans* olefin has the *trans* structure as evidenced by the fact that it is identical with that obtained by peracid epoxidation of the same olefin. This could be a very significant result in that it may provide evidence for an initial olefin-ozone adduct in which the olefin

(18) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

stereochemistry is preserved, and which is capable of proceeding to products, in this case the epoxide. Such an initial adduct could be the π complex proposed earlier by Bailey¹⁸ or the σ complex proposed by us.¹³ This is the type of complex which we have proposed may proceed stereospecifically to ozonide particularly in the case of hindered *cis* olefins. Further work on the mechanism of production of epoxides and their stereochemistry is in progress.

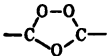
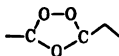
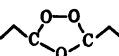
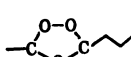
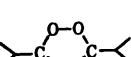
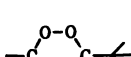

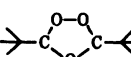
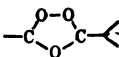
The results described here indicate a definite influence of olefin stereochemistry and steric factors on the ozonide *cis:trans* ratios produced. Olefin stereochemistry also exerts a strong influence on the total yield of ozonide as well as on the possibility of producing such minor products as acids, esters, and epoxides. We have attempted to describe a mechanistic scheme to account for all of these observations and, while we feel that the scheme proposed does provide a cohesive framework for the ozonolysis reaction, it has some obvious shortcomings. Further refinement of the scheme must await the results of studies in progress on the effects of solvent, concentration, and temperature.

Experimental Section

The nmr spectra were determined on a Varian A-60 high-resolution nmr spectrometer. Elemental analyses are by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. 11377. The glpc analyses were carried out on an Aerograph Model A-700 gas chromatograph using a 10 ft, 10% cyanosilicone column.

Ozonolyses. A Welsbach Model T-23 ozonator was used as a source of ozone. The ozonolyses were carried out at ca. -70° using a 1 *M* solution of the olefin in pentane. Ozonolysis was continued to 75% of the theoretical ozone required. The reaction mixtures were analyzed by glpc using an Aerograph Model 471 digital integrator to obtain quantitative data. The assignment of *cis* and *trans* structures to the ozonide geometric isomers was made on the basis of glpc, infrared, and nmr data and the correlation of these data with the unequivocal assignment based on partial resolution

Table V. Summary of Ozonide Experimental Data

Ozonide		Elemental anal.						Nmr data		Wt ratio
		Calcd, %			Found, %			τ (multiplicity) ^a		
C	H	O	C	H	O					
	<i>trans</i>	46.15	7.75	46.10	46.36	7.80	46.00	4.75 (q), 8.72 (d)	1:3	
	<i>cis</i>	46.15	7.75	46.10	46.01	7.66	...	4.70 (q), 8.63 (d)	1:3	
	<i>trans</i>	50.83	8.53	40.63	50.82	8.49	40.56	4.7-5.15 (m), 8.2-8.7 (m), 8.67 (d), 9.05 (t)	2:2:3:3	
	<i>cis</i>	50.83	8.53	40.63	50.77	8.46	...	4.79 (q), 4.95 (t), 8.0-8.5 (m), 8.68 (d), 9.07 (t)	1:1:2:3:3	
	<i>trans</i>	54.53	9.15	36.32	54.39	9.21	34.17	5.04 (t), 8.05-8.6 (m), 9.03 (t)	1:2:3	
	<i>cis</i>	54.53	9.15	36.32	54.62	8.65	...	5.02 (t), 8.1-8.9 (m), 9.09 (t)	1:2:3	
	<i>trans</i>	54.53	9.15	36.32	54.38	9.00	36.67	4.68-5.05 (m) [8.4-9.3 (m), 8.68 (d), 9.07 (t)]	1:5 ^b	
	<i>cis</i>	54.53	9.15	36.32	54.71	9.24	36.21	4.68-5.16 (m) [8.25-9.3 (m), 8.71 (d), 9.1 (t)]	1:5 ^b	
	<i>trans</i>	59.98	10.07	29.96	60.10	10.23	29.84	5.25 (d), 7.86-8.47 (m), 9.09 (d)	1:1:6	
	<i>cis</i>	59.98	10.07	29.96	59.96	10.18	30.02	5.23 (d), 7.86-8.62 (m), 9.11 (d)	1:1:6	
	<i>trans</i>	57.51	9.65	32.84	57.26	9.61	...	4.9 (q), 5.3 (s), 8.67 (d), 9.08 (s)	1:1:3:9	
	<i>cis</i>	57.51	9.65	32.84	57.63	9.52	33.01	4.79 (q), 5.32 (s), 8.68 (d), 9.11 (s)	1:1:3:9	
	<i>trans</i>	59.98	10.07	29.96	59.92	9.85	29.83	5.08 (t), 5.35 (s), 8.15-8.65 (m) [8.96 (t), 9.10 (s)]	1:1:2:12 ^b	
	<i>cis</i>	59.98	10.07	29.96	60.18	9.89	30.12	5.01 (t), 5.35 (s), 8.15-8.70 (m) [9.12 (t), 9.13 (s)]	1:1:2:12 ^b	
	<i>trans</i>	63.79	10.71	25.50	63.33	10.53	...	5.37 (s), 9.08 (s)	1:9	
	<i>cis</i>	63.79	10.71	25.50	63.55	10.68	25.61	5.3 (s), 9.10 (s)	1:9	
	<i>trans</i>	54.53	9.15	36.32	54.76	9.27	36.58	4.87 (q), 5.19 (d), 7.94-8.45 (m), 8.67 (d), 9.06 (d)	1:1:1:3:6	
	<i>cis</i>	54.53	9.15	36.32	54.74	9.02	...	4.78 (q), 5.20 (d), 7.94-8.5 (m), 8.69 (d), 9.09 (d)	1:1:1:3:6	

^a Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^b Corresponds to the weight ratio for the total peaks indicated in the bracket.

of the *trans-dl* pair for diisopropylazonide.¹⁴ The *cis* isomer has the longest glpc retention time. In the infrared spectra the *trans* isomer is characterized by a band at *ca.* 1320 cm⁻¹ which is absent in the *cis* isomer. Likewise the *cis* isomers have a band at *ca.* 830 cm⁻¹ which is missing in the *trans* spectra. Examination of the data in Table III will reveal a consistent correlation in the nmr spectra as well. For a symmetrical ozonide the methine hydrogens are always at lower field in the *cis* isomer. In the case of an unsymmetrical ozonide at least one of these protons will be at lower field in the *cis* isomer.

The *cis:trans* ratios reported are the result of several integrations of the glpc peak areas and have a maximum variation of $\pm 0.5\%$. Control experiments demonstrated that the glpc conditions used do not affect the ozonide *cis:trans* ratios. A summary of yields, analytical data, and nmr data is given in Table V.

In the case of *trans*-2,2-dimethylhexene-3 sufficient quantities of two additional materials were produced to permit their isolation. The first of these has a relatively low glpc retention time (6.2 min

at 70°). Its nmr spectrum consists of just two singlets at 2.21 and 8.58 with an integrated area ratio of 1:9. Of the two most likely structures for this material, the aldehyde, pivalaldehyde, is eliminated on the basis of nmr spectra since the aldehyde has two sharp singlets at 0.52 and 8.87. This material is therefore assigned the other possible structure containing highly deshielded protons, namely *t*-butyl formate. The second new material, isolated in 4% yield, has nmr and infrared spectra identical with those for authentic *trans*-2,2-dimethylhexene-3 epoxide obtained by the epoxidation of *trans*-2,2-dimethylhexene-3 using *m*-chloroperbenzoic acid.

Anal. Calcd for C₈H₁₆O: C, 74.94; H, 12.58. Found: C, 74.94; H, 12.60.

Acknowledgment. P. R. S. acknowledges the support of the U. S. Public Health Service through Grant No. AP00505-01.

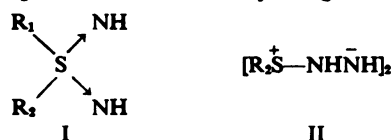
Dialkyl Sulfone Diimines. Synthesis, Raman Spectra, Chemical and Physical Properties

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Contribution from the Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239. Received November 30, 1966

Abstract: An improved synthesis of the recently described dialkyl sulfone diimines^{1,2} in acetonitrile is described. Reaction of chloramine-ammonia with dialkyl sulfides in 2-propanol has been shown to yield sulfoxide and sulfone imine by-products, as well as sulfone diimines. Their formation is best accounted for by assuming that displacement of sulfur on chloramine occurs to some extent on chlorine, as well as on nitrogen. The crystalline and aqueous solution Raman spectra of dimethyl, diethyl, and methyl dodecyl sulfone diimine have been measured and are shown to be consistent with tetrahedral bonding for sulfur (C_{2v} local symmetry). Tentative band assignments are presented based on comparison with analogous compounds and the Raman spectra of dimethyl sulfide, diethyl sulfide, and dimethyl sulfone imine. Characteristic vibrational bands for $R_2S(NH)_2$ are tabulated and the spectral evidence for hydrogen bonding of this new semipolar group is discussed. The sulfone diimines were shown to be considerably more stable thermally than sulfinimines but less stable than sulfoxides. Hydrolysis by acid or base catalysis could not be effected, although decomposition *via* other routes occurred in acid.² The basicity and metal complexing abilities of sulfone diimines parallel those of amine oxides, except toward silver. Silver ion reacts in aqueous solution with the formation of a precipitate and a decrease in pH to 2–3.

Cogliano and Braude¹ recently isolated from the reaction of chloramine with dialkyl sulfides a new class of compounds to which they assigned structure II.



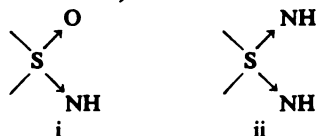
The alternative structure, I, was recently proposed by Appel, *et al.*,² for these compounds, on the basis of their inertness toward oxidizing agents, the absence of hydrazine or nitrogen in the hydrogen chloride cleavage products, and mass spectral studies. The present work provides further support for structure I derived from Raman and infrared spectral studies, an improved synthesis, new information regarding the chemistry involved in the synthesis, and some further chemical and physical properties of sulfone diimines.³

Synthesis

The sulfone diimines are best synthesized by allowing the dialkyl sulfide to react with excess chloramine and ammonia⁵ in acetonitrile.² They are easily isolated in

- (1) J. A. Coglianò and G. L. Braude, *J. Org. Chem.*, **29**, 1397 (1964).
- (2) R. Appel, H. Fehlhaber, D. Hänssgen, and R. Schöllhorn, *Chem. Ber.*, **99**, 3108 (1966).

(3) The nomenclature of the imines with which we are concerned has not developed systematically. A system based on analogy with the nomenclature of quinone imines and diimines is proposed, in which i (usually termed a "sulfoximine") is termed a "sulfone imine," and ii,



a "sulfone diimine." The "quinone imine" terminology is broadly applicable to most semipolar $S \rightarrow N$ (or $P \rightarrow N$) compounds one might imagine.

The term "sulfoximine" for the monoimine of a sulfone is unfortunate in that it may connote the sulfoxide oxidation state, and thus the structure $>S \rightarrow NH$, which has been variously termed a "sulfinimine," "sulfilimine," or a "sulfinime." The latter term, which has been adopted by Appel,⁴ seems simplest and least ambiguous.

- (4) R. Appel, W. Büchner, and E. Guth, *Ann.*, **618**, 53 (1958); R. Appel and W. Büchner, *Chem. Ber.*, **95**, 855 (1962).

(5) The necessary chloramine was generated from gaseous chlorine

45% yields as the free base by solvent extraction from the ammonium chloride.⁶

Acetonitrile is superior to 2-propanol^{1,2} as a reaction medium because reaction in the latter solvent produces several previously unrecognized by-products.⁷ For example, methyl dodecyl sulfide in 2-propanol yields, in addition to sulfone diimine, the sulfone imine (6%), sulfoxide (1%), 1-dodecene (10%), and dodecanenitrile (1%). The olefin and nitrile are formed in either solvent. Unfortunately, methyl tetradecyl and hexadecyl sulfides crystallize from acetonitrile at low temperatures, necessitating the use of 2-propanol for these homologs and resulting in more difficult purification.

The formation of the product by a sequence of nucleophilic displacement reactions on the nitrogen of chloramine has been suggested.^{1,2} Further evidence for intervention of a sulfinimine intermediate is isolation of the olefin and nitrile, which are likely decomposition products of sulfinimines.^{4,8} The conditions encountered during work-up were too mild for the olefin and nitrile to have been formed from the diimine.

The formation of sulfoxide and sulfone imine suggests that nucleophilic attack of sulfur on chloramine occurs to some extent on chlorine as well as on nitrogen, as is the case with other nucleophiles.⁹ Displacement by the dialkyl sulfide on chlorine would yield a dialkyl-chlorosulfonium ion, R_2S^+Cl , which would be expected to undergo alcoholysis to sulfoxide. Displacement by the sulfur atom of the sulfinimine on chlorine would yield

and ammonia using a modified version of the Sisler generator [H. H. Sisler, F. T. Neth, R. S. Drago, and D. Yaney, *J. Am. Chem. Soc.*, **76**, 3906 (1954)].

(6) The dimethyl homolog was more difficult to isolate, and was obtained in 12–39% yields. The sulfone diimines were actually formed to the extent of ca. 60%.

(7) Appel² reported the isolation only of dimethyl sulfinimine chloride from dimethyl sulfide in acetonitrile. The diimine must have been formed but was liberated into the solvent as the free base.

(8) A recent paper [D. W. Cornell, R. S. Berry, and W. Lwowski, *J. Am. Chem. Soc.*, **88**, 544 (1966)] suggests the possibility that the nitrile might have been formed by reaction of the olefin with NH_3 , generated by thermal cleavage of an $S \rightarrow N$ bond. Neither olefin nor nitrile was found if the reaction was worked up by chromatography and the recrystallization step omitted.

(9) W. Theilacker and E. Wegner, *Angew. Chem.*, **72**, 127 (1960).

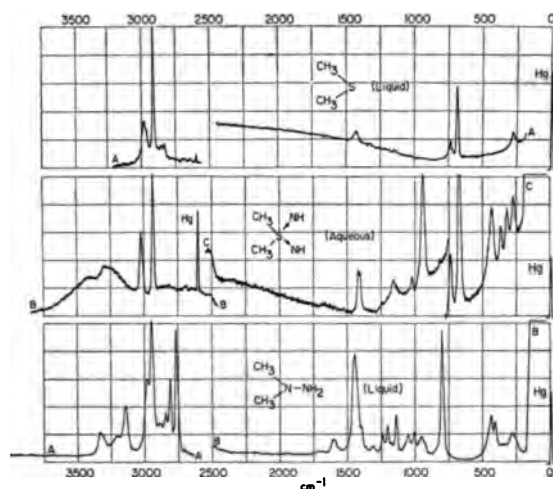


Figure 1. Raman spectra of dimethyl sulfide, aqueous dimethyl sulfone diimine, and unsymmetrical dimethylhydrazine. Gain: A, 100; B, 200; C, 500.

an intermediate, $R_2S^+(NH)Cl$, which is structurally analogous to sulfoxonium ions and which would solvolyze to the sulfone imine.

The sulfoxide could also conceivably have been formed by hydrolysis of the reactive sulfimine by adventitious moisture, although not by alcoholysis.⁴ No alternate scheme for the formation of sulfone imine is apparent. The sulfone diimine is hydrolytically inert (see later), and the possibility that the sulfone imine could have been formed by amination of sulfoxide was also ruled out. The sulfoxide is nearly inert to chloramine under the reaction conditions, and it is inconceivable that the observed high sulfone imine:sulfoxide ratio (ca. 6:1) would have occurred if sulfoxide amination were the mode of sulfone imine formation.

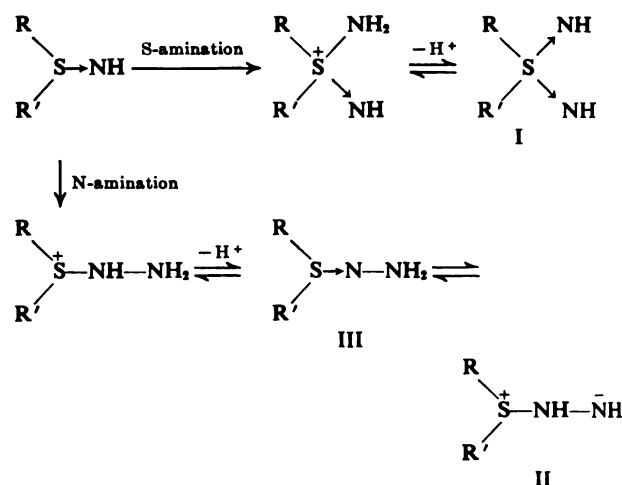
It is clear from these results why hydroxylic solvents are to be avoided in the synthesis if possible. Displacement on chlorine likely occurs to some extent in acetonitrile; however, ammonolysis of the S-chloro species would lead to the same product as if direct displacement on nitrogen had occurred.¹⁰

Proof of Structure

The reported nmr spectra of the diimines formed from dimethyl and diethyl sulfide^{1,2} clearly establish that the alkyl groups remain intact and exist in magnetically equivalent environments. The structural problem is reduced by these facts to determining whether the sulfimine intermediate is aminated by chloramine in the second stage of the synthesis on nitrogen or on sulfur. Amination on sulfur leads to structure I and tetrahedral coordination of sulfur, while N-amination yields II or III and trigonal sulfur. The dipolar form II would probably be much less stable than its tautomeric isomer III. Both tautomers have equivalent skeletal symmetry that is distinctly different from the tetrahedral diimine structure, I. Thus, the vibrational spectrum ought to allow one to distinguish between these two forms.

Here we report the Raman spectra of the dimethyl, diethyl, and methyl dodecyl derivatives of the chloramine-dialkyl sulfide reaction product. A vibrational

(10) H. Takei, I. Watanabe, and T. Makaiyama, *Bull. Chem. Soc. Japan*, **38**, 1989 (1965).



analysis and band assignment for the dimethyl derivative is consistent with C_{2v} symmetry, and strongly supports I as the correct structure of the group. Additional evidence has been obtained from infrared spectra and from the chemical properties of the compounds. The latter evidence is considered later at appropriate points in the description of these properties.

Dimethyl Sulfone Diimine. A. Spectroscopic Evidence. The Raman spectrum of a concentrated aqueous solution of the dimethyl sulfone diimine is exhibited in Figure 1 along with comparison spectra of liquid dimethyl sulfide and unsymmetrical dimethylhydrazine (u-DMH). Qualitative inspection of the spectra indicates the preservation of bands arising from the $(CH_3)_2S$ functional group and the completely different pattern for the hydrazine spectrum. In particular, we note the absence of an intense, polarized band in the 700–900- cm^{-1} range which can be assigned as the N–N stretching region for a hydrazine structure (808 cm^{-1} (Raman), 802 cm^{-1} (infrared) for u-DMH). In addition, we can find no evidence for bands associated with the NH_2 group. In u-DMH, the $\delta(NH_2)$ deformation occurs at 1606 cm^{-1} with $2\delta(NH_2)$ at 3207 cm^{-1} , probably in Fermi resonance with $\nu_{sym}(NH)$ at 3332 cm^{-1} . These NH_2 motions persist as discernible features in 25% aqueous solutions of u-DMH. In chloroform solution, both the Raman and the infrared spectra of I exhibit a single band at 3311 cm^{-1} , indicating degeneracy of the in-phase and out-of-phase NH stretch consistent with $R_2S(NH)_2$ and not $R_2S-N-NH_2$.

Table I summarizes the Raman data obtained on the aqueous sample of dimethyl sulfone diimine. Frequency assignments are based on comparison with the Raman spectra of dimethyl sulfide $((CH_3)_2S)$ ¹¹ and dimethyl sulfone $((CH_3)_2SO_2)$,¹² and the infrared data on sulfamide $((NH_2)_2SO_2)$.¹³ For clarity, bands associated with the sulfonyl group or interaction of SO_2 with other modes have been omitted from the table.

The dimethyl sulfide group appears to be unperturbed by formation of the diimine structure though the methyl hydrogen stretches do appear to be sensitive to changes in sulfur bonding. Again, note the absence of bands associated with the NH_2 group: NH_2 rocking modes at 720 and 1131 cm^{-1} , the NH_2 scissors at 1557

(11) The data tabulated here are in substantial agreement with that of R. Fonteyne, *J. Chem. Phys.*, **8**, 60 (1940).

(12) W. R. Fairheller, Jr., and J. E. Katon, *Spectrochim. Acta*, **20**, 1099 (1964).

(13) I. W. Herrick and E. L. Wagner, *ibid.*, **21**, 1569 (1965).

Table I. Raman Spectra of Dimethyl Sulfone Diimine and Comparison Compounds (cm⁻¹)^a

Aqueous ^b (CH ₃) ₂ S(NH) ₂	Liquid ^b (CH ₃) ₂ S	Aqueous ^c (CH ₃) ₂ SO ₂	Infrared cryst ^d (NH ₃) ₂ SO ₂	Assignment
278 m	282 s	292 s		δ(SC ₂), scissors
326 m		320 s		r(SC ₂), rock
371 m			362	δ(SN ₂), scissors
			422	τ(SNH ₂), NH ₂ torsion
436 m			506	r(SN ₂), rock
460 w			486	t(SN ₂), twist
679 vs, P	691 vs, P	700 vs, P		ν _s (CS), sym stretch
			720	r(NH ₂), NH ₂ rock
741 m	742 s	770 s		ν _{as} (CS), asym stretch
947 s, P			902	ν _s (SN), sym stretch
(975 vw) ^e			929	ν _{as} (SN), asym stretch
1162 w			1131	r(NH ₂), NH ₂ rock
1026 w, P	1149 w	950 w		r(CH ₃), rock
	1221 w	1006 m, P		
	1266 w	1090 w		
	1341 w	1292 w		
1225 vw	1427 m	1407 s		δ(CH ₃), bend
1408 m	1444 m	1430 ms		
1420 m			1557	δ(NH ₂), NH ₂ scissors
	2831 w			2δ(CH ₃) (?)
	2853 w			
2932 vs, P	2914 vvs, P	2928 vs, P		ν _s (CH), sym stretch
3018 s	2968 s			ν _{as} (CH), asym stretch
	2982 s	3024 vs		
			3112	
3250 m, B			3223	
			3323	ν(NH), stretch

^a Abbreviations used are: w, weak; m, medium; s, strong; v, very; P, polarized; B, broad. ^b This work. ^c Reference 12. ^d Reference 13. ^e Shoulder visible only with axial polarization.

Table II. Raman Spectra (cm⁻¹)^a

(CH ₃) ₂ S(NH) ₂ Solid	(CH ₃) ₂ S(O)NH Solid	50% aqueous	Assignment
274 w	285 m	285 s	δ(SC ₂), scissors
325 m	315 m	319 s	r(SC ₂), rock
368 w	374 w	373 m	δ(SN ₂ , SNO), scissors
435 s	466 s	457 s	r(SN ₂ , SNO), rock
452 w	442 m		t(C ₂ -S-N ₂), twist
685 vs	694 vs	690 vs, P	ν _s (CS), sym stretch
746 m	762 m	762 s	ν _{as} (CS), asym stretch
	814 w		?
		934 w	r(CH ₃), rock ?
918 s	971 m		ν _s (SN), stretch
933 s	989 w	989 s, P	(crystal splitting ?)
962 vw			ν _{as} (SN), asym stretch
1006 vw			
	1031 w	1050 m, P	ν(SO), stretch
1161 w	1122 w		δ(SNH), bend ?
	1150 w	1132 w, P	
	1212 w	1206 w	
1405 w	1403 m	1406 m	r(CH ₃), rock
1418 w	1434 m	1423 m	δ(CH ₃), bend
2930 vs	2925 s	2933 s, P	ν _s (CH), sym stretch
3015 s	3009 m	3019 s	ν _{as} (CH), asym stretch
3190 m	3191 w	3274 m, B	ν(NH), stretch
		3410 m, B	ν(OH), water band

^a Abbreviations used are: w, weak, m, medium; s, strong; v, very; P, polarized; B, broad.

cm⁻¹, and the NH₂ stretch triplet at 3112, 3223, and 3323 cm⁻¹ in the sulfamide.

The Raman spectrum of crystalline (CH₃)₂S(NH)₂ and of a 50% aqueous solution of dimethyl sulfone imine ((CH₃)₂S(O)NH) are presented in Figure 2. Table II summarizes the observed positions of the vibrations and proposed assignments. The similarity in the skeletal vibrations for these two molecules is immediately

apparent. Not only is the visual display (pattern) of the spectra of these two tetrahedral molecules quite similar, but there are, in addition, many close coincidences in the actual positions of bands arising from similar modes of vibration. The replacement of NH by O transforms the weak ν_{asym}(SN) at 962 cm⁻¹ into the more intense ν(SO) at 1031 cm⁻¹ (1050 cm⁻¹ in aqueous media).

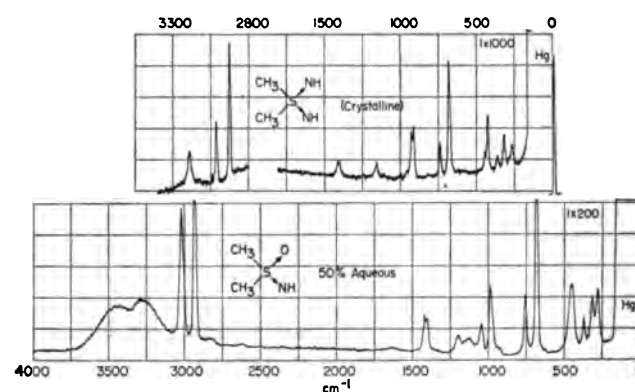


Figure 2. Raman spectra of crystalline dimethyl sulfone diimine and aqueous dimethyl sulfone imine.

B. Vibrational Assignment. The dimethyl sulfide reaction product can be analyzed as a pseudo-pentatomic molecule if we neglect all hydrogen motions. This is a reasonable approximation since we expect only very weak coupling between the light hydrogen atom vibrations and motions of the heavier skeletal atoms. For each of the pentatomic models we expect nine fundamental skeletal vibrations with all modes observable

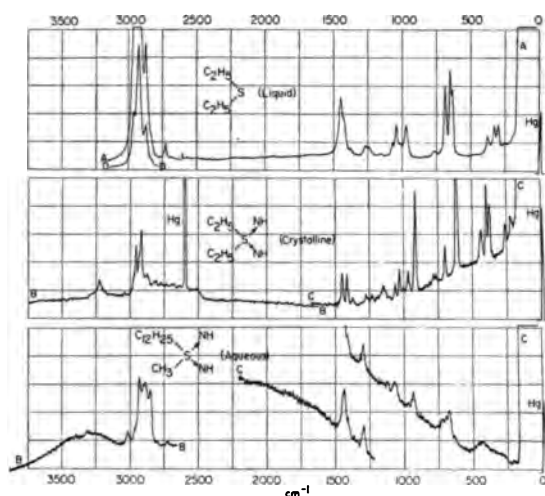


Figure 3. Raman spectra of diethyl sulfide, crystalline diethyl sulfone diimine, and methyl dodecyl sulfone diimine. Gain: A, 100; B, 200; C, 500; D, 40.

in the Raman. Four of these fundamentals should arise primarily from stretching motions and five from angle deformations.

The diimine structure I has C_{2v} symmetry. Its vibrational representation is $4A_1 + A_2 + 2B_1 + 2B_2$. There should be one inactive infrared fundamental (A_2 , a torsional mode) and four polarized Raman lines. Two of the latter should be intense and arise from C-S and N-S stretching motions.

The hydrazine structure III (or II) has C_s molecular symmetry. With a vibrational representation of $6A' + 3A''$, all modes should be active in both the infrared and Raman. However, the six A' modes should be polarized in the Raman and three of these should be strong lines related to C-S, S-N, and N-N stretching motions.

Since hydrogen deformations are weak scatterers in the Raman, we can expect all strong bands observed below 1100 cm^{-1} to arise from skeletal motions. The Raman spectrum of an aqueous solution of the alkyl sulfide reaction product exhibits only two strong polarized lines in the skeletal stretching region and no evidence for a third, strong, polarized band associated with the N-N stretch. We associate the paired couplets 679, 741, and 947, 975 cm^{-1} with the symmetric and asymmetric motions of $(\text{CH}_3)_2\text{S}$ and $(\text{NH})_2\text{S}$, respectively, and note the absence of strong interaction between the two pairs of vibrators. The remaining five bands we assign to the predicted five deformation modes. The proposed band assignments for the skeletal motions are summarized in Table III. The assignment of ν_7 and ν_8 to SNH motions is based on the increase in apparent intensity of the respective Raman bands upon crystallization and the formation of intermolecular hydrogen bonds (see below). All assignments are consistent with those of ref 12 and 13.

Dialkyl Sulfone Diimines. In addition to the methyl derivative, we have also examined the Raman spectra of the diethyl and the methyl dodecyl derivatives. Representative data are listed in Table IV with typical spectra illustrated in Figure 3. Spectral assignments are complicated by the presence of rotational isomers¹⁴

(14) D. W. Scott, J. P. McCullough, *et al.*, *J. Am. Chem. Soc.*, **74**, 4656 (1952) (cites unpublished work of J. R. Nielsen, on diethyl sulfides).

Table III. Symmetry Assignment for $(\text{CH}_3)_2\text{S}(\text{NH})_2$

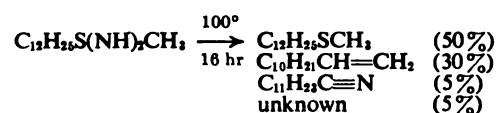
Symmetry Class	Specie	Frequency, ^a cm^{-1}	Approximate mode description
A_1	ν_1	947	S-N symmetric stretch
	ν_2	679	C-S symmetric stretch
	ν_3	371	NSN bend
	ν_4	278	CSC bend
A_2	ν_5	460	Torsion, $\text{S}(\text{NH})_2$ twist
B_1	ν_6	975	S-N antisymmetric stretch
	ν_7	436	$\text{S}(\text{NH})_2$ rock \perp $\text{S}(\text{CH}_3)_2$ plane
B_2	ν_8	741	C-S antisymmetric stretch
	ν_9	326	$\text{S}(\text{NH})_2$ wag \parallel $\text{S}(\text{CH}_3)_2$ plane

^a Aqueous solution

which generate multiple strong Raman bands in the $600\text{--}700\text{ cm}^{-1}$ region. Diethyl sulfide data have been included to aid in the comparison. Again we note the persistence of the characteristic vibrations of the dialkyl sulfide group and the absence of strong perturbation by amination. These data are also quite consistent with the diimine structure proposed for the dimethyl sulfide reaction product. The characteristic positions for Raman bands associated with the $\text{S}(\text{NH})_2$ structural unit in dialkyl sulfone diimines are summarized in Table V. The variation in characteristic frequency appears to be consistent with the effects of hydrogen bonding on each vibrational mode and the presence of water in the sample. The S-N asymmetric stretch and the SNH deformation would be expected to be more prominent in the infrared, and may be of some diagnostic value.

Properties

Thermal Stability. The thermal stability of dimethyl and diethyl sulfone diimines is sufficient to allow them to be analyzed by gas chromatography at 150° , with partial decomposition at the inlet. After 16 hr at 100° , neat methyl dodecyl sulfone diimine is largely decomposed, to the products shown.



Ammonia, azide (N_3^-), and thiocyanate (SCN^-) were also detected.

As with amine oxides,¹⁵ the thermal stability of the sulfone diimines is greatly enhanced in hydroxylic solvents. An aqueous solution of methyl dodecyl sulfone diimine underwent less than 10% decomposition under the same conditions which completely decomposed the neat sample (above).

Hydrolysis and Reduction Reactions. The extraordinary resistance of sulfone diimines toward acid- or base-catalyzed hydrolysis² has been confirmed. Dimethyl sulfone diimine was recovered unchanged after 67 hr at 100° in water; no hydrolysis products were detectable either by infrared spectra or gas chromatographic analysis. Similar results were obtained after 1.5 hr at 100° in 2 *N* sodium hydroxide.

The cleavage of the C-S bond in sulfone diimines by aqueous hydrochloric acid to form alkyl chlorides and sulfinic acids has been reported,² and we obtained

(15) D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *ibid.*, **84**, 1734 (1962).

Table IV. Raman Spectra (cm⁻¹)^a

(CH ₃ CH ₂) ₂ S ^b Liquid	(CH ₃ CH ₂) ₂ S(NH) ₂ Crystal	Aqueous	(C ₁₂ H ₂₅) ₂ S(NH) ₂ Crystal	Aqueous	Qualitative description
187 w	227 w				CSC skeletal bend
256 vw	267 w	260 vw			
305 m, P		313 w	306 w	303 w	
334 m, P		343 m			Skeletal deformations
383 w	382 m		376 w	356 w	
	407 s	407 m	417 vw		SN ₂ rock
	444 m	444 w	445 vw	437 m	
		475 w	470 vw		
		521 w	510 vw		
		621 s	610 vw		
639 vs, P	619 s	636 vs, P		643 w, P	C ₂ S sym stretch (rotational isomers)
657 vs, P		662 m, P		683 s, P	
693 s	707 w	700 m	707 s	707 m, P	C ₂ S asym stretch
764 vw	774 vw	779 vw	734 m	732 m, P	
778 vw	792 vw	817 vw	817 w		S-N sym stretch C-C sym stretch Combination?
	922 s	945 s, P	925 m	943 m, P	
975 s	976 w	979 w	957 w	979 w, P	
1017 w	1010 vw	1026 w			CH ₂ deformation
1047 s	1043 w	1041 w	1056 w	1071 w	
1074 m	1068 w	1074 w	1083 w	1084 w	
	1155 w, B	1150 w, B	1125 m	1131 w	SNH bend?
			1167 vw	1165 vw	
1249 w	1238 vw	1236 w	1207 vw		Overtone?
1274 w, P	1282 vw		1295 m	1306 s	
1382 w	1380 vw	1382 w			CH ₂ deformation
1427 s	1421 w	1414 m	1412 w	1418 m	
1450 s	1456 w	1456 m	1442 m	1444 s	
			1458 m		CH stretch
2729 m, P					
2874 s, P	2877 w	2885 s	2850 vs	2857 vs, P	
	2922 vs		2879 vs	2895 vs, P	
2929 vs, P	2937 m	2939 vs	2928 vs	2934 vs, P	
2966 s	2959 m				NH stretch
	2976 w	2988 s		3018 m	
	3227 w	3290 s, B	3180 w		
			3222 w		H ₂ O stretch
			3307 w	3304 m, B	
				3397 m, B	

^a Abbreviations used are: w, weak; m, medium; s, strong; v, very; P, polarized; B, broad. ^b Data below 1500 cm⁻¹ from ref 14.

Table V. Characteristic R₂S(NH)₂ Raman Bands

Type of motion	Position, cm ⁻¹	Quality
SN ₂ deformation	340-380	m, P
SN ₂ rock	435-445	m
S-N sym stretch	920-950	s, P
S-N asym stretch	960-980	w
SNH deformation	1125-1160	w
NH stretch	3190-3335	m

identical results. Unexpectedly, the reaction took a completely different course in aqueous hydrochloric acid containing potassium iodide (2.4 N HCl, 6 N KI). A few per cent cleavage to alkyl halides was again observed, but the major products were the dialkyl sulfide and iodine. Sulfoxides are also reduced to sulfides by iodide in acidic solution.¹⁶

The reluctance of the group to undergo acid- or base-catalyzed hydrolysis to sulfone imines or sulfones constituted supporting evidence for structure I. The related sulfone imines are also resistant to hydrolysis, whereas structures II or III, being N-substituted sulfinimines, should resemble the parent sulfinimines in being readily hydrolyzable.

Methyl dodecyl sulfone diimine reacted exothermically with massive quantities of hydrogen-bearing W-2

(16) D. Landini, F. Montanari, H. Hogeveen, and G. Maccagnani, *Tetrahedron Letters*, 2691 (1964).

Table VI. Acid Dissociation Constants of Protonated Sulfone Diimines and Other Compounds

Compound	pK _A
(CH ₃) ₂ S(NH)NH ₂ ⁺ , Cl ⁻	5.59 ± 0.01 ^a
(C ₂ H ₅) ₂ S(NH)NH ₂ ⁺ , Cl ⁻	5.93 ± 0.05 ^a
C ₁₂ H ₂₅ (CH ₃)S(NH)NH ₂ ⁺ , Cl ⁻	4.73 ± 0.1 ^a
(CH ₃) ₂ S(O)NH ₂ ⁺ , Cl ⁻	3.24 ± 0.02 ^b
(CH ₃) ₂ S ⁺ (O)OH, Cl ⁻	-12.3 ^c
(CH ₃) ₂ S ⁺ OH, Cl ⁻	0 ^d
(CH ₃) ₂ NOH ⁺ , Cl ⁻	4.65 ^d

^a Calculated from potentiometric titration curves following the method of A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962, p 33. ^b Calculated following the method of Albert and Serjeant, p 38. ^c S. K. Hall and E. A. Robinson, *Can. J. Chem.*, 42, 1113 (1964). ^d P. Nylen, *Z. Anorg. Allgem. Chem.*, 246, 227 (1941).

Raney nickel in alcohol. Methyl dodecyl sulfide (18%) and dodecane (10%) were isolated.

Basicity and Metal Complexing. The pK_A data in Table VI show that the sulfone diimines are weakly basic molecules. They are about 2.5 pK units more basic than sulfone imines.

The pK_A data also constitute evidence which favors I as the correct structure of the group. Structure III can be viewed as a modified hydrazine, in which a partial negative charge resides on one nitrogen.

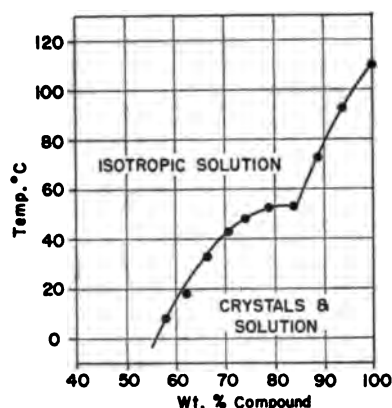
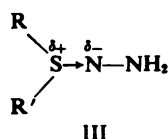


Figure 4. Solubility diagram of dimethyl sulfone diimine in water.



This negative charge would be expected to increase the basicity of III over that of hydrazine itself, so that the predicted pK_A of the conjugate acid of III should be >8.5 . The much lower values observed rule against structure III. It is impossible to predict exactly what the basicity of I should be, but if the same difference exists between its basicity and that of NH_2^- as exists between that of sulfones and OH^- , a value in the neighborhood of 6 for the pK_A of its conjugate acid would be anticipated.¹⁷ The original structure proposal,¹ $R_2S^+-NH-NH^-$, is not stabilized by semipolar bonds and, in having an amide ion insulated from the sulfur by the $-NH-$ group, should be considerably more basic than was observed (compare $R_3N^+NH_2$ with a $pK_A > 15$).

The metal complexing ability of the sulfone diimine group with metal salts from vanadium to zinc in the first long row of the periodic table (in convenient oxidation states) was screened in a qualitative fashion. Obvious complexing occurred only with V(IV), Cr(III), Fe(III), and Cu(II). The complexing ability of the sulfone diimine thus parallels that of aliphatic amine oxides in general, in line with the close similarity in basicity of the two groups (Table VI).

With silver nitrate, each of the sulfone diimines formed an insoluble grayish precipitate which was accompanied by a sharp decrease in the pH of the solution to 2–3.¹⁸ It thus appears that actual liberation of mineral acids occurs in aqueous solution through reaction with silver ion, although potentiometric titration with base revealed no clean-cut stoichiometry. No such pH effect was noted with any other metal ion. Formation of the precipitate was reversible: addition of nitric acid redissolved it. Also, it was not formed from silver acetate in glacial acetic acid. The latter system constituted a convenient qualitative test for chloride in the presence of sulfone diimines.

(17) The pK_A of $H-OH$ (15) is lowered to -12 in $R_3S^+(O)-OH$, a difference of 27 pK units. Taking 33 as the pK_A of NH_4 , $R_3S^+(O)NH_2$ should have a value of 6 if the same difference were observed (the actual value is 3), and $R_3S(NH)-NH_2$ would not be expected to be terribly different. This crude line of reasoning only shows that the observed values are in a reasonable range.

(18) The formation of a precipitate with silver ion was previously reported,² but not the pH effect.

Polarity and Hydrogen Bonding. The sulfone diimine group is a polar functional group, as indicated by the high water solubility of the dialkyl derivatives. Figure 4 describes the water solubility of dimethyl sulfone diimine. Methyl dodecyl sulfone diimine is likewise water soluble, while methyl dodecyl sulfone is by contrast totally insoluble.

The vibrational spectral data suggest that the sulfone diimine group readily engages in hydrogen bonding. Spectrally, hydrogen-bond formation is manifested in intensity changes, band broadening, and frequency shifts.¹⁹ For dimethyl sulfone diimine ν_7 , ν_1 , and ν (NH) are shifted from 415, 933, and 3311 cm^{-1} in relatively inert chloroform to 436, 947, and 3250 cm^{-1} in aqueous solution. This corresponds to an increase in the resistance to deformation of a bending mode and an effective elongation of the NH bond upon hydrogen bond formation. Dimethyl sulfone imine exhibits similar spectral effects in a comparison of chloroform and aqueous solution spectra: $\nu(SN)$ shifts from 982 to 989 cm^{-1} , $\nu(SO)$ from 1020 to 1050 cm^{-1} , and $\nu(NH)$ from 3340 to 3274 cm^{-1} .

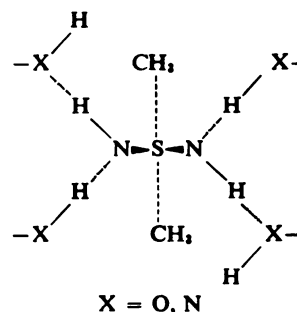
Hydrogen-bond formation is more pronounced in the crystalline state, as indicated by the larger shift of the NH stretching frequencies summarized in Table VII. Extensive hydrogen bonding is evident in crystal-

Table VII. NH Stretching Bands, cm^{-1}

Compound	Crystal	Aqueous	$CHCl_3$
$(CH_3)_2S(NH)_2$	3190	3250	3311
$(CH_3)_2S(O)NH$	3191	3274	3340
$(C_2H_5)_2S(NH)_2$	3227	3290	...
$(CH_3)(C_{12}H_{25})S(NH)_2$	3178 3222	3304	...

line dimethyl sulfone diimine: ν_3 and ν_7 are stronger and sharper bands and ν_1 is split into two components. The splitting is interpreted as arising from intermolecular interaction rather than local site symmetry effects since ν_2 is not split in the crystalline spectrum.²¹

Only one type of imine hydrogen is indicated in the solution and crystalline spectrum for the dimethyl derivative; thus we propose a general structural model of the form



(19) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960.

(20) All aqueous NH stretching bands are broadened and their positions are less certain owing to variation in internuclear distance caused by hydrogen bonding.

(21) Preliminary X-ray diffraction studies²² indicate each of the eight molecules in the unit cell is situated at a local site with C_2 symmetry. Thus, ν_1 and ν_2 should be similarly affected if crystal site splitting is operative.

(22) N. Webb, these laboratories, personal communication.

present the spatial interaction with either water (aqueous) or diimine (crystal). This model also illustrates the dual nature of the diimines in accepting donating hydrogens in interaction with other electronegative atoms.

The shift of $\nu(\text{NH})$ for crystalline diethyl sulfone diimine is 35 cm^{-1} less than for the dimethyl derivative, indicating a weaker hydrogen bond. This probably results from van der Waals repulsion of the alkyl fragments leading to lattice packing problems. When one of the alkyl groups is replaced by a bulky long chain unsymmetrical methyl dodecyl derivative we observed two NH bands, indicating both a long and short $\text{NH} \cdots \text{N}$ bond.

If we assume a value of 3350 cm^{-1} for free imine stretching frequency,^{23,24} then the average shift of 35 cm^{-1} allows us to estimate the crystalline hydrogen-bond strengths for these diimines as 2.5–3.0 kcal/mole for the $\text{NH} \cdots \text{N}$ bond.^{19,25,26} On the same basis, the interaction with water is probably of the order of 2.0–3.0 kcal/mole. Thus the solvation of the diimines is aided by the availability of 4–5 kcal/mole of diimine–water interaction energy.

Discussion

In the synthesis of the sulfone diimines, all the available imines of sulfoxides⁴ and sulfones have been used. It is, therefore, of interest to compare the results with each other and with the parent oxygen compounds.

The various imines may be conveniently divided into two classes: sulfoxide-like structures incorporating one semipolar bond, and sulfone-like structures in which two semipolar bonds are formed to the same heteroatom. Comparison of the sulfone diimines with the sulfoxide diimines reveals that the same fundamental relationship in properties which exist between sulfones and sulfoxides also exist between the two classes of imines. The thermal stability of the sulfone diimines clearly exceeds that of the sulfoxide diimines. For comparable decomposition, roughly 100° higher temperatures are required for the sulfone diimines. Also, the basicity of the sulfone diimines appears to exceed that of the sulfoxide diimines, as is the case with sulfoxides and sulfones (Table VI). While direct measurement of the basicity of sulfoxide diimines in aqueous solution is precluded by their hydrolytic instability, they are known to form an adduct with carbon dioxide in nonhydroxylic solvents, $\text{R}_2\text{N}^+\text{HCO}_2^-$,²⁷ whereas the sulfone diimine group does not. A chloroform solution of the latter saturated with carbon dioxide shows the free CO_2 infrared band, with absorption corresponding to $-\text{CO}_2^-$ or $-\text{CO}_2\text{H}$. On the other hand, the sulfoxide diimines are not sufficiently stable to prevent their liberation from their conjugate acid at least in part, by ammonia. The aqueous pK_a of the species $\text{R}_2\text{S}^+-\text{NH}_2$ is therefore most likely in the range 8–10.

A higher frequency than the 3311 cm^{-1} observed in CHCl_3 is expected since self-association and/or interaction with the acidic proton of chloroform would tend to lower the free $=\text{NH}$ frequency.

N. B. Colthup, *J. Opt. Soc. Am.*, **40**, 397 (1950), cites a range of 1400 cm^{-1} for an imine NH.

R. Schroeder and E. R. Lippincott, *J. Phys. Chem.*, **61**, 921 (1957).

D. Nakamoto, M. Margoshes, and R. E. Rundle, *J. Am. Chem. Soc.*, **77**, 6480 (1955).

R. Appel and G. Büchler, *Ann.*, **684**, 112 (1965).

Examination of the presently known imines reveals a striking difference between the two classes, above, with regard to hydrolytic reactivity. It appears to be generally true that sulfoxide-like imines are readily hydrolyzable to the parent oxygen compounds, while sulfone-like imines are hydrolytically inert. The acid- or base-catalyzed hydrolysis of a sulfone imine or diimine has so far never been observed.²⁸ Examples of hydrolytically reactive sulfoxide-like imines include $\text{R}_2\text{S}=\text{NH}^+$ and $\text{R}-\text{S}(\text{NH})\text{NH}_2$.²⁹ Similarly reactive phosphorus imines which are "sulfoxide-like" in the above sense include $\text{R}_3\text{P}=\text{NH}^+$ and $(\text{H}_2\text{N})_3\text{P}=\text{NH}$.³¹

Now let us consider the relationship between sulfoxides and sulfones, and their imine derivatives. It is apparent that the thermal stability of the imines is significantly lower than that of the oxygen compounds. Sulfoxide diimines decompose at room temperature and below, sulfoxides in the vicinity of 150° and higher. Sulfone diimines decompose rapidly at slightly over 100° , sulfones only at temperatures well over 200° .³² The sulfone monoimine is more like the sulfone than the sulfone diimine in this respect.

Another fundamental distinction between the S–N and S–O compounds is the course which thermal decomposition takes. Both fragment to olefins, when β elimination is permitted by the structure. However, the S–N compounds (both sulfoxide diimines and sulfone diimines) yield the parent dialkyl sulfide as a major decomposition product whereas with sulfoxides and sulfones the dialkyl sulfide is a very minor product.³³ The possibility that the dialkyl sulfide is not a primary decomposition product but is formed by a secondary reaction between olefin and mercaptan cannot be rigorously excluded.

Another prominent difference between the oxygen and nitrogen analogs exists with regard to basicity and metal complexing. The figures in Table VI indicate the two sulfone imines to be 15–18 pK units more basic than the corresponding sulfone, a figure comparable to the difference between amide and hydroxide ion (pK_a of $\text{NH}_3 \cong 33$, pK_a of $\text{H}_2\text{O} \cong 15$). The cause for the large difference in each case stems from the difference in nuclear charge of nitrogen and oxygen.

It is evident from this work that the sulfur atom of sulfoxide diimines is appreciably more nucleophilic toward chloramine than is that of sulfoxides. Chloramine reacts preferentially with the sulfoxide intermediate in the presence of high ammonia concentrations at temperatures below 0° . Sulfoxides, by contrast, compete

(28) Indirect hydrolysis of the monoimine by reaction with hydrogen peroxide or nitrous acid has been carried out [A. Schöberl and A. Wagner, "Methoden der Organischen Chemie (Houben-Weyl)," Vol. 9, Eugen Müller Ed., Georg Thieme Verlag, Stuttgart, 1955, p. 220; F. Misani, T. W. Fair, and L. Reiner, *J. Am. Chem. Soc.*, **73**, 459 (1951)]. However, the monoimines have been recovered unchanged from refluxing 50% sodium hydroxide (J. S. Berry, private communication from these laboratories).

(29) This species is presumably formed as the initial sulfur-containing product of the hydrochloric acid cleavage of sulfone diimines. Hydrolytically reactive aromatic derivatives have also been reported [G. Kresse, C. Seyfried, and A. Trede, *Tetrahedron Letters*, 3933 (1965)].

(30) H. H. Sisler, A. Sarkis, H. S. Ahuja, R. J. Drago, and N. L. Smith, *J. Am. Chem. Soc.*, **81**, 2982 (1959); R. Appel and A. Hauss, *Chem. Ber.*, **93**, 405 (1960).

(31) M. Becke-Goehring and K. Niedenzu, *ibid.*, **90**, 2072 (1957).

(32) Methyl dodecyl sulfone distills with some decomposition at 355° at atmospheric pressure.

(33) Methyl dodecyl sulfoxide at $190\text{--}230^\circ$ in an open system gave less than 1% sulfide. The yield of sulfide from pyrolysis of the sulfone was still less, if formed at all. See W. Carruthers, I. D. Entwistle, R. A. W. Johnstone, and B. J. Millard, *Chem. Ind. (London)*, 342 (1966).

Table VIII. Melting Points and Analyses of Dialkyl Sulfone Diimines, RR'(NH)₂

R	R'	Mp, °C	% C		% H		% S		% N	
			Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
CH ₃	CH ₃	108.5–110	26.1	26.1	8.7	8.8	34.8	34.1	30.4	30.4
C ₁₀ H ₂₁	CH ₃	56–57	60.5	60.1	12.1	11.7	14.8	15.1	12.9	12.9
C ₁₂ H ₂₅	CH ₃	64.5–66.5	63.4	63.7	12.3	12.2	13.0	13.4	11.4	11.4
C ₁₄ H ₂₉	CH ₃	73.5–74.5	65.6	65.6	12.5	12.1	11.7	12.0	10.2	10.2
C ₁₆ H ₃₃	CH ₃	79–80	67.5	67.7	12.7	12.4	10.6	10.4	9.3	9.3

Table IX. Nmr Chemical Shifts of S-Methyl Groups (τ units)

	CDCl ₃ ^a	D ₂ O ^b
(CH ₃) ₂ S	7.89	...
(CH ₃) ₂ SO	7.39	...
(CH ₃) ₂ SO ₂	7.08	...
(CH ₃) ₂ S(O)NH	6.90	...
(CH ₃) ₂ S(NH) ₂	6.94	6.59
(CH ₃) ₂ S ⁺ (NH)NH ₂ , Cl ⁻	6.36	6.10
(CH ₃) ₂ S ⁺ (O)NH ₂ , Cl ⁻	6.23	5.98 ^c
C ₁₂ H ₂₅ SCH ₃	7.94	...
C ₁₂ H ₂₅ SOCH ₃	7.44	...
C ₁₂ H ₂₅ S(NH) ₂ CH ₃	7.02	6.73
C ₁₂ H ₂₅ S(O)(NH)CH ₃	7.10	...
C ₁₂ H ₂₅ SO ₂ CH ₃	7.15	...

^a Internal tetramethylsilane reference. ^b Tetramethylsilane capillary reference. ^c In the presence of excess HCl.

Table X. Nmr Spectra of (C₂H₅)₂S(NH)₂ (τ units)

Solvent	CH ₂ (3)	CH ₂ (4)	NH(1)	J, cps
D ₂ O	8.42	6.60	5.00	7.4
CDCl ₃	8.61	7.00	8.27 (broad)	7.4
CCl ₄	8.70	7.17	8.49 (sharp)	7.7
CCl ₄ ^a	8.7	7.1	8.1	...

^a Reference 1.

very poorly with ammonia for chloramine under comparable conditions.

Experimental Section

Melting point (capillary, Mel-Temp apparatus, uncorrected) and analytical data are listed in Table VIII. Elemental analyses were performed by our analytical department. Nmr data were determined with a Varian HA-100 spectrophotometer. The chemical shifts of S-methyl groups in various compounds are tabulated in Table IX. The spectra of the long-chain compounds included other features expected from the structure, namely a triplet for the -CH₂-α to the sulfur downfield from the S-methyl absorption, characteristic long-chain absorption at τ 8.75 and 9.15 (methylene protons and terminal methyl protons), plus broad absorption slightly downfield from most of the methylene protons attributable to the β-methylene group. Table X gives complete nmr data for diethyl sulfone diimine in various solvents.

Raman spectra were obtained on the Cary 81 Raman spectrophotometer using 4358-A mercury excitation and capillary cells (0.2-cc capacity). The instrument was calibrated with respect to argon, neon, and helium emission lines from low-pressure discharge lamps, and all strong Raman bands are believed accurate to ±2 cm⁻¹. The hygroscopic nature of the samples made it convenient to obtain spectra from aqueous solutions although crystalline and chloroform solution spectra were also obtained. All solutions were filtered through activated charcoal and 0.45-μ Millipore filters to minimize fluorescence and scattering from particulate matter. Polarization data were obtained in the conventional manner using Polaroid cylinders.

Good infrared spectra were difficult to obtain free from the interfering effects of absorbed moisture. The solution spectra reported were taken on a Perkin-Elmer 421 grating spectrometer.

Gas chromatography was carried out on a Model 700 F & M instrument, using a 10% Apiezon on polytetrafluoroethylene column. Partial decomposition of the dimethyl sulfone diimine in the inlet (kept <170°) prevented quantitative application of gc,

but a standard mixture of dimethyl sulfone, sulfone imine, and sulfone diimine approached the expected peak area ratios sample levels (several milligrams). Relative retention times of dimethyl sulfone, sulfoxide, sulfone imine, and sulfone diimine were 1.0, 0.87, 1.53, and 1.90, respectively. At a column temperature of 135° (0.25-in. columns, 50 cc of He/min), the sulfone had a retention time of ca. 3 min.

The reference sulfone imines were prepared from sulfoxide and hydrazoic acid by the method of Whitehead and Bentley. Thin layer chromatography (tlc) was carried out on standard G plates, developed with methanol except where noted. The spots were visualized by spraying with 25% acid and charring.

Dimethyl Sulfone Diimine. In a 500-ml, three-necked flask equipped with a 10-mm diameter gas inlet tube, stirrer, and cold-finger condenser fitted with a drying tube were placed (0.10 mole) of dimethyl sulfide and 180 ml of acetonitrile (dried over 4A molecular sieves). Chloramine-ammonia from a generator operating at 10 mmole/min of Cl₂ and 10:1 NH₃:Cl₂ ratio was passed in at -15° for 1 hr (ca. 0.4 mole), and the flask placed in an ice-salt bath and stirred overnight. The temperature in the morning. The reaction was filtered, the filtrate evaporated to dryness *in vacuo*, and the residue sublimed at 80–90° (0.1 mm). Yields varied from 12 to 39% of material which was largely dimethyl sulfone contaminated by sulfoxide and sulfone imine and was used for gas chromatography. The hygroscopic crystals could be purified by recrystallization from acetonitrile or resublimation attempts to improve this work-up procedure or scale up the reaction to 0.3 mole gave poorer yields.

Diethyl Sulfone Diimine. Diethyl sulfide (9.0 g, 0.10 mole) was aminated as described above for dimethyl sulfide. The filtrate was evaporated, taken up in acetonitrile, and washed with 50% aqueous potassium carbonate until chloride free (see preparation of dodecyl homolog for description of test), the solvent evaporated and the residue distilled; bp 70° (0.1 mm). The distillate (51%) had a freezing temperature of 48°,^{1,2} and was identical with its nmr and infrared spectra with the compound synthesized by Cogliano and Braude. It could be gas chromatographed through the same column used for the dimethyl homolog.

Methyl Dodecyl Sulfone Diimine. In a 2-l. apparatus similar to that described above, but without the condenser, were placed (0.400 mole) of methyl dodecyl sulfide and 1300 ml of acetone (dried over 4A molecular sieves). Chloramine was passed in a flask at 0–5° during four 1-hr periods, at an average rate of 0.5 mole/hr. After each 1-hr period, the glass wool-ammonium chloride filter was replaced. The reaction was then stirred over 0° and filtered cold.

The filter cake was extracted thoroughly with 2-propanol; the bulk of the 2-propanol removed *in vacuo* using a rotary evaporator.³⁴ The residue was then redissolved in 2-propanol washed several times with 50% aqueous potassium carbonate a test sample of ca. 1 ml, dissolved in 3–5 ml of glacial acetic acid gave no precipitate with a few drops of aqueous 0.5% silver nitrate reagent. The 2-propanol was again evaporated and the residue recrystallized from ethyl acetate or acetonitrile, yield 45%. Tlc indicated the once recrystallized product to be pure but contaminated with sulfone imine, sulfoxide, and a n-dodecane. Multiple recrystallizations reduced these impurities to a level not detectable on the chromatogram with a 1000-μg sample (<0.5%). Work-up of the mother liquors from recrystallization of the main product yielded 11% recovered sulfide, plus 1% dodecane and 1% dodecanenitrile. Each was unambiguously identified by gas chromatography retention times on a polar nonpolar column, infrared spectra, and (in the case of the

(34) J. K. Whitehead and H. R. Bentley, *J. Chem. Soc.*, 1572 (1952).

(35) If this evaporation was omitted, it proved to be essentially impossible to wash the system free of chloride with the potassium carbonate.

the nmr spectrum. The sulfone diimine (Infracord, mull) showed infrared bands at 3.02 (m), 3.4 (s), 3.5 (s), 3.85 (m), 7.1 (m), 7.65 (m), 9.1 (s, broad), 9.5 (s), 9.75 (m), 10.15 (m), 10.45 (m), 10.85 (s), 13.1 (w), 13.45 (m), 13.55 (m), 13.9 (m), and 14.2μ (w).

A similar preparation was carried out in molecular sieve dried 2-propanol. After stirring overnight, the reaction was filtered and the ammonium chloride precipitate washed with 2-propanol. The combined filtrate and washings were evaporated, taken up in 2-propanol, and worked up as described above; yield 44%.

Tlc of the crude 2-propanol reaction product after the carbonate washes showed four spots at R_f 0, 0.48, 0.64, and 0.75, which corresponded to an unknown compound (possibly the sulfimine or its hydrochloride, or the hydrochloride of the sulfone diimine), the sulfone diimine, the sulfone imine and/or sulfoxide, and the sulfide, respectively. To determine the amounts of these quantitatively, the amination was repeated under identical conditions on 2.00 g of sulfide, and the entire reaction product chromatographed on a silica gel column (22×280 mm), eluting first with 2-propanol and then with 3A ethanol. The yield of recovered sulfide (free of dodecene) was 8%, the sulfone imine-sulfoxide fraction 7%, and the sulfone diimine fraction 64%. The nmr spectrum of the sulfone imine-sulfoxide fraction showed the two components to be present in ca. 5:1 ratio, from the relative intensities of the $S-CH_3$ peaks at τ 7.05 and 7.46. A ratio of this magnitude was confirmed by tlc using a solvent system later found to resolve sulfoxide from sulfone imine (95:9:1:0.5 chloroform-methanol-water-acetic acid).

Methyl Decyl Sulfone Diimine. This compound was prepared from 0.3 mole of methyl decyl sulfide and 1.2 moles of chloramine in acetonitrile following the same procedure described above for the dodecyl homolog. The compound was isolated in 45% yield.

Methyl Tetradecyl (and Hexadecyl) Sulfone Diimine. These homologs could not be obtained in satisfactory yield in acetonitrile reaction medium, because the sulfide starting material crystallized from acetonitrile solution at the desired reaction temperature. They were, therefore, prepared in 2-propanol, in which the sulfides are more soluble in the cold. Tlc showed, however, that recrystallization failed to remove the sulfone imine impurity. It was necessary to resort to column chromatography on silica gel (described above) for purification.

Thermal Decomposition and Hydrolysis Experiments. These were carried out in sealed tubes immersed in a steam bath. In the case of the dimethyl homologs, the products were isolated by adding the reaction mixture to several volumes of 50% potassium carbonate and extracting with 2-propanol. It was shown that dimethyl sulfoxide, sulfone, sulfone imine, and sulfone diimine could all be recovered from aqueous solution in high yield by this technique. In 2 *N* acid, no recoverable products were found after 30 min at 100°. Decomposition products of the dodecyl compound in acid were unambiguously identified by comparison of gas chromatography retention times and infrared spectral data with those of authentic materials. Yields, where reported in the text, were determined by injecting several large samples (30–40 μ l) in the gc and weighing the fractions collected.

Decomposition experiments on the dodecyl homolog in 2.4 *N* HCl–6 *M* KI at 100° for 30 min gave I_2 (1.2 moles/mole of diimine)

and a liquid which was principally methyl dodecyl sulfide (48%) containing dodecyl chloride and dodecyl iodide (combined yield 3%). However, when methyl dodecyl sulfone diimine was heated with 2 *N* HCl and worked up with a carbonate wash, a water-soluble long-chain potassium salt lacking an $S-CH_3$ in the nmr was isolated, in addition to dodecyl chloride, and was shown to be potassium dodecanesulfinate by reaction in aqueous solution with methyl iodide. Methyl dodecyl sulfone, identified unambiguously by infrared spectra and gas chromatography retention time, was isolated. The experiment was repeated, and the dodecyl chloride and dodecanesulfinic acid yields were estimated to be 53 and 37%, respectively.

No dodecyl mercaptan was ever detected among the decomposition products (gas chromatography).

Metal Complexing. Solutions (0.1 *M*) of dimethyl sulfone diimine, trimethylamine oxide, or trimethylphosphine oxide solutions were mixed with an equal volume of 0.1 *M* solutions of the metal salts. The phosphine oxide caused no visible change with any salt but $VOSO_4$ (blue \rightarrow green). The visible changes with diimine and amine oxide were indistinguishable: $VOSO_4$, blue \rightarrow green; $Cr(NO_3)_3$, blue \rightarrow green; $MnCl_2$, no change; $FeCl_3$, yellow \rightarrow red-orange, prevented precipitation on standing which occurred in the control solution; $CoCl_2$, no change; $NiCl_2$, no change; $CuSO_4$, blue-green precipitate, identified as $Cu_2SO_4(OH)_2$ by the X-ray powder pattern; $ZnCl_2$, no change. Adding $CuSO_4$ solutions to a concentrated solution of the sulfone diimine gave an obvious deepening of the blue color.

Addition of $AgNO_3$ test reagent to any of the sulfone diimines in aqueous solution gave a gray precipitate, and a decrease in pH of the solution from ca. 8 to ca. 2.5. The precipitate did not form when the chloride test described above was used. Potentiometric titration with KOH of a system containing $AgNO_3$ and $(CH_3)_2S(NH)_2$ in 2.48:1 mole ratio gave a gradually sloping curve. The pH at 1 mole of KOH per mole of diimine was 4.8, and at 1.5 moles of KOH per mole of diimine was 6.8. Neither a precipitate nor a pH lowering was observed when dimethyl sulfone imine was mixed with $AgNO_3$.

Solubility Curve. The solubility of dimethyl sulfone diimine (Figure 4) was described by determining the temperature at which crystals separated on cooling and dissolved on heating with synthetic mixtures. The separating phase below the discontinuity is probably a quarter-hydrate. Nitrogen analyses on a sample crystallized from water and dried by blowing nitrogen over the sample at room temperature (which, incidentally, slowly evaporates the compound itself) gave values of 29.0, 28.9, and 29.2%; calculated for $(CH_3)_2S(CH_2)_8 \cdot 0.25H_2O$, 29.0%. The separating phase above the discontinuity is presumed to be anhydrous crystals.

Acknowledgments. The authors are particularly indebted to Mr. A. L. Voegele for assistance in performing the synthetic experimental work, to Mrs. M. K. Sargent who performed most of the tlc analyses, and to Mr. G. Wayne Emmert for assistance in obtaining infrared and Raman spectra.

Lincomycin. II. Characterization and Gross Structure^{1,2}

Ross R. Herr and George Slomp

Contribution from the Research Laboratories of the Upjohn Company, Kalamazoo, Michigan. Received December 20, 1966

Abstract: Physical and chemical characteristics of lincomycin, together with spectral data and examination of the products of hydrolysis and periodate oxidations, allow the postulation of a gross structure as a working hypothesis.

Lincomycin, as has been reported,³⁻⁶ is a new antibiotic produced by an actinomycete designated *Streptomyces lincolnensis* var. *lincolnensis*, n.sp. Clinical use has shown it to be an effective agent for treatment of infections in humans.⁷ This paper presents the general characteristics of the antibiotic and the preliminary degradations which led to the postulation of the gross structure as a working hypothesis.

Lincomycin is a basic compound in which the single amine group is tertiary with a pK_a' of 7.6. The free base is soluble in water and most organic solvents other than the hydrocarbons and has the empirical formula $C_{18}H_{34}N_2O_6S$. The crystalline hydrochloride salt, which is soluble in water and the lower alcohols, forms hydrates and was isolated as the hemihydrate, $C_{18}H_{34}N_2O_6S \cdot HCl \cdot 0.5H_2O$. Group analyses showed the presence of two C-methyl, one N-methyl, and no acetyl or methoxyl groups. The infrared absorption spectrum indicates multiple OH and NH groups and a mono-substituted amide function (amide I and II bands). Lincomycin shows no absorption maxima in the ultra-violet or visible regions.⁴

Although the nmr spectrum of lincomycin hydrochloride (Figure 1) is quite complex, with many overlapping areas, it provides some valuable information. An anomeric hydrogen is indicated by a doublet at 322 cps,⁸ one C-methyl appears as a triplet at 53 cps, indicating two neighboring hydrogens, and the other C-methyl as a doublet at 70 cps, indicating one neighboring hydrogen. The N-methyl is readily recognized at 178 cps and, with no acetyl or methoxyl groups present, the remaining sharp singlet at 128 cps can be attributed to an S-methyl group. In addition, although the spectrum was not factorable, nor could complete assignments be made, area measurements to indicate the total number of hydrogens and their distribution were used to exclude certain otherwise possible structures.

These characterization data suggested a possible close structural similarity to celesticetin, an antibiotic isolated previously in these laboratories and on which

some structure work had been done.⁹ For this reason, initial experiments on lincomycin paralleled those on celesticetin, and results substantiated this similarity. Subsequent work elucidated the complete structural relationship.¹⁰

Vigorous acid hydrolysis of lincomycin was accompanied by considerable charring but afforded two products, methyl mercaptan, isolated and identified as its 2,4-dinitrophenyl thioether, and an amino acid, isolated as a crystalline hydrated hydrochloride. Analysis and titration of the amino acid indicated an empirical formula $C_9H_{17}NO_2 \cdot HCl \cdot 0.5H_2O$. No color was produced with ninhydrin or isatin. A similar C_9 amino acid from celesticetin had been identified as L-hygric acid (N-methylproline), and comparison of the nmr spectrum of the lincomycin moiety with that of a synthetic sample of DL-hygric acid¹¹ showed the new amino acid to be a *n*-propylhygric acid (Figure 2). The similarity of the spectra in the 100–300-cps region can be seen, together with the obvious differences in the lower frequency range. The presence in the spectrum of the lincomycin amino acid of a C-methyl group as a triplet at 45 cps and an area equivalent to four hydrogens in the 80-cps region representing the two methylene groups of the alkyl chain give a clear picture of a *n*-propyl group. The position and configuration of the alkyl group could not be determined from the spectrum, since the ring hydrogen multiplets could not be factored.

The specific rotation of the amino acid hydrochloride in water, $[\alpha]_D -153^\circ$, and the slight positive rotational shift of the free amino acid from $[\alpha]_D -67^\circ$ in water to $[\alpha]_D -62^\circ$ in 5 *N* hydrochloric acid suggested the L configuration, although this was not definite due to the presence of the second asymmetric center.¹² The position of the propyl group and the complete stereochemistry of the amino acid was determined by subsequent work.¹³

Although the sugar portion of the molecule is destroyed during acid hydrolysis, much could be deduced from other chemical and nmr data. The ease of removal of the S-methyl under acid conditions, plus the clear indication of an anomeric hydrogen by nmr, placed this as a glycosidic group. Acetylation of lincomycin showed the presence of four hydroxyls by formation

(1) This work was presented in part at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1964.

(2) Part I of this series was a preliminary communication: H. Hoeksema, B. Bannister, R. D. Birkenmeyer, F. Kagan, B. J. Magerlein, F. A. MacKellar, W. Schroeder, G. Slomp, and R. R. Herr, *J. Am. Chem. Soc.*, **86**, 4223 (1964).

(3) D. J. Mason, A. Dietz, and C. DeBoer, *Antimicrobial Agents Chemotherapy*, 554 (1962).

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(7) G. K. Daikos, *et al.*, *ibid.*, 197 (1963); W. J. Holloway, *et al.*, *ibid.*, 200 (1963); J. Harnecker, *et al.*, *ibid.*, 204 (1963); E. W. Walters, *et al.*, *ibid.*, 210 (1963); J. C. Trakas and H. E. Lind, *ibid.*, 216 (1963).

(8) Frequencies in water solutions are measured from sodium 4,4-dimethyl-4-silapentanesulfonate (SDSS); in chloroform solution from tetramethylsilane (TMS).

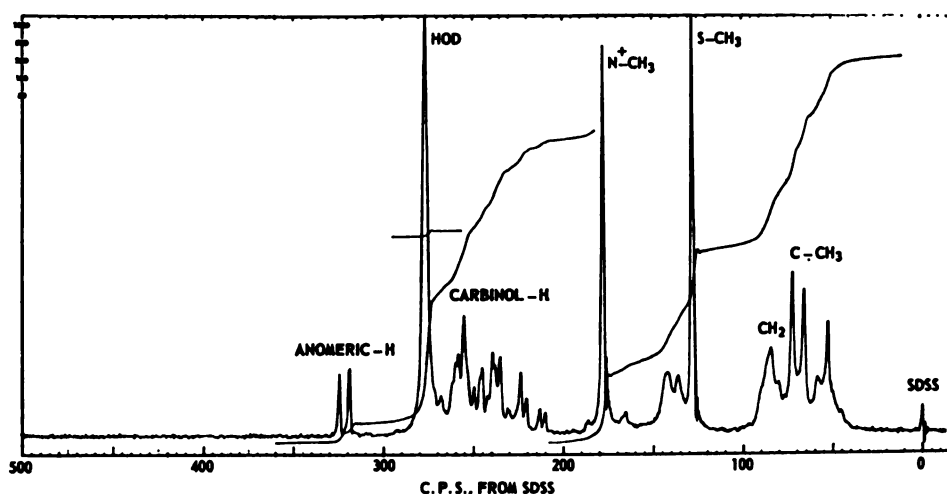
(9) H. Hoeksema and J. W. Hinman, *J. Am. Chem. Soc.*, **86**, 4979 (1964).

(10) H. Hoeksema, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug–Sept 1964, p 385.

(11) Furnished by Dr. W. Schroeder; obtained by acid hydrolysis of the methyl ester, which was prepared by dry distillation of stachydrin. See G. Trier, *Z. Physiol. Chem.*, **67**, 324 (1910).

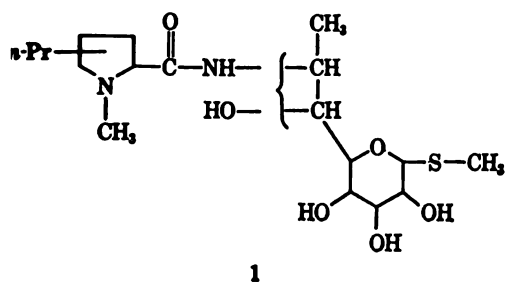
(12) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1961, p 83.

(13) B. J. Magerlein, R. B. Birkenmeyer, R. R. Herr, and F. Kagan, *J. Am. Chem. Soc.*, **89**, 2459 (1967).



I. Nuclear magnetic resonance spectrum (60 Mc) of lincomycin hydrochloride in water.

etra-O-acetate, as shown by group analyses and The nmr spectrum of the tetraacetate in chloro- solution showed four resolved acetyl methyl- tions at 114, 119, 124, and 127 cps (Figure 3). eriodate oxidations about 4 moles of periodate- nsumed per mole of lincomycin. The quantita- however, was somewhat unreliable because of- end points due to the influence of the oxidized- group.¹⁴ Replacement of the S-methyl group- drogen on treatment with Raney nickel gave a- ct designated anhydrolincomycitol, which cleanly- ned 2 moles of periodate/mole. As expected,- rolincomycitol showed no S-methyl group or- ric hydrogen in its nmr spectrum (Figure 4).- preparative scale, periodate oxidation of linco- followed by brief acid hydrolysis allowed isola- of glyoxal as its 2,4-dinitrophenylhydrazone.- titration with alkali following periodate oxidation- d the formation of 1 mole of formic acid. Based- se data, plus the proton distribution data obtained- he nmr spectrum, structure 1 was proposed as a- le partial structure for lincomycin.



1

odate results require the three adjacent hydroxyls- ring, with the glyoxal derived from carbons 1 and- the formic acid from carbon 3. The nmr spec- (Figure 1) shows that, other than the methyl hy- is, all the remaining hydrogens in the sugar por- of the molecule are on carbons bearing negative- i. Thus, the methyl group represented by the- t at 70 cps is attached to a carbon holding one- gen plus either an oxygen or nitrogen function.- facts require the pyranose ring since any furanose- ructure would either contain a tertiary hydroxyl

V. A. Bonner and R. W. Driski, *J. Am. Chem. Soc.*, 73, 3699

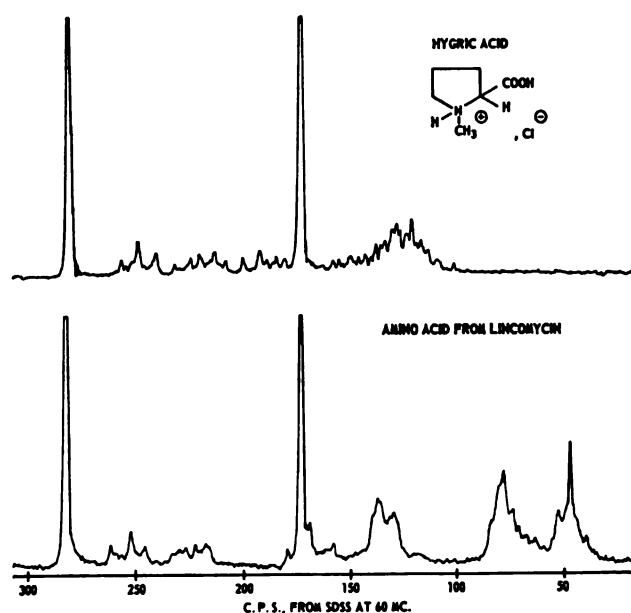


Figure 2. Nuclear magnetic resonance spectra of DL-hygric acid hydrochloride (synthetic) and the amino acid hydrochloride from lincomycin, in water.

and additional paraffin hydrogens which are not seen in the nmr spectrum or would not account for the formation of formic acid on oxidation. Another pyranose structure with a branched sugar skeleton is allowed by these data, but structure 1 was used as a working hypothesis, and the straight chain skeleton was confirmed by subsequent examination of degradation products.¹⁵

The relative positions of the amide function and the last hydroxyl group were uncertain. The fact that lincomycin and some of its degradation products give negative iodoform tests led us to postulate the positions shown in 1, but later nmr data was in better agreement with the reverse arrangement.¹⁶ Subsequent chemical work showed conclusively that their true positions are the latter.¹⁵

(15) W. Schroeder, B. Bannister, and H. Hoeksema, *ibid.*, 89, 2448 (1967).

(16) G. Slomp and F. A. MacKellar, *ibid.*, 89, 2454 (1967).

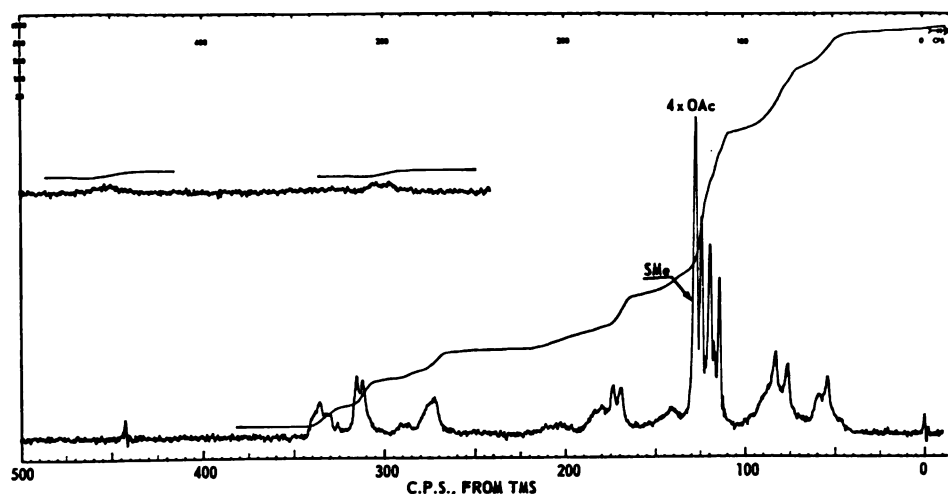


Figure 3. Nuclear magnetic resonance spectrum (60 Mc) of tetraacetyllincomycin in chloroform.

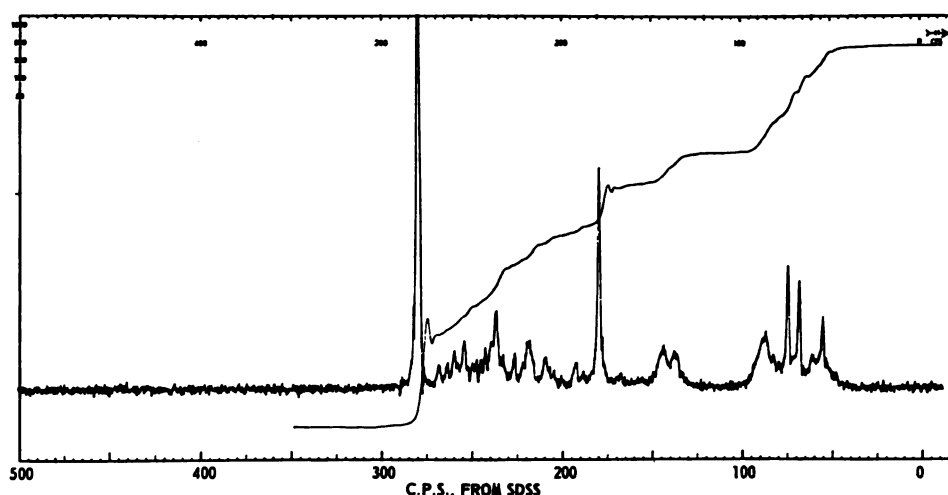


Figure 4. Nuclear magnetic resonance spectrum of anhydrolincomycin hydrochloride in water.

Experimental Section¹⁷

Acid Hydrolyses. (a) **For Methyl Mercaptan.** A solution of lincomycin hydrochloride (1 g) in 5 *N* sulfuric acid (10 ml) was refluxed and the evolved gases were passed through a mixture of 0.3 ml of 3.3 *N* sodium hydroxide (aqueous) and 3 ml of ethanol. To the resulting solution was added a solution of 1-chloro-2,4-dinitrobenzene (200 mg) in warm benzene (3 ml). The yellow crystals which formed immediately were collected and recrystallized from ethanol to give 58 mg of shiny yellow plates, mp 127–128; lit. for methyl 2,4-dinitrophenyl thioether, mp 128.¹⁸ The infrared spectrum was identical with that of an authentic sample.

Anal. Calcd for $C_7H_8N_2O_4S$: C, 39.25; H, 2.83; N, 13.08; S, 14.97. Found: C, 39.03; H, 2.67; N, 12.84; S, 14.95.

(b) **For Propylhygric Acid.** A solution of lincomycin hydrochloride (2 g) in 6 *N* hydrochloric acid (50 ml) was refluxed for 30 min and then distilled to dryness. The dry residue was dissolved in water (20 ml) and extracted twice with chloroform (two 10-ml portions). The aqueous solution was diluted with 60 ml of water and extracted twice with butanol (two 20-ml portions). The aqueous solution was then evaporated to dryness and the dry residue was dissolved in ethanol (20 ml). The ethanolic solution was decolorized with carbon, and ether (100 ml) was added to the filtrate. A gummy precipitate which separated was removed by filtration and discarded. The filtrate was again treated with carbon, and additional ether (1000 ml) was added to the filtrate. After standing several weeks in the refrigerator crystals formed; yield 650 mg.

A sample for analysis was recrystallized several times from ethanol-ether. On heating, the crystals softened at about 123° and finally melted with decomposition at 160–170°. The pK_a 's in water were 2.4 and 10. The infrared spectrum in mineral oil suspension suggested a tertiary amino acid hydrochloride, hydrated, and had bands at 3530, 3460, 2720 (broad), 1740, 1225, 1210, 1190, 1150, 1120, 1105, 1040, 1025, 980, 925, 845, and 810 cm^{-1} .

Anal. Calcd for $C_{18}H_{17}NO_7 \cdot HCl \cdot 0.5H_2O$: C, 49.87; H, 8.84; N, 6.46; Cl, 16.36; mol wt, 216.7. Found: C, 49.35; H, 8.55; N, 6.75; Cl, 16.96; mol wt (electrometric titration), 216.

Lincomycin Free Base. A solution of lincomycin hydrochloride (100 g) in deionized water (1700 ml) was adjusted to pH 10 by the addition of 5 *N* sodium hydroxide and extracted three times with chloroform (three 1700-ml portions). The extracts were combined and dried over sodium sulfate, and the chloroform was evaporated under reduced pressure while deionized water was added. The resultant aqueous solution was freeze dried to yield 85 g of white amorphous lincomycin base. Karl Fischer determination showed this material to contain 1.50% water. Analytical values shown are corrected for the water content, with actual values shown in parentheses. The optical rotation was $[\alpha]_D^{25} +158^\circ$ (156°) (c 1, water). The nmr spectrum was very similar to that of the hydrochloride except that the N-methyl absorption of the free base was shifted 38 cps upfield as a result of the removal of the charge from the nitrogen.

Anal. Calcd for $C_{18}H_{16}O_6N_2S$: C, 53.18; H, 8.43; N, 6.89; S, 7.89; mol wt, 406.5. Found: C, 53.11 (52.31); H, 8.40 (8.44); N, 6.95 (6.83); S, 7.98 (7.86); mol wt (electrometric titration), 408 (415).

Lincomycin Tetraacetate. Lincomycin base (1.7 g) was acetylated with pyridine (50 ml) and acetic anhydride (25 ml) at room temperature. After 24 hr the excess reagents were removed under

(17) Melting points were determined on a Kofler hot-stage apparatus.

(18) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1940, p 225.

ed pressure and the residue was dissolved in methylene chloride and water. The mixture was neutralized with saturated sodium bicarbonate, phases were separated, and the aqueous layer extracted with methylene chloride. The combined methylene chloride extracts were washed until they were neutral and dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The glassy residue did not crystallize and was therefore butted countercurrently for 500 transfers using the solvent in Skellysolve B-acetone-water in the ratio 7:16:3. The distribution was analyzed by the determination of solids and showed a single peak with the center at tube 323, $K = 1.8$, which fit well with the theoretical curve. Tubes 310-350 were pooled and the solvents removed under reduced pressure. The residue, a glass which did not crystallize, was converted to the hydrochloride salt by adding ether and bubbling in hydrogen chloride. The hydrochloride which precipitated was collected by filtration and dissolved in a small amount of chloroform, which was then layered with ether and chilled in the refrigerator. Crystallization began at the interface and ether was added gradually, and finally the layers were separated. The crystals were collected, recrystallized by the same procedure, and air dried, mp 226-233°; $[\alpha]_D^{25} +149^\circ$ (c 1, water). The infrared spectrum was consistent with the formation of a tetrahydrate; the NH absorption at 3200 cm^{-1} remained but the OH absorption at $3400\text{--}3600\text{ cm}^{-1}$ had disappeared. Analyses indicated the crystalline hydrochloride as prepared to be a hemihydrate. *Anal.* Calcd for $C_{17}H_{23}N_3O_8 \cdot HCl \cdot 0.5H_2O$: C, 50.35; H, 8.43; N, 6.90; O, 25.62; S, 5.17; Cl, 5.72; H_2O , 1.45; acetyl, 7.8; equiv wt, 620. Found: C, 49.83; H, 7.57; N, 4.52; S, 4.99; Cl, 5.81; H_2O , 1.72; acetyl, 25.53; equiv wt,

Iodate Oxidation of Lincomycin Hydrochloride. (a) **Titration.** Oxidation of lincomycin hydrochloride by the Fleury-Lange procedure using 0.23 *M* sodium metaperiodate solution showed consumption of periodate varying from 3.5 to 5 moles because of fading endpoints. Titration of the products of oxidation was carried out as follows. Two 45-mg samples of lincomycin hydrochloride each dissolved in 20 ml of water. Five milliliters of a 50-mg/ml solution of sodium metaperiodate in water was added to each beaker and the beakers were wrapped with foil. A blank, using 20 ml water and 5 ml of the periodate solution, was similarly treated, standing at room temperature for 45 min, ethylene glycol (2 ml) was added to each beaker; the mixture was again let stand for 45 min. The solutions were then titrated with 0.02 *N* sodium hydroxide. A second blank containing 47.6 mg of lincomycin hydrochloride in 20 ml of water was also titrated with the sodium hydroxide. Comparison of the results indicated 1.2 moles of acid, ± 0.1 , formed per mole of lincomycin (lit. for formic acid is 3.75).

Isolation of Glyoxal 2,4-Dinitrophenylhydrazone. A solution of lincomycin hydrochloride (1 g) in 25 ml of water was added to a solution of sodium metaperiodate (2 g) in 75 ml of water. After standing at room temperature for 1 hr, barium hydroxide solution was added until no more precipitate formed. The mixture was filtered and the filtrate was extracted with methylene chloride (three portions). The extracts were combined and concentrated under reduced pressure. The almost colorless oily residue was dissolved in ethanol (25 ml) and added to a hot solution of 2,4-

dinitrophenylhydrazine (1 g) in ethanol (75 ml). Concentrated hydrochloric acid (2.5 ml) was added and heating continued. The remaining undissolved reagent went into solution and almost immediately a precipitate began to separate. The product was collected, washed with ethanol, and air dried; mp 319-325° (lit.¹⁹ for the glyoxal derivative 328°). It was identified as the 2,4-dinitrophenylhydrazone of glyoxal by comparison of its infrared and ultraviolet spectra with those of an authentic sample.

Anhydrolincomycitol. Raney nickel (W-3) was washed with water until the washings were neutral, and about 40 g of this nickel was added to a solution of lincomycin hydrochloride (5 g) in water (125 ml). The mixture was stirred and refluxed for 1 hr, at which time about 25 g of fresh, washed Raney nickel was added. Again the mixture was stirred and refluxed for 1 hr, and again 25 g of fresh nickel was added. After a third hour of stirring and reflux, the mixture was cooled and the nickel was removed by filtration. The filtrate was adjusted to pH 9.2 with sodium hydroxide and extracted exhaustively with chloroform (six 250-ml portions, then six 500-ml portions). The chloroform extracts were combined and the solvent was removed under reduced pressure. The glassy residue (2.6 g) was distributed for 300 transfers using the solvent system methyl isobutyl ketone-water-ethanol in the ratio 5:5:2. The distribution was analyzed by the determination of solids and showed a single peak, peak tube 82, $K = 0.38$, with an excellent fit to the theoretical curve. Tubes 65-100 were pooled and concentrated to an aqueous solution (10 ml) under reduced pressure. This concentrate was acidified with concentrated hydrochloric acid (ten drops) and acetone was added slowly while stirring until the solution became cloudy (140 ml of acetone). Another 60 ml of acetone was added, and scratching the flask induced crystallization. The crystals were collected and dried in a vacuum desiccator; 1.52 g. Addition of 150 ml of acetone to the mother liquor gave a second crop of crystals, 214 mg; total yield of anhydrolincomycitol hydrochloride, 1.73 g (38%). A sample for analysis was recrystallized from acetone-water, mp 206-210°. The nmr spectrum was consistent with the proposed removal of a thiomethyl glycosidic group; both the anomeric hydrogen doublet at 314 cps and the S-methyl singlet at 120 cps had disappeared. Analyses indicated the crystalline hydrochloride to be a hemihydrate. The compound showed no measurable optical rotation at the sodium D line.

Anal. Calcd for $C_{17}H_{23}N_3O_8 \cdot HCl \cdot 0.5H_2O$: C, 50.29; H, 8.43; N, 6.90; O, 25.62; Cl, 5.73; H_2O , 2.22; equiv wt, 406. Found: C, 50.35; H, 8.40; N, 6.77; O, 25.79; Cl, 5.84; H_2O , 2.43; equiv wt, 396.

Periodate Oxidation of Anhydrolincomycitol Hydrochloride. Anhydrolincomycitol hydrochloride was titrated by the Fleury-Lange procedure using 0.23 *M* sodium metaperiodate solution. The consumption of periodate was, in hours (moles): 0.5 (2.00), 1.5 (2.06), 3.5 (2.00), 19 (2.00).

Acknowledgments. The authors wish to thank Mr. Forrest MacKellar for technical assistance and Mr. Raymond Anderson and his associates for the analytical results.

(19) Reference 18, p 188.

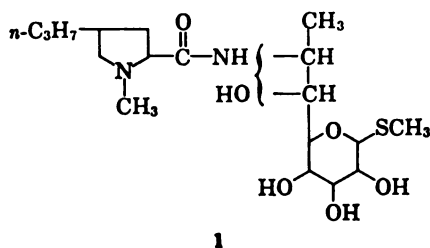
Lincomycin. III.^{1a-c} The Structure and Stereochemistry of the Carbohydrate Moiety

W. Schroeder, B. Bannister, and H. Hoeksema²

Contribution from the Research Laboratories of the Upjohn Company, Kalamazoo, Michigan. Received December 20, 1966

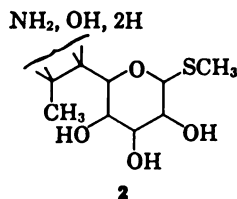
Abstract: Cleavage of lincomycin at the amide bond into methyl thiolincosaminide and an amino acid was readily effected in refluxing hydrazine. The carbohydrate structure was determined by various physical and chemical procedures to be an unbranched 6-aminooctose. The stereochemistry of six of its seven asymmetric centers was established by isolation of D-galactose α -methylphenylhydrazone and N-2,4-dinitrophenyl-D-allothreonine, following oxidative cleavages of the appropriate derivatives. The configuration of the thiomethyl group was assigned from considerations of optical rotations.

Partial structure 1 for lincomycin was derived in paper II^{1c} of this series. The strenuous hydrolytic procedures employed therein freed the peripheral moieties, methyl mercaptan and a propylhygric acid, but failed to provide the intact carbohydrate. Hydrazine hydrate at reflux temperatures³ efficiently cleaved the amide bond, liberating methyl thiolincosaminide (MTL) in high yield. MTL appeared to be the intact carbohydrate.



The amino acid fragment was isolated as the hydrazide which could be hydrolyzed in aqueous acid to the propylhygric acid described in the earlier work. To show that the vigorous reaction conditions had induced no rearrangements or racemizations in MTL, highly purified MTL was reacylated with the amino acid moiety. The reconstituted lincomycin so obtained was identical in every way with the antibiotic isolated from fermentations.

Consideration of the partial structure 1 led to working structure 2 for MTL.⁴ Regardless of the ambiguity



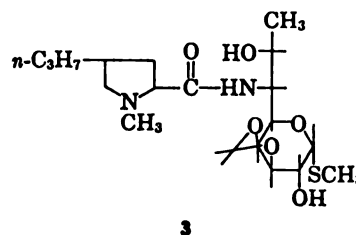
(1) (a) Preliminary accounts of this work appeared during the 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug-Sept 1964; (b) part I: H. Hoeksema, B. Bannister, R. D. Birkenmeyer, F. Kagan, B. J. Magerlein, F. A. MacKellar, W. Schroeder, G. Slomp, and R. R. Herr, *J. Am. Chem. Soc.*, **86**, 4223 (1964); (c) part II: R. R. Herr and G. Slomp, *ibid.*, **89**, 2444 (1967); (d) part IV: G. Slomp and F. A. MacKellar, *ibid.*, **89**, 2454 (1967); (e) part V: B. J. Magerlein, R. D. Birkenmeyer, R. R. Herr, and F. Kagan, *ibid.*, **89**, 2459 (1967).

(2) To whom inquiries should be addressed.

(3) M. L. Wolfrom and B. O. Julaiano, *J. Am. Chem. Soc.*, **82**, 2588 (1960).

(4) Hereafter, the complete structural formulas as ultimately determined will be employed, although some uncertainties, particularly that relating to substituents on C₆ and C₇ as illustrated in 2, actually persisted to the very end of this investigation.

of the C₆ and C₇ substituents, oxidative cleavage of the vicinal amino alcohol would provide an aldehyde capable of either oxidation or reduction to a known compound after removal of the thioaglycone. Thus, structural and stereochemical information concerning most of the MTL would be provided. Blocking of the ring hydroxyls of 2 to periodate cleavage would provide an intermediate suitable for cleavage at the desired position. Since an acetonide 3 of lincomycin itself formed



readily with ring hydroxyls as the most likely locations for the isopropylidene group, hydrazinolysis of this compound was expected to provide the desired intermediate (7). However, isopropylidenelincomycin proved completely resistant to hydrazinolysis and could be recovered unchanged following 140 hr of refluxing in hydrazine hydrate. Reasons for this are not completely clear. It may be due to the high degree of insolubility of the compound at reaction temperatures. Alternately, studies of models show that the back-side attack of the amide carbonyl by hydrazine is severely hindered when the conformation is such that the large acyl group is adjacent to the isopropylidene group. Hindrance to hydrazinolytic cleavage of amides has recently been reported.⁵

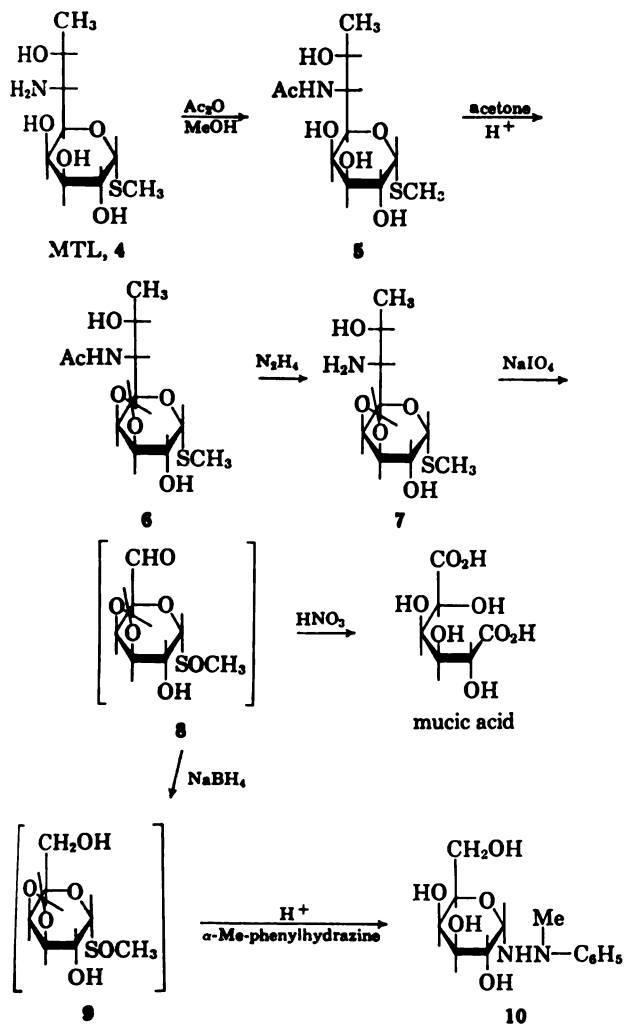
An alternate route to the desired intermediate was to convert MTL (4) to N-acetyl-MTL (5) with acetic anhydride in methanol. Subsequent treatment of 5 with acetone and sulfuric acid gave N-acetylisopropylidene-MTL (6) in good over-all yield. This compound underwent hydrazinolysis more readily, affording the key intermediate 7. Consumption by 7 of 3 moles of periodate produced acetaldehyde and a compound considered to be aldehyde 8.

Oxidation of 8 with nitric acid yielded a dibasic acid which was identified by infrared spectra and mixture melting points as mucic acid. Treatment of 8 with borohydride, followed by acid hydrolysis in the pres-

(5) M. Fujinaga and Y. Matsushima, *Bull. Chem. Soc. Japan*, **39**, 185 (1966).

ence of α -methylphenylhydrazine, afforded D-galactose α -methylphenylhydrazone, presumably *via* 9 which was not isolated. The isolation of the hydrazone in 58% (from 7) yield confirmed stereochemistry of carbons 2-5, as well as establishing the D series (see Chart I).

Chart I



Relative locations of nitrogen and oxygen and the stereochemistry on carbons 6 and 7 remained to be elucidated. Although lincomycin and MTL (and subsequently compounds 11, 15, and 16) failed to give an iodoform test, the nmr⁶ spectrum of MTL favored assignment of nitrogen to C₆ and oxygen to C₇. This issue was further clouded by the positive iodoform test obtained following nitrous acid deamination of 4. Efforts to resolve the impasse by periodate studies⁷ in the open-chain series of compounds 11-16 (Chart II) were inconclusive.

The location of the groups was established by characterization of the ketone formed by oxidation of the hydroxyl in question. Thus, compound 6, obtained from MTL, was desulfurized with Raney nickel, affording 17, containing one ring hydroxyl which was inert to mild chromic acid oxidation and a side-chain hydroxyl. Such oxidation of 17 in either pyridine or glacial acetic acid yielded a crystalline ketone 18, dis-

playing carbonyl absorption at 1720 cm⁻¹, which now gave a positive iodoform test. Furthermore, nmr studies of 17 and 18 show that the terminal methyl doublet of 17 at 1.10 and 1.21 ppm had disappeared in the spectrum of 18. Instead, a new singlet at 2.33 ppm was displayed. Thus, formulation A for the side chain cannot obtain, leaving the alternative B. Reduction of 18 with borohydride afforded a mixture from which iodoform again could not be obtained.

Confirmation of the above information as well as elucidation of the stereochemistry of carbons 6 and 7 were derived through the isolation of the terminal four carbons as an amino acid. Following numerous unsuccessful attempts to obtain such fragments from such intermediates as 14, 15, 16, or N-benzoylated 13 and 15, a single compound was finally isolated using 19, the dinitrophenyl (DNP) derivative of 15. After oxidation with periodate-permanganate mixture,⁸ an amorphous product was purified by countercurrent distribution. The analytical data and paper chromatograms indicated an allothreonine-DNP, excluding the alternate choice, alanine-DNP. Rotational data, appearing in Table I, for the isomeric threonine and for L-allothreonine leave no doubt that the acid here isolated was D-allothreonine-DNP.

Table I. Comparison of Known 2,4-DNP Derivatives of the Isomeric Threonines with the 2,4-DNP Acid from Lincomycin

Compd	[M] _D , degrees			Unknown
	D-Thre- onine	L-Thre- onine ^a	L-Allo- threo- nine ^a	
HOAc	+141	-141	-84	+83.4
NaHCO ₃	-305	+305	+305	-320 ^b

^a J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1961, p 1564. ^b The error in this value is considered to be due to the necessity for a vacuum filtration of the test solution through a Millipore filter, resulting in some evaporative concentration.

The assumption of stereochemical assignment at carbon 1 was based originally on considerations of the nmr spectrum of MTL.^{1e} That the configuration of the methylthio group was α , however, was an important consideration in the process of factoring the entire spectrum and predicting galactose stereochemistry.

Proof of the axial configuration of the thioglycoside was obtained as follows. Acetylation of MTL in acetic anhydride-pyridine gave the pentaacetyl derivative 20, mp 218-220°, [α]_D +223° (CHCl₃). In ethanol-free chloroform solution, this pentaacetyl thioglycoside reacted rapidly with bromine⁹ with the formation of the acetobromo derivative, considered to be the β anomer 21, but which could not be isolated crystalline.

The acetobromo sugar reacted readily with thiourea¹⁰ in acetone and the isothiuronium salt, which was not isolated, was hydrolyzed and the resulting mercaptan methylated with methyl iodide in aqueous carbonate.

(8) R. V. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1711 (1955).

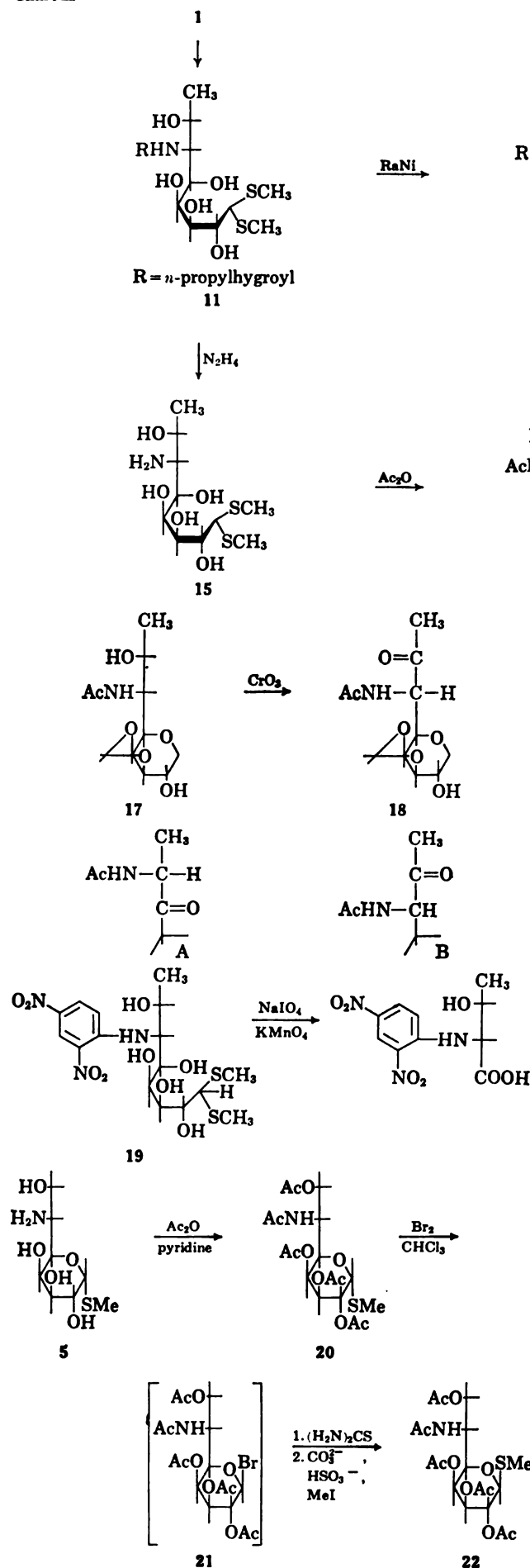
(9) (a) W. A. Bonner, *J. Am. Chem. Soc.*, **70**, 770, 3491 (1948); (b) F. Weygand and H. Ziemann, *Ann.*, **657**, 179 (1962); (c) M. L. Wolf from and W. Groebke, *J. Org. Chem.*, **28**, 2986 (1963).

(10) M. Cerny, J. Vrkoc, and J. Stanek, *Collection Czech. Chem. Commun.*, **24**, 64 (1959); M. Cerny and J. Pacak, *ibid.*, **24**, 2566 (1959).

(6) Nmr studies on MTL, which also led to the conclusion that the stereochemistry of C₂-C₅ was *galacto*, appear in ref 1d.

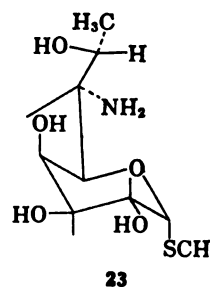
(7) Both the sulfur [see L. Hough and M. I. Taha, *J. Chem. Soc.*, 3994 (1957)] and propylhydryl fragments can contribute to periodate complications.

Chart II



A crystalline methyl pentaacetylthioglycoside, **22**, was isolated in excellent yield as the sole reaction product, mp 272–274°, $[\alpha]_D^{25} +31^\circ$ (CHCl₃). Since no opportunity exists in this sequence of reactions for a change in ring size to occur, stereospecific anomerization due to participation by the neighboring acetate group leads to the β anomer, showing a much lower positive rotation than pentaacetyl-MTL.

MTL, then, can best be represented by structure **23**, methyl 6-amino-6,8-dideoxy-1-thio-D-erythro- α -D-galacto-octopyranoside.



Experimental Section¹¹

Hydrazinolysis of Lincomycin. Methyl Thiolincosaminide (4). A solution of 4.06 g (0.01 mole) of lincomycin base in 40 ml of hydrazine hydrate was refluxed for 21 hr. The excess hydrazine was then distilled off on the steam bath under reduced pressure (house vacuum). The residue set to semisolid mush of crystals when most of the hydrazine was gone. The residue was cooled and then stirred with acetonitrile until all of the lumps had broken up. The crystals were collected and washed with acetonitrile and then ether. After being dried *in vacuo* the crude product weighed 2.1 g (83%). This material was recrystallized by dissolving 1.5 g in a mixture of 5 ml of H₂O and 10 ml of methanol and adding 40 ml of 1-butanol. The resulting solution was filtered and the water and methanol were slowly evaporated *in vacuo*. The crystals which slowly separated from the butanol were collected, washed with butanol, and dried *in vacuo* to afford 700 mg of white crystals, mp 225–228°, $[\alpha]_D^{25} +264^\circ$ (c 0.718, H₂O). Material crystallized in this manner was

(11) Melting points were determined on a Kofler micro hot-stage apparatus. Infrared spectra were consistent with the proposed structures.

scopic. The analytical sample contained 3.15% H₂O by Fisher titration.

al. Calcd for C₁₁H₁₉NO₅S + 3.15% H₂O: C, 41.6; H, 5.42; N, 12.35; equiv wt (for hemihydrate), 262. Found: C, 41.86; H, 5.45; N, 5.63; S, 12.07; equiv wt (by titration), 257; = 7.5.

Material subsequently recrystallized from ten volumes of dimethylformamide was found not to be hygroscopic.

Hydrolysis of Lincomycin. Propyl-L-hygric Acid Hydrazide rate. Evaporation to dryness of the acetonitrile washes from procedures as described above yielded crude propyl-L-hygric acid hydrazide. A 5-g sample of crude 4-*n*-propylhygric hydrazide so obtained was dissolved in water and extracted several equal volumes of chloroform. The chloroform extracts were then reextracted with one-fourth volume of water. This procedure served to remove hydrazine and methyl thiolincoside from the hydrazide. The chloroform solution was then evaporated over sodium sulfate and evaporated on a rotary evaporator at 0.5 mm to leave 2.5 g of a heavy oily residue. This residue of partially crystallized hydrazide crystallized on standing overnight, but the waxy, melting material was hygroscopic and resisted crystallization a number of common solvents. An alcoholic solution when dried with picric acid, however, deposited a crystalline material which could be recrystallized from ethanol to afford an analytical sample.

al. Calcd for C₁₁H₂₃N₃O₅: C, 39.19; H, 3.92; N, 19.60. Found: C, 39.47; H, 3.71; N, 19.39.

Conversion of 4-*n*-Propylhygric Acid Hydrazide to 4-*n*-Propyl-L-hygric Acid Hydrochloride. A solution of 6 g of crude 4-*n*-propyl-L-hygric acid hydrazide in 20 ml of 6 *N* hydrochloric acid was refluxed for 2 hr. The reaction mixture was evaporated to dryness *in vacuo*. The gummy residue was washed thoroughly with boiling *n*-propanol until it became granular. This was dissolved in 20 ml of 2-propanol, treated with activated carbon, then diluted with 10 ml of acetone and treated again with carbon at boiling temperature.

Finally, 50 ml of ether (and later a second 50-ml portion) was added. The mixture was stirred until crystallization for a total yield of 2.96 g. Recrystallization of 0.5 g of this from 15 ml of acetonitrile yielded crystals melting at 46.8° (c 3.42, H₂O).

Methyl N-Acetylthiolincosaminide (5). Methyl thiolincosaminide (4) was suspended in 50 ml of methanol and treated under stirring with 3.75 ml of acetic anhydride at room temperature.

Most of the solid dissolved within a few minutes, and then replaced by a new precipitate. After stirring overnight at room temperature, the solid was removed at the pump, washed with methanol, and recrystallized from the same solvent, giving small needles, mp 243–245°; [α]_D²⁰ +248° (95% EtOH), +265° (c 0.4136, H₂O).

al. Calcd for C₁₁H₂₃O₆NS: C, 44.72; H, 7.17; N, 4.74; S, 10.99. Found: C, 44.87; H, 7.10; N, 4.65; S, 10.99.

Synthesis of Lincomycin. A suspension of finely divided *n*-propyl-N-methylproline hydrochloride (4.14 g, 0.02 mole) in 150 ml of dry acetone was treated with 11.2 ml (0.08 mole) of triethylamine. The acid hydrochloride dissolved rapidly and triethylamine hydrochloride precipitated. To this suspension was added 2.3 g (0.02 mole) of *n*-propyl chloroformate and the mixture was stirred at room temperature for 1 hr. The resulting suspension was cooled in ice and filtered rapidly with suction into a 150-ml solution of 5.06 g (0.02 mole) of methyl thiolincosaminide.

150 ml of water. The mixture was stirred well for 15 min when air sucked through the filter for 45 min to evaporate most of the acetone. The remainder of the acetone was removed in a rotary evaporator at 40°. The remaining aqueous phase was extracted with 150-ml portions of methylene chloride and the extracts were dried with 30 ml of water and dried over MgSO₄. The methylene chloride was removed *in vacuo* to leave 2 g of residue. This residue was dissolved in 10 ml of 1 *N* HCl and 20 ml of acetone was added. The amount of insolubles was removed by filtration and 180 ml of acetone was added to the filtrate. Crystals separated and were collected after standing for a while and washed with methanol and ether. After drying *in vacuo* at room temperature, 1.0 g of white crystals was obtained. The substance was recrystallized from acetone-water and dried *in vacuo* at room temperature for analysis. Karl Fisher titration showed the presence of 0.615% of water; p*K*_a in water = 7.55; [α]_D²⁰ +137° (c 1.044, H₂O). Infrared spectrum was identical with that of a lincomycin reference standard.

al. Calcd for C₁₈H₃₃N₂O₆SCl·0.615H₂O: C, 47.61; H, 7.85; N, 6.17; S, 7.05; Cl, 7.82. Found: C, 47.41; H, 8.24; N, 6.76; S, 6.92; Cl, 7.75.

8.05; N, 6.17; S, 7.05; Cl, 7.82. Found: C, 47.41; H, 8.24; N, 6.76; S, 6.92; Cl, 7.75.

3,4-O-Isopropylidenelincomycin (3). A solution of 9.8 g of lincomycin in 150 ml of acetone was added to a solution of 9.8 g of *p*-toluenesulfonic acid monohydrate in 100 ml of acetone with good stirring. The mixture was stirred at ambient temperature for 1 hr, after which 100 ml of anhydrous ether was added and stirring was continued in an ice bath for 0.5 hr. The crystals were filtered off and dried *in vacuo* at 50°; yield 13.35 g (85.5%) of 3,4-O-isopropylidenelincomycin *p*-toluenesulfonate. An additional 1.15 g (7.4%) could be recovered from the mother liquors by adding 350 ml of anhydrous ether and chilling the solution for 1 hr. Conversion to the free base was achieved by suspending the combined crops in 200 ml of ether and shaking vigorously with 125 ml of 5% potassium bicarbonate solution. The aqueous layer was back-extracted with two 100-ml portions of ether. The ether extracts were washed with 50 ml of saturated sodium chloride solution and filtered through anhydrous sodium sulfate, and the ether was evaporated *in vacuo*, leaving 7.9 g (73.1%) of 3,4-O-isopropylidenelincomycin, which was then dissolved in 25 ml of ethyl acetate. The solution was concentrated to about 10–15 ml and allowed to stand at room temperature for several hours. After refrigerating overnight, the crystals were filtered from the solution and washed sparingly with cold ethyl acetate; yield 4.55 g (42.2%) of 3,4-O-isopropylidenelincomycin having a melting point of 126–128°, [α]_D²⁰ 102° (c 1, methylene chloride).

Anal. Calcd for C₂₁H₃₃N₂O₆S: C, 56.48; H, 8.58; N, 6.27; S, 7.18. Found: C, 56.37; H, 8.55; N, 6.01; S, 7.24.

Methyl N-Acetylisopropylidenethiolincosaminide (6). A suspension of 5.3 g of finely powdered methyl N-acetylthiolincosaminide (5) was stirred for 60 hr at room temperature with 500 ml of acetone and 0.5 ml of concentrated H₂SO₄. Most of the starting material was still insoluble at this time. An additional 5 ml of H₂SO₄ was added and the insoluble material dissolved rather rapidly. Stirring was continued for 30 min at room temperature. The solution was then added to a suspension of 150 g of barium carbonate in 100 ml of water and the mixture stirred until neutral. The barium salts were filtered off and washed with acetone. The filtrate was evaporated to dryness *in vacuo* at 50°. The residue was taken up in acetone-ether (10:1) and the insolubles were filtered off. The filtrate was evaporated to dryness and the residue was taken up in 100 ml of ethanol, which was then removed *in vacuo* to leave a yellow gum. The gum was dissolved in 20 ml of warm water containing a small amount of sodium carbonate, some insolubles were filtered off, and the filtrate was cooled. The crystals which formed were collected after standing in the refrigerator for 4 hr and washed with cold water. After drying *in vacuo* they weighed 2.0 g. A portion was recrystallized from water for analysis, mp 174–175°; [α]_D²⁰ +189° (c 0.4136, H₂O).

Anal. Calcd for C₁₄H₂₅NO₆S: C, 50.12; H, 7.52; N, 4.17; S, 9.55. Found: C, 49.87; H, 7.46; N, 4.11; S, 9.56; H₂O, none by Karl Fisher.

Methyl Isopropylidenethiolincosaminide (7). A solution of 1 g of methyl N-acetyl-3,4-O-isopropylidenethiolincosaminide (6) in 10 ml of hydrazine hydrate was refluxed for 24 hr. The excess hydrazine was distilled off in a nitrogen stream on the steam bath. The crystalline residue was taken up in 5 ml of water and allowed to recrystallize. The crystals were collected and washed with cold water. After drying *in vacuo* the crystals weighed 450 mg. Recrystallization from ethanol afforded the analytical sample, mp 177–178°; [α]_D²⁰ +186° (c 0.689, H₂O).

Anal. Calcd for C₁₂H₂₁NO₅S: C, 49.12; H, 7.90; N, 4.78; S, 10.91. Found: C, 49.27; H, 8.0; N, 5.01; S, 10.92.

Larger Scale Preparation of Methyl 3,4-O-Isopropylidenethiolincosaminide (7). A suspension of 20 g of MTL (4) in 400 ml of methanol was stirred and 20 ml of acetic anhydride added. All of the solid dissolved in a few minutes, and then crystals of the N-acetyl derivative started to separate. After cooling in the refrigerator 1 hr the crystals were collected and washed with methanol. Drying *in vacuo* overnight afforded 19.3 g of N-acetate. This material was well powdered and suspended in 1500 ml of acetone. While stirring, 15 ml of concentrated H₂SO₄ was added. After stirring for 1 hr at room temperature, all was in solution. After cooling in the refrigerator for an additional hour a slight excess (Hydriol paper) of ammonia gas was passed in to neutralize the sulfuric acid. The ammonium sulfate was filtered off and washed with acetone. The colorless filtrate was evaporated *in vacuo* at 50° to a frothy gum. The yield of crude N-acetylisopropylidene derivative was 24.8 g. This crude material was dissolved in 210 ml of hydrazine hydrate. Crystals started to form, but they redissolved on heating. The

resulting solution was refluxed for 23 hr. The excess hydrazine was removed *in vacuo* on the steam bath. The residue was taken up in ethanol, some insolubles were filtered off, and the ethanol was then removed *in vacuo*. The crystalline residue was slurried with 50 ml of acetonitrile to break up lumps and the crystals were collected, washed with acetonitrile and ether, and dried *in vacuo*. The yield of first crop was 12.35 g. The filtrate upon evaporation afforded another 1.0 g of product. The total yield of material identical with that prepared previously was 13.35 g (57.5%).

Mucic Acid from 7. A solution of 3.2 g (slight excess of 3 equiv) of sodium periodate in 25 ml of warm water was cooled to room temperature and 1.5 g of methyl 3,4-O-isopropylideneethiolincosaminide was added simultaneously with good stirring. The MTL derivative dissolved rapidly and some salt precipitated (probably NaIO_3). The temperature was maintained at room temperature by occasional cooling. The odor of acetaldehyde was strong. The solution was placed in a flask fitted with a sparger, N_2 gas was passed through, and the acetaldehyde was converted to its 2,4-DNP derivative with Brady's reagent. After 3 hr the formation of 2,4-DNP had practically ceased. The yield of acetaldehyde 2,4-DNP was 750 mg (65%). The original reaction mixture was filtered from precipitated sodium iodate and a slight excess of barium acetate was added to the filtrate to remove the remainder of the iodate. The salts were removed and washed with water. The filtrate (50 ml) was treated with 15 ml of concentrated HNO_3 and heated in an open beaker on the steam bath for 3 hr. By this time the solution had gone to dryness. The residue was dissolved in 15 ml of water and the resulting solution was permitted to stand overnight. After cooling in the refrigerator for 1 hr, the crystals which had separated were collected and washed with water, ethanol, and ether. After being dried *in vacuo* they weighed 250 mg and were identified by solubility, infrared spectrum, and direct comparison with mucic acid; $[\alpha]_D^{20}$ 0° (c 0.5, NaOH). An additional 205 mg of mucic acid separated from the filtrate on standing in the refrigerator for several days. The total yield was therefore 455 mg (41%).

D-Galactose α -Methylphenylhydrazine (10) from 7. A solution of 6.4 g of sodium periodate in 75 ml of water was cooled and 3.0 g of isopropylidene-MTL (7) added all at once. The mixture was stirred and cooled to moderate the reaction. After standing in the refrigerator overnight, the salts were filtered off and barium acetate was added in slight excess to remove the remainder of the iodate. The salts were again removed and the filtrate was treated with 400 mg of sodium borohydride. After standing at room temperature for 1 hr, an additional 400 mg of borohydride was added. After 30 min, acetic acid was added dropwise to pH 6 to destroy excess borohydride. Some insoluble material was filtered off and about one-fifth volume of IR 120- H^+ resin added along with a few milligrams of sodium bisulfite to reduce some iodine liberated on acidification. The resulting suspension was heated on the steam bath for 4.5 hr, at which time a test for reducing sugar (Benedict) was at its maximum. Some Darco G-60 was added and the mixture was filtered. The filtrate was then reduced in volume to about 70 ml *in vacuo* at 50° . To this solution was added 2 g of sodium acetate, 2 g of sodium bisulfite, 1.5 g of α -methylphenylhydrazine, and 1 ml of acetic acid. Crystals separated on standing. After overnight in the refrigerator, the crystals were collected, washed with water, and dried *in vacuo*. The slightly orange crystals weighed 900 mg, mp $187\text{--}189^\circ$. After standing an additional day in the refrigerator, the filtrate had deposited another 800 mg of product; total yield 1700 mg (58.5%). Recrystallization from hot water afforded colorless crystals of D-galactose α -methylphenylhydrazine; $[\alpha]_D^{20} +12.4^\circ$ (c 2.06, DMSO). An authentic sample of D-galactose α -methylphenylhydrazine had $[\alpha]_D^{20} +12.2^\circ$ (c 2.0, DMSO) and was identical in melting point and infrared spectrum with the material derived from isopropylidene-MTL.

N-(4-Propyl-L-hygroyl)lincosamine Dimethyl Mercaptal (11). In a three-necked flask equipped with a Dry Ice condenser, 150 ml of concentrated hydrochloric acid and 50 ml of methanethiol were chilled to 0° . After rapid addition of 15 g of lincomycin hydrochloride the mixture was vigorously stirred for 5 hr, then diluted with one volume of ice water and extracted with two 100-ml portions of pentane (or Skellysolve B). The extract was discarded. The 6 N hydrochloric acid solution was next partially neutralized by addition of a subequivalent amount (100 g) of potassium hydroxide pellets at $20\text{--}30^\circ$ (Dry Ice-acetone cooling permitted rapid addition). The potassium chloride was removed by filtration. Next, 200 ml of chloroform was added to the filtrate which was then brought to pH 10 with sodium hydroxide. The chloroform layer was removed and a second extract was made with chloroform. The combined extracts were washed with three 50-ml portions of water

(emulsions), and the chloroform was evaporated *in vacuo* presence of water, transferring the product to the aqueous which was then freeze dried.

The freeze-dried product was crystallized from 75 ml of acetone to give 7.5 g, mp $134\text{--}140^\circ$. A second crystallizable material, mp $146\text{--}148^\circ$; $[\alpha]_D^{20} -33^\circ$ (c 1, methylene chloride).

Anal. Calcd for $\text{C}_{19}\text{H}_{36}\text{N}_2\text{O}_6\text{S}_2$: C, 50.19; H, 8.42; N, 5.14. Found: C, 50.15; H, 8.20; N, 5.94; S, 14.31.

N-(4-Propyl-L-hygroyl)-1-deoxyincosaminol (12). A susp of 100 g of W-3 Raney nickel (washed to pH 7 with water; washed three times with absolute ethanol) was stirred and to reflux in 1 l. of absolute ethanol with 15 g of the me (11). After 4 hr the hot reaction mixture was filtered a nickel was washed with 600 ml of hot ethanol. The cor filtrate and washings were evaporated to dryness. A fiv countercurrent distribution at 60 ml/phase was run in the 1-butanol-water, moving the upper phase. The contents of 4 and 5 were evaporated to dryness (7 g) and crystallized fro ml of ethyl acetate (5.7 g), mp $105\text{--}108^\circ$.

Anal. Calcd for $\text{C}_{17}\text{H}_{34}\text{N}_2\text{O}_6$: C, 56.33; H, 9.46; N, 7.68. Found: C, 56.23, 56.29; H, 9.16, 9.30; N, 7.68.

1-Deoxyincosaminol (13) by Acid Hydrolysis. A solutic g of N-(4-propyl-L-hygroyl)-1-deoxyincosaminol (12) was under reflux in 50 ml of 4 N sulfuric acid for 4 hr. The soluti cooled, brought to pH 8 with saturated barium hydroxide so and filtered. The filtrate was passed through a 0.75-in. c containing 10 g of Dowex 2 in the hydroxyl cycle, and the e was freeze dried, yielding 200 mg of white solid. A 120-mg e was crystallized from absolute ethanol to yield 40 mg of produ $177\text{--}185^\circ$.

Anal. Calcd for $\text{C}_8\text{H}_{13}\text{NO}_5$: C, 45.92; H, 9.15; N, 6.69; wt, 209.24. Found: C, 46.29; H, 9.24; N, 6.40; equiv titration showed 1 basic function, $\text{pK}_a' = 8.5$.

1-Deoxyincosaminol (13) by Hydrazinolysis. A 5-g quan compound 12 was heated under reflux for 6 days in 100 ml of zine hydrate. The hydrazine was evaporated *in vacuo* and th due was crystallized in two crops from 2 ml of water in 75 absolute ethanol; yield 60%.

N-Benzoyl-1-deoxyincosaminol. To 700 mg of 1-deoxy aminol (13) in 50 ml of absolute ethanol was added 1 g of b anhydride. This was stirred until all dissolved and until th precipitate was completely formed. After overnight stand room temperature 730 mg (70% yield) of white crystals w tained, mp $188\text{--}190^\circ$.

Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_6$: C, 57.49; H, 7.40; N, 4.22. Found: C, 57.33; H, 7.45; N, 4.22.

N-Acetyl-1-deoxyincosaminol (14). To 1 g (0.0048 m 1-deoxyincosaminol (13) in 100 ml of methanol was add (0.01 mole) of acetic anhydride at 5° . This mixture was until everything dissolved, and then refrigerated. After 20 l ml of ether was added, and the precipitate was filtered. Tl mg of dried white solid was recrystallized from 30 ml of at ethanol, yielding 630 mg of white crystals, mp $174\text{--}176^\circ$.

Anal. Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_6$: C, 47.39; H, 8.43; N, 5.43. Found: C, 48.09; H, 8.27; N, 5.43.

Lincosamine Dimethyl Mercaptal (15). A 10-g quantity o pound 11 in 100 g of hydrazine hydrate was heated under for 6 days. The hydrazine hydrate was evaporated *in vacuo* i nitrogen ebullator. The residue was crystallized from hot nitrile (100 ml) in two crops, for a total of 4.3 g (64% yield). analytical sample was further crystallized from absolute e yielding a sample, mp $142\text{--}144^\circ$; $\text{pK}_a' = 7.95$ in water.

Anal. Calcd for $\text{C}_{10}\text{H}_{21}\text{NO}_6\text{S}_2$: C, 39.84; H, 7.69; N, 5.21. Found: C, 39.74; H, 7.09; N, 5.20. Found: C, 39.74; H, 7.09; N, 5.20. Found: C, 39.74; H, 7.09; N, 5.20.

N-Benzoyllincosamine Dimethyl Mercaptal. A solution of (0.006 mole) of 15 in 100 ml of ethanol was heated under reff 1 hr with 3.6 g (0.016 mole) of benzoic anhydride. The r was evaporated to dryness and the residue washed with ac Recrystallization from acetone gave 300 mg, mp $182\text{--}184^\circ$.

Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_6\text{S}_2$: C, 50.35; H, 6.71; N, 5.15. Found: C, 50.34; H, 6.81; N, 5.37; S, 15.96.

N-Acetylincosamine Dimethyl Mercaptal (16). A 1-g (mole) quantity of compound 15 suspended in 30 ml of me was stirred with 1 ml (0.011 mole) of acetic anhydride at temperature for 2 hr. During this time, the starting materia into solution. Upon dilution with 20 ml of ether crystalli occurred, yielding 660 mg (59%) of dried, ether-washed, solid, mp $177\text{--}179^\circ$. Recrystallization from 15 ml of at ethanol gave 0.5 g mp $179\text{--}179.5^\circ$.

Anal. Calcd for $C_{12}H_{23}NO_5S_2$: C, 41.96; H, 7.34; S, 18.67. Found: C, 41.92; H, 7.18; S, 19.15.

N-Acetyl-1-deoxylicosaminol (14) by Desulfurization. From 2.49 g (0.007 mole) of 16 and ca. 50 g of nickel catalyst, refluxed 10 hr in 200 ml of absolute ethanol, was obtained 1 g (0.004 mole) of N-acetyl-1-deoxylicosaminol, identical with that above.

N-Acetyl-3,4-O-isopropylidene-1-deoxylicosamine (17). A 15-g quantity of methyl N-acetyl-3,4-O-isopropylidenethiolinosaminide (6) was heated under reflux for 7 hr with 100 ml, loosely packed, of Raney nickel in 500 ml of ethanol. The mixture was filtered and the catalyst was washed with a total of 1 l. of boiling ethanol. The filtrate and washings were combined and evaporated to dryness, leaving a partially crystalline residue. This residue was purified by countercurrent distribution, 200 transfers, in the system 1-butanol–water. A major fraction, $K = 0.48$, was isolated by evaporation to give a white crystalline solid, mp 220–235° dec, $[\alpha]_D^{20} +70^\circ$ (c 1, 50% ethanol). This material gave a negative iodoform test.

Anal. Calcd for $C_{15}H_{25}NO_6$: C, 53.96; H, 8.09; N, 4.84. Found: C, 53.87; H, 8.23; N, 5.67, 4.92.

N-Acetyl-3,4-O-isopropylidene-7-dehydro-1-deoxylicosamine (18). **A. Oxidation in Pyridine.** To a solution of 1 g (0.0034 mole) of compound 17 in 10 ml of pyridine and 1 ml of water was added 1 g (0.0066 mole) of chromic oxide in 7 ml of pyridine and 1 ml of water. The mixture was stirred overnight, then added to a solution of 125 ml of ether and 125 ml of ethyl acetate. After standing 3 hr, this mixture was filtered and the filtrate was evaporated to dryness. The residual crystalline material was triturated with acetone and dried, yielding 225 mg of crystalline material. A second crop of 50 mg was recovered from the filtrate by countercurrent distribution in 1-butanol–water, $K = 0.78$. On recrystallization from acetone, a total of 185 mg of material was recovered which melted at 205–210°. This material showed new infrared absorption at 1730 cm^{-1} , and the nmr spectrum showed a new signal at 2.35 ppm. This product gave a positive iodoform test. Upon treatment of the product with sodium borohydride in methanol, the iodoform test again was negative. *Anal.* Calcd for $C_{12}H_{21}NO_6$: C, 54.34; H, 7.37; N, 4.88. Found: C, 54.39; H, 7.59; N, 5.06.

B. Oxidation in Glacial Acetic Acid. To a solution of 1 g (0.0034 mole) of compound 17 in 10 ml of glacial acetic acid was added 1 g (0.0066 mole) of chromic oxide in 10 ml of acetic acid. The mixture, which warmed immediately, was stirred overnight. A 250-ml solution of ethyl acetate and ether (1:1) was added and the mixture was filtered, then evaporated to dryness. Trituration of the residue with acetone produced 40 mg of white crystals identical with those obtained from the pyridine oxidation.

N-(2,4-Dinitrophenyl)licosamine Dimethyl Mercaptal (19). To 1 g (0.0033 mole) of lincosamine dimethyl mercaptal in 20 ml of 50% ethanol was added 0.5 g of sodium bicarbonate and 1 g (0.0054 mole) of 1-fluoro-2,4-dinitrobenzene, the latter in 10 ml of ethanol. After 2 hr of stirring, the mixture was evaporated to dryness and the residue was leached with 50 ml of benzene, which was then discarded. Upon washing the residue twice with 25 ml of water, 1.2 g of yellow solid remained. This was recrystallized from boiling acetone to give a total of 820 mg of yellow crystals, mp 138–140 dec.

Anal. Calcd for $C_{16}H_{23}N_3O_8S_2$: C, 41.10; H, 5.39; N, 8.99; S, 13.72. Found: C, 41.12; H, 5.38; N, 8.69; S, 13.33.

Isolation of D-Allothreonine. Oxidative Cleavage of N-2,4-Dinitrophenyllincosamine Dimethyl Mercaptal. A suspension of 4.3 g (0.0092 mole) of N-2,4-dinitrophenyllincosamine dimethyl mercaptal (19), 30 g of sodium metaperiodate, 3 g of sodium carbonate, and 650 mg of potassium permanganate in 1900 ml of water was stirred 6 hr. The mixture was extracted with 700 ml of ether, then acidified and further extracted with 200 ml of ether. The combined extracts, washed with 100 ml of water, were then dried over sodium sulfate and finally evaporated to dryness. The residue was taken into 50 ml of ether and washed with 50 ml of 5% bicarbonate, then with water. After acidification and reextraction of the alkaline layer, the dried (magnesium sulfate) ether solution was evaporated to dryness and the residue was subjected to countercurrent distribution in the system ethyl acetate–cyclohexane–95% ethanol–water (1:1:1:1, v/v). The contents of tubes 270–360 ($K = 1.28$) were pooled and isolated by evaporation to an aqueous phase and freeze drying to yield 175 mg of yellow amorphous solid, which failed to

crystallize; $[M]_D^{20} -320^\circ$ (4% sodium bicarbonate solution), $+83^\circ$ (glacial acetic acid). Paper chromatographic comparison with DL-allothreonine-DNP and DL-threonine-DNP in the system 1-butanol–water–ethanol (4:5:1, v/v, use upper phase) showed similar R_f values for DL-allothreonine and the unknown compound (0.64), while that of threonine was lower (0.61).

Anal. Calcd for $C_{10}H_{11}N_3O_7$: C, 42.11; H, 3.89; N, 14.73. Found: C, 42.12; H, 4.19; N, 13.93.

Iodoform from Nitrous Acid Treated Methyl Thiolincosaminide. A solution of 100 mg of MTL in 1 ml of water and five drops of acetic acid was treated with 100 mg of sodium nitrite in portions over a 2-min period at room temperature. Gas evolution was vigorous and the solution turned pink. After standing at room temperature for 2 hr, 5 ml of 2 N sodium hydroxide and seven 1-ml portions of I₂–KI solution were added. Iodoform started to precipitate immediately. After cooling in the refrigerator for 2 hr, the precipitate was collected and dried in air. The yield of iodoform melting at 121–122° (Kofler) was 60 mg (39%).

The control experiment which contained no sodium nitrite gave no evidence of iodoform production.

Pentaacetyl-MTL (22) (Methyl 6-N-Acetyl-2,3,4,7-tetra-O-acetyl-1-thio- α -lincosaminide). Methyl 1-thio- α -lincosaminide (3.0 g) was acetylated by allowing a solution in pyridine (50 ml) and acetic anhydride (25 ml) to stand overnight at room temperature. Solvent was removed on the rotating evaporator at 40° (15 mm), and the syrupy residue was distributed between water and methylene chloride. The organic extract, after washing with dilute hydrochloric acid (1 N), water, and saturated aqueous sodium bicarbonate and drying over anhydrous sodium sulfate, was taken to dryness *in vacuo*, giving a colorless crystalline residue which was recrystallized from ethyl acetate–Skellysolve B to give rods, showing a double melting point of 210–212 and 218–200°; $[\alpha]_D^{20} +223^\circ$ (c 0.906, CHCl₃).

Anal. Calcd for $C_{14}H_{23}NO_{10}S$: C, 49.22; H, 6.31; N, 3.02; S, 6.92. Found: C, 49.10; H, 6.57; N, 3.23; S, 6.91.

Pentaacetyl- α -MTL (22) (Methyl 6-N-Acetyl-2,3,4,7-tetra-O-acetyl-1-thio- α -lincosaminide). The above α -pentaacetate (2.0 g, 4.3 mmoles), dissolved in ethanol-free chloroform (50 ml), was stirred magnetically and a solution of bromine (1.11 g, 0.36 ml, 6.9 mmoles) in the same solvent (20 ml) was added over the course of 10 min (Drierite tube). After stirring for an additional 15 min, no trace of starting material could be detected by thin layer chromatography (SiO₂, ethyl acetate–Skellysolve B, 1:1). Solvent was removed on a rotating evaporator at 40° (7 mm), giving a yellow-orange syrup which was redissolved in chloroform, the solvent removed as above, and the process repeated twice more, giving a colorless syrup which could not be induced to crystallize. This procedure removes the methylsulfinyl bromide.

A solution of this syrup in acetone (analytical reagent, 25 ml) was heated under reflux (Drierite tube) with thiourea (656 mg, 8.6 mmoles) for 1 hr. After cooling, potassium carbonate (680 mg), sodium bisulfite (860 mg), water (10 ml) and methyl iodide (3.06 g, 1.34 ml, 21.6 mmoles) were added, and the mixture was stirred vigorously for 3 hr at room temperature.

The acetone was removed *in vacuo*, and the residue was distributed between water and chloroform. The aqueous layer was extracted thoroughly with chloroform, and the combined extracts were washed twice with water and dried over anhydrous sodium sulfate. Removal of the solvent on a rotating evaporator at 40° (7 mm) gave a colorless solid (1.48 g) showing only one spot on thin layer chromatography (SiO₂, ethyl acetate–Skellysolve B, 1:1). The solid crystallized from ethyl acetate–Skellysolve B in colorless platelets, mp 272–274° (1.12 g, 56%), unchanged by further crystallization. Countercurrent distribution of the crude product in the system water–acetone–methyl ethyl ketone–cyclohexane (3:5:4:4, v/v) showed only one material, of $K = 1.14$, to be present; $[\alpha]_D^{20} +31^\circ$ (c 0.680, CHCl₃).

Anal. Calcd for $C_{10}H_{13}NO_{10}S$: C, 49.22; H, 6.31; N, 3.02; S, 6.92. Found: C, 49.15; H, 6.23; N, 3.00; S, 6.75.

Acknowledgment. The authors wish to thank Mr. James Shiley for valuable technical assistance and Mr. Raymond Anderson and his associates for the analytical results.

Lincomycin. IV. Nuclear Magnetic Resonance Studies on the Structure of Lincomycin, Its Degradation Products, and Some Analogs¹

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Contribution from the Research Laboratories of the Upjohn Company, Kalamazoo, Michigan. Received December 20, 1966

Abstract: The contributions of nmr spectroscopy to the determination of the structure of lincomycin are reported. The amino acid portion was partially identified by nmr by comparison with synthetic samples. The structure of the sugar portion was independently determined by analysis of nmr spectra. The observation of an unusual intramolecular hydrogen bonding yielded the configuration of the sugar by conformational analysis. The spectra of some analogs and degradation products are correlated with their structures and conformations.

The structure of lincomycin,² an important new antibiotic with activity against gram-positive organisms, was the subject of a brief communication from these laboratories.³ The present paper describes the nmr studies on lincomycin, some degradation products, and some analogs.

The nmr spectrum of lincomycin hydrochloride ($C_{18}H_{26}N_2O_6S$) (Figure 1) is complex, containing many superimposed multiplets which were difficult to factor. There are several prominent signals which can be interpreted, but the severe overlapping, especially in the carbinol hydrogen region, makes complete interpretation impossible. The spectrum observed at 100 Mc⁴ is not greatly different, indicating the close proximity of the shifts of the carbinol hydrogens. Attention was therefore turned to degradation products and derivatives.

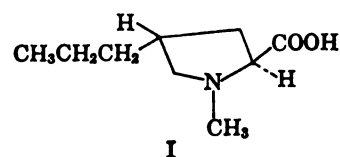
Chemical experiments⁵ showed that the molecule could be hydrolyzed at the amide linkage into an amino acid ($C_9H_{17}NO_2$) (I) and an amino thio sugar (methyl thiolincosaminide, MTL) ($C_9H_{19}NO_6S$) (II). Various aspects of the structures of these two compounds were determined by nmr, and when combined with chemical information the complete structure for the antibiotic was determined.

Amino Acid Portion. The nmr spectrum of the amino acid moiety (I) is shown in Figure 2. The material was thought to be a propyl-substituted hygric acid by comparison with known L-hygric acid.⁶ The location and configuration of the alkyl group could not be determined from the spectrum because the 2- and 5-hydrogen multiplets could not be factored. The 2-hydrogen multiplet was an unsymmetrical three-line pattern with some additional absorptions between the three peaks. It could be rationalized as several partly superimposed doublets, each arising from the 2-hydrogen of molecules having a different ring conformation or different N-methyl configurations.

Similar reasoning might also apply to the 5 β -hydrogen resonance. Subsequent experiments at increased temperature⁷ showed that at 100° the 2-hydrogen resonance collapsed to a regular triplet ($J = 9.0$ cps) and the 5 β -hydrogen resonance became a doublet of doublets ($J = 5$ and 10 cps). The original spectrum was regenerated when the sample returned to room temperature. Abraham and McLauchlan indeed found such ring buckling in the closely related *cis*- and *trans*-4-hydroxy-L-prolines⁸ and further concluded that the latter was a mixture of conformers.^{8c}

A synthetic sample of D-*cis*-4-propylhygric acid gave a spectrum which appeared to represent only one conformer (Figure 3). It was noted from the nmr spectrum that a sample of the unknown hygric acid was unexpectedly isomerized to the *cis*-4-propylhygric acid. This focused attention on the possibility that the unknown acid was the 4-*trans* isomer and that it had epimerized at C-2 in this experiment.

The structure of the amino acid was proved as L-*trans*-4-*n*-propylhygric acid (I) by synthesis and degradation.⁹



The analogous *trans*-4-methylproline reported by Abraham and co-workers^{8c} gave an nmr spectrum uncomplicated by conformers as did also the amide of *trans*-4-propylhygric acid hydrochloride and the quaternary analog *trans*-4-propylstachydrine (the betaine of I). L-Proline gave a spectrum similar to that of I with conformational complications. This was not noted by Abraham, *et al.*,^{8c} in their analysis of this spectrum. We plan to investigate this isomerism further.

Amino Thio Sugar Portion. The nmr spectrum of MTL (II) in deuterium oxide (Figure 4) showed absorptions for six kinds of hydrogen, as follows: (a) a doublet

(1) This material was presented in part at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug-Sept 1964, Abstracts, p 37S.

(2) See footnotes 1-5 of ref 3.

(3) H. Hoeksema, B. Bannister, R. D. Birkenmeyer, F. Kagan, B. J. Magerlein, F. A. MacKellar, W. Schroeder, G. Slomp, and R. R. Herr, *J. Am. Chem. Soc.*, **86**, 4223 (1964).

(4) We are grateful to Dr. Leroy Johnson of Varian Associates for this determination.

(5) W. Schroeder, B. Bannister, and H. Hoeksema, *J. Am. Chem. Soc.*, **89**, 2448 (1967).

(6) R. R. Herr and G. Slomp, *ibid.*, **89**, 2444 (1967).

(7) We thank Mr. C. R. Joller and his staff at the Pittsburgh Service Center of Varian Associates for assistance in these measurements.

(8) (a) R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, **5**, 195 (1962); (b) R. J. Abraham and K. A. McLauchlan, *ibid.*, **5**, 513 (1962); (c) R. J. Abraham, K. A. McLauchlan, S. Dalby, G. W. Kenner, and R. C. Sheppard, *Nature*, **192**, 1150 (1961).

(9) B. J. Magerlein, R. D. Birkenmeyer, R. R. Herr, and F. Kagan, *J. Am. Chem. Soc.*, **89**, 2459 (1967).

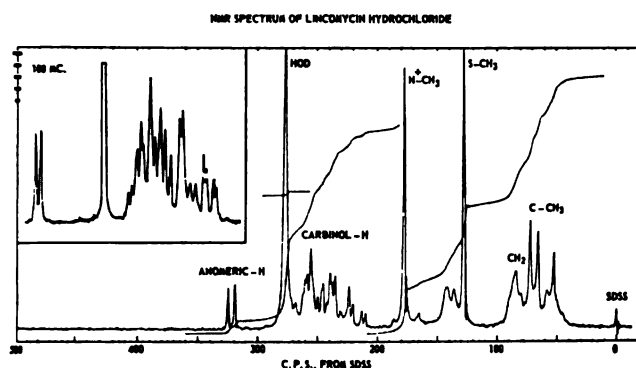
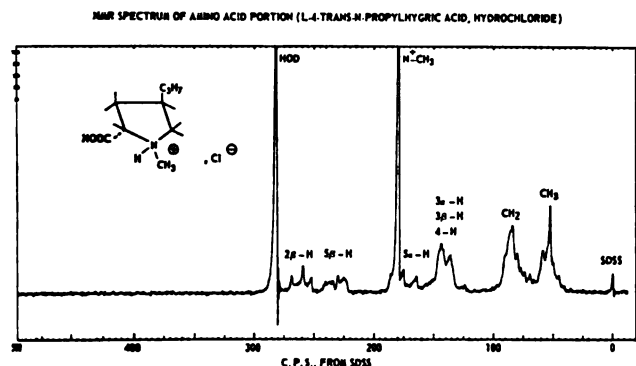


Figure 1. Nmr spectrum of lincomycin hydrochloride.

Figure 2. Nmr spectrum of amino acid portion (L-4-trans-n-propylhygric acid hydrochloride) in D₂O.

of area 3 at 68.0 cps,¹⁰ $J = 6.5$ cps, indicative¹¹ of a carbinol methyl group coupled to only one neighboring hydrogen; (b) a singlet of area 3 at 127 cps, assigned to the S-methyl group; (c) a doublet of doublets of area 1 at 188.5 cps, $J = 10.5$ and 3.0 cps, indicative of a carbamine hydrogen coupled differently to two neighbors; (d) a group of resonance lines with a total area of 5, lying between 212 and 256 cps, arising from the carbinol hydrogens of the sugar; (e) the HOD line at 276 cps, containing the resonances of six exchangeable hydrogens on oxygen and nitrogen; and (f) a doublet of area 1 at 320 cps, $J = 5.5$ cps, attributed to the anomeric hydrogen of the sugar. The multiplets are expanded for further study in Figure 5.

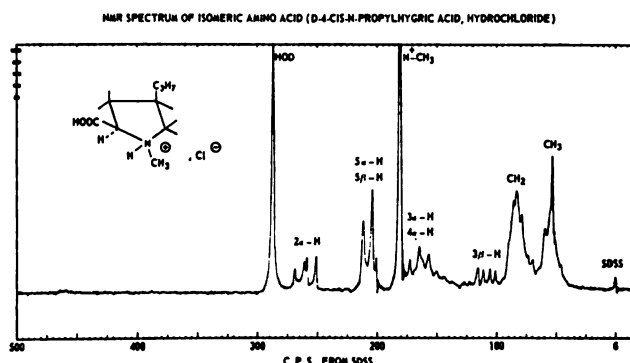
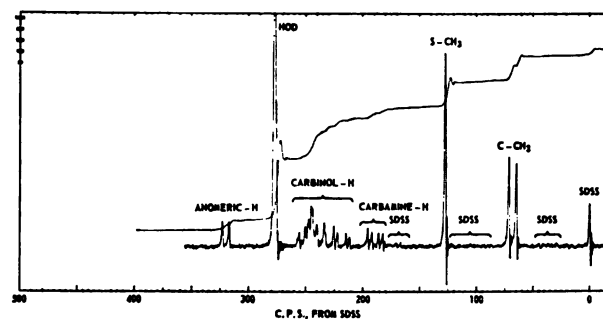
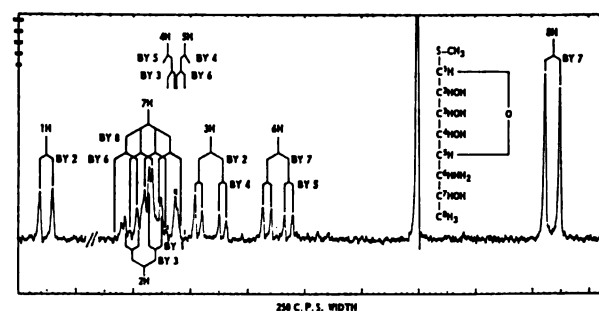
The nmr spectrum of MTL contained evidence that the molecule was a sugar. The presence of an anomeric hydrogen signal suggested an aldose, but aldoses are usually mixtures of many isomeric forms. The absence of mixture characteristics and the presence of a methylthio group suggested it was a methyl thioglycoside. The size of all the couplings and the general lack of sharpness suggested the rigidity of an aldopyranoside rather than a furanoside.¹²

The spectrum was empirically factored as much as possible using a dividers and making use where possible of the line shapes of the simple multiplets to evaluate J/δ frequency and to determine δ frequency (see Figure 5). The empirical factoring was subsequently confirmed

(10) Spectra were calibrated in cps units at 60 Mc, downfield from internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate (SDSS) [G.V.D. Tiers and R. I. Coon, *J. Org. Chem.*, 26, 2097 (1961)].

(11) K. Nukada, *et al.*, *Anal. Chem.*, 35, 1892 (1963).

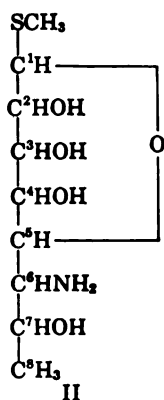
(12) Furanosides owing to their rapid ring conversion often give sharp spectra, and most of the coupling constants are of an averaged magnitude which is about 3 cps.

Figure 3. Nmr spectrum of isomeric amino acid (D-4-cis-n-propylhygric acid hydrochloride) in D₂O.Figure 4. Nmr spectrum of methyl thiolincosaminide in D₂O.

The methyl group embodying the 8-hydrogens¹³ absorbed as a doublet at 68 cps. These hydrogens were therefore coupled to one neighboring hydrogen at C-7. The absorption of this 7-H was found at 245 cps, again in the carbinol hydrogen region, and C-7, therefore, bears one hydrogen and one hydroxyl group. The 7-H absorption was actually a doublet of quartets and in addition to the coupling to the three hydrogens at C-8 it was further split ($J_{6,7} = 9.25$ cps) by one hydrogen at C-6. The absorption of this 6-H was accordingly found at 188 cps, in the carbamine hydrogen region. Thus, C-6 bears one hydrogen and one amine group. This 6-hydrogen absorption was actually a doublet of doublets with the same $J_{6,7}$ but with a second coupling ($J_{5,6} = 3.75$ cps) to one neighboring hydrogen at C-5. The absorption of this 5-H could be extracted from the spectrum only by spin decoupling⁷ and it was observed at 228 cps, in the carbinol hydrogen region, but again this multiplet could not be factored. Thus, C-5 bears one hydrogen and one oxygen substituent which in this case must be the pyran ring (*vide supra*).

The similarity of the shift of the 4- and 5-hydrogens apparently resulted in a very closely coupled multiplet which was not factored by empirical procedures. Such a multiplet would have an intense center at about 234 cps as shown in Figure 5, but the outlying portions would be weak and would not be seen in the spectrum.

Since all the peaks in the spectrum have been accounted for and all the allotted hydrogens have been used, it remains to connect C-4 and C-5 to yield structure II for this sugar. This analysis independently



confirmed earlier chemical evidence⁶ that MTL was a thiomethyl pyranoside of an aminodideoxyoctose but disagreed in the position of the NH_2 substituent.¹⁴

The data so far obtained also provided some information regarding the conformation and configuration of MTL. In a pyranoside ring some deformation is possible, as for example in β -glucopyranose,¹⁵ and the dihedral angles are not always exactly 60 or 180°. Even though the Karplus relationship does not yield *exact* dihedral angles from coupling constants,¹⁶ the *magnitude* of the calculated angle does allow a distinction between neighboring hydrogens that are diaxial *vs.* those which are diequatorial or axial-equatorial. The observed coupling constants are, therefore, summarized in Table I, and the appropriate conformational

(13) The empirical formula and subsequent reasoning (*vide infra*) showed that the molecule terminated with C-8.

(14) The negative iodoform test⁶ required the NH_2 group to be at C-7, but this test was subsequently shown to be anomalous.

(15) R. W. Lenz and J. P. Heeshen, *J. Polymer Sci.*, **51**, 247 (1961).

(16) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2871 (1963).

Table I. Couplings^a and Possible Conformations of the Sugar Hydrogens^b

J_{xy}	Cps	Conformational relationship	Dihedral angle, deg— Calcd	Found ^c
1,2	5.5	<i>ea</i> or <i>ee</i> ^d	33 or 127	60
2,3	10.5	<i>aa</i>	180	161
3,4	3.0	<i>ae</i> or <i>ee</i>	50 or 112	42
4,5	?	?	?	60
5,6	3.75	<i>ae</i> or <i>ee</i>	46 or 117	45
6,7	9.25	<i>aa</i>	150	163
7,8	6.5	Free rotation

^a The coupling constants are simply first-order values obtained from the spacings in the spectra. Some of these approximate values may thus be in error by as much as 0.5 cps but this is not serious since exact fitting of angles was not sought. ^b The italic values were the ones that fit the final structure. ^c Observed in the Dreiding model of Ia. ^d a = axial, e = equatorial.

relationships have been deduced from the Karplus angles.

The configuration of the sugar can now be deduced from the dihedral angle data of Table I. Since the 2-H-3-H dihedral angle must be about 180°, these two hydrogens must be *trans* diaxial. A chair-formed pyranose ring was arbitrarily drawn in the D form and axial hydrogens were placed at carbons 2 and 3. Now if 2-H and 3-H are axial, the 1-H-2-H and the 3-H-4-H relationships cannot be equatorial-equatorial but must be equatorial-axial and axial-equatorial, respectively. Equatorial hydrogens were placed at carbons 1 and 4. Now the 4-H-5-H angle is not known because these multiplets could not be factored. However, one may assume that the alkyl chain at C-5 is equatorial because this is the more stable form which is reached by ring conversion between the two possible chair forms. Thus, the 5-H must be axial and the ring has the α -galactoside configuration.

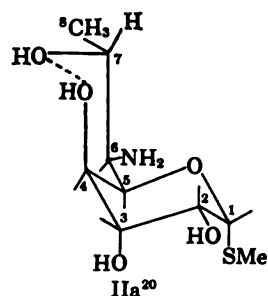
It was noteworthy that the signals arising from the 6- and 7-hydrogens were not very sharp. This was observed by comparing their ringing with that from the methyls. Also, the coupling constants of the 5-, 6-, and 7-hydrogens were not about 7 cps as would be expected for a freely rotating side chain. It was therefore concluded that this chain was held rigid, in one preferred conformation. Steric effects observed from Catalin models did not seem to be serious enough to bring about this rigidity, but the opportunity for hydrogen bonding from the side chain to the ring in several different ways was clearly apparent from the Dreiding models. To adequately immobilize the side chain the 7-hydroxyl was suspected of involvement. Although several sites were possible, the chelate formed by bonding the 7- to the 4-hydroxyl group looked ideal in the models.¹⁷ This chelate ring contained seven atoms.¹⁷

Further information on the configuration of the side chain was now obtained by conformational analysis. From the coupling constants (Table I) the 6-H-7-H angle must be about 150° and the 5-H-6-H angle about 46 or 117°. The eight possible side-chain conforma-

(17) Hydrogen bonds vary in energy but are strongest when certain spatial requirements are met. The optimum OH-O distance in alcohols is about 2.74 Å and collinearity is desirable.¹⁸ Thus, intramolecular hydrogen bonds lead to various-sized rings, but those containing five to seven atoms are common.

(18) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, Chapters 5 and 7; J. D. Bernal in "Hydrogen Bonding," D. Hadzi and H. W. Thompson, Ed., Pergamon Press Inc., New York, N. Y., 1959, p 7.

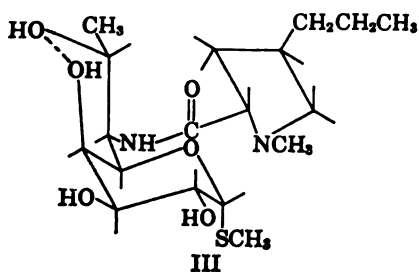
tions allowed by these angle requirements were examined with the aid of Dreiding models and only that shown in IIa affords both the approximate required



angles and the possibility of hydrogen bonding from the 7-OH to the ring.¹⁹ Thus, the analysis led to the conclusion that MTL was either IIa or its enantiomorph.

This structure, containing two *cis*-fused rings, both in the chain form, looked reasonable. The 8-methyl and 7-amine were both in the low-energy equatorial conformation. The foregoing reasoning was admittedly speculative at several points, but the results were completely confirmed and the D series was indicated by subsequent chemical degradations of MTL yielding D-galactose⁵ from the pyranose portion, and D-allo-threonine^{5,21} from the side-chain portion.

Reconstitution of the amide linkage yields III as the structure of lincomycin.



Resonance data obtained on some analogs and derivatives of MTL are collected in Table II. The glycoside configurations were determined from the nmr data. The spectrum (Figure 6) of 2-hydroxyethyl thiocelastosaminide (HTC) (IV), the sugar portion of celesticetin,²² was identical with that of MTL after allowing for the replacement of the S-methyl absorbance by the A₂X₂ absorbance of the hydroxyethylthio substituent and the addition of a 7-methoxy signal,²³ thus confirming²² that the sugar moieties of both antibiotics have the same configuration and showing that

(19) A second-choice structure had less desirable ring size and poorer agreement with observed angles but the same side-chain configuration as Ia. It had the 7-OH bonded to the ether oxygen to make a six-membered ring with an unusually long O—O distance. This model also required 5H—6H and 6H—7H angles to be 120° instead of 150 and 117° as observed. The rejection of this chelate was later confirmed when the 7-methoxy sugar was studied. It, too, showed the same hydrogen bonding; *vide infra*.²⁰

(20) Since the exact location of the hydrogens in the hydrogen bond is not known, the structure is written in this noncommittal form. It may be possible that both hydrogens are involved in a diamond arrangement with the two oxygens.¹⁹

(21) B. Bannister and H. Hoeksema, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug–Sept 1964, p 6P.

(22) H. Hoeksema, *J. Am. Chem. Soc.*, **86**, 4224 (1964).

(23) The 6-hydrogen of HTC absorbed 16 cps higher than that of MTL. This carbamate hydrogen could easily shift this much as a result of pH differences in these two solutions.

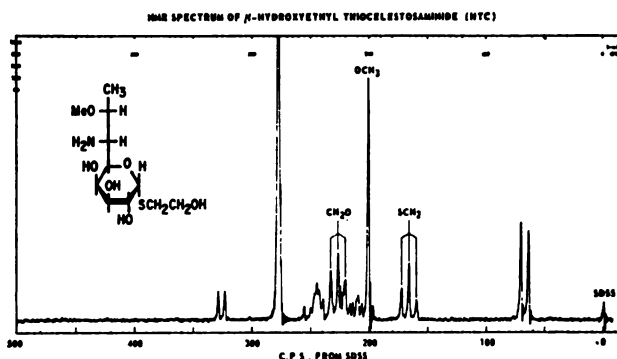
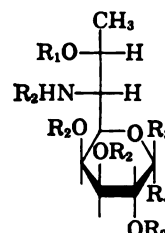


Figure 6. Nmr spectrum of β -hydroxyethyl thiocelastosaminide in D₂O.

HTC must be the α anomer. The presence of a 7-methoxy group in HTC did not alter the chelation.

Compounds V, VI, VII, and VIII constitute two anomeric pairs of sugars and the glycoside configuration was deduced from the following observations.



- II, R₁ = R₂ = R₃ = H; R₄ = SCH₃
 IV, R₁ = CH₃; R₂ = R₃ = H; R₄ = SCH₂CH₂OH
 V, R₁ = R₂ = Ac; R₃ = SCH₃; R₄ = H
 VI, R₁ = R₂ = Ac; R₃ = H; R₄ = SCH₃
 VII, R₁ = R₂ = Ac; R₃ = OAc; R₄ = H
 VIII, R₁ = R₂ = Ac; R₃ = H; R₄ = OAc
 IX, R₁ = CH₃; R₂ = Ac; R₃ = OAc; R₄ = H
 X, R₁ = CH₃; R₂ = Ac; R₃ = H; R₄ = SCH₂CH₂OAc

The nmr spectra, summarized in Table II of the β anomers of MTL-pentaacetate (V) and lincosamine hexaacetate (VII), differed from the α anomers (VI and VIII) by showing 1-H resonances at lower frequency and J_{1,2} couplings that were larger.²⁴ Since the 2-H in galactose is axial, the 1-H of the β isomer would be in a diaxial relationship to it, and this is in agreement with the 7.5- and 9-cps coupling constants.

Additional conclusions can be drawn from the 2-, 3-, and 5-H resonance frequencies. In the α anomers, the axial S or O atom at 1 is nearer the symmetrically located axial hydrogens at 3 and 5 than it is in the β anomers. This deshielding effect of the O or S would be expected to increase the 3- and 5-H resonance frequency, and this was indeed observed as assigned. The differences were 20, 20, 34, and 17 cps. One would accordingly expect the 2-H to resonate at higher frequency in the β anomers since the O or S atom is now slightly closer than in the α anomer. This was also observed on these pairs. The actual differences were 9 and 13 cps.

(24) In a study of the nmr of many pyranosides, Lemieux, *et al.*,²⁵ reported that in cases of rigid six-membered rings, equatorial hydrogens absorbed at a lower magnetic field (larger cps from TMS) than axial hydrogens did. Similar results have been observed in these laboratories. Further, it was noted that diaxial hydrogen neighbors showed a coupling constant of 5–10 cps and axial-equatorial or diequatorial hydrogen neighbors a coupling of 3–5 cps (the variation arises from some departure from perfect chair conformations¹⁴).

(25) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958); **82**, 6427 (1960).

Table II. Sugar Moiety Proton Absorbances^a and Coupling Constants

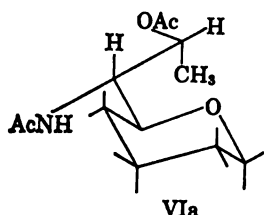
Material	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈	J _{1,2}	J _{2,3}	J _{3,4} ^c	J _{4,5}	J _{5,6}	J _{6,7}	J _{7,8}
α-MTL ^b (II)	320	248 ^a	218	240 ^a	228 ^a	188	245	68	5.5	10.5	3.0	...	3.75	9.25	6.5
α-HTC ^c (IV)	325	248 ^d	220	240	225	204	245	67	5.5	10.0	2.5	...	3.0	9.5	6.5
β-MTL pentaacetate (V)	261	318	300	326	224	272	307	78	9.0	10.0	3.0	<1	9.5	3.0	7.0
α-MTL pentaacetate (VI)	339	305 ^d	320 ^d	326	258	277	306	77	4.75	<1	10.5	2.5	7.0
β-Lincosamine hexaacetate (VII)	344	322	305	326	231	277	307	73	7.5	10.0	2.5	<2	10.0	3.0	7.0
α-Lincosamine hexaacetate (VIII)	383	313 ^d	325 ^d	329	248	272	306	73	2.0	10.0	2.5	<1	10.0	3.0	7.0
β-Celestosamine pentaacetate (IX)	343	321	307	327	238	268	210	71	7.0	10.0	3.0	<1	10.0	2.5	7.0
α-HTC ^c pentaacetate (X)	348	305 ^d	315 ^d	326	260	275	211	71	5.0	...	2.0	...	10.0	2.5	7.0
7-Chloro-7-deoxylincomycin (XV)	325	249	219	235	260	264	272	87	5.5	10.5	3.5	1	10.5	1.5	7.0

^a II, IV, and XV were observed in D₂O with SDSS reference, others were in CDCl₃ with TMS reference. ^b MTL, methyl thiolincosaminide; HTC, 2-hydroxyethyl thiocelestosaminide. ^c Centers of absorbances located by spin-decoupling experiments. ^d Absorbances not factored completely, centers are approximated.

The celestosamine pentaacetate (IX) was judged to be β from the nmr data because of the very close similarity to that of β-lincosamine hexaacetate (VII) in all four of the above criteria. The fact that all the shifts and couplings in IX compared so closely to those of β-lincosamine hexaacetate (VII) confirms the conclusions that the two sugars are the same configuration and conformation.

The HTC pentaacetate sample X, when compared by nmr spectroscopy to the α- and β-MTL pentaacetates (VI and V), was judged to be the α anomer because of the high-frequency 1-H resonance, the small J_{1,2}, the high-frequency 3- and 5-H resonance, and the low-frequency 2-H resonance. Since this compound came from celesticetin with no possible inversion at C-1, the celesticetin precursor must have been the α anomer.

Inspection of Table II reveals that the coupling constants of the 5-, 6-, and 7-hydrogens in the spectra of the acetylated sugars as a group were now quite different from those found in the MTL and HTC spectra. It is apparent that the esterification of the OH groups destroyed the chelate ring and as a result the side chain shifted to a second preferred orientation VIa. In

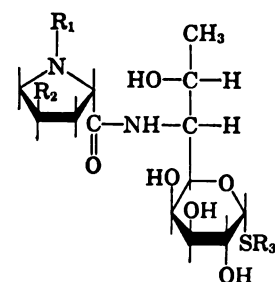


these acetylated molecules steric effects may well be the decisive factor. Catalin models indeed showed VI with the 5,6-hydrogens *trans* and the 6,7-hydrogens *gauche* to be a conformation with minimum steric interference among bulky acetyl groups.

Analogs. Many analogs of lincomycin have been studied by nmr. Extensive alterations of either the amino acid or sugar portions of lincomycin brought appropriate changes in the nmr spectrum. Minor modifications only altered the spectrum slightly. Thus, nmr served as a convenient tool for the identification of these analogs.

Alteration of the fermentation conditions and ingredients has produced several close analogs of lincomycin which were identified as XI–XIV.²⁶ When the R₁ substituent was hydrogen instead of methyl the N-

(26) A. D. Argoudelis, J. A. Fox, D. J. Mason, and T. E. Eble, *J. Am. Chem. Soc.*, **86**, 5044 (1964); also presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, N. Y., Oct 26–28, 1964.



III, R₁ = CH₃; R₂ = *n*-C₂H₅; R₃ = CH₃
 XI, R₁ = CH₃; R₂ = C₂H₅; R₃ = CH₃
 XII, R₁ = CH₃; R₂ = *n*-C₃H₇; R₃ = C₂H₅
 XIII, R₁ = H; R₂ = *n*-C₂H₅; R₃ = CH₃
 XIV, R₁ = H; R₂ = *n*-C₃H₇; R₃ = C₂H₅

methyl singlet disappears from the spectrum and the new N-hydrogen appears with the exchangeable hydrogens. When R₁ was higher alkyl, the position and shape of the new absorptions from these alkyl groups were observed as expected.²⁷ The appropriate carbamine and terminal hydrogen frequencies are collected in Table III. It was noteworthy that the two methyls of

Table III. Characteristic Absorptions of N-Alkyl Analogs of Lincomycin Hydrochloride^a

N substituent	Frequency, cps (J, cps)	
	N-CH	C-CH ₃
Methyl	179	
Ethyl	199 (7.5)	77 (7.5)
<i>n</i> -Propyl	193 ^b (7.5)	57 (7.5)
Isopropyl	217 ^b (6.5)	78, 80 (6.5)
<i>n</i> -Butyl	190 ^b (6.5)	53 (7.0)

^a D₂O was the solvent. ^b Unusually broad.

the isopropyl group experience slightly different shielding. It is proposed that this arises from restricted rotation of this isopropyl group.

When the R₂ substituent was an alkyl group other than propyl, very little change was observed in the spectrum compared to that of lincomycin hydrochloride. The area of the methylene absorption and the characteristics of the terminal methyl absorption varied as expected²⁷ for these substituents.

When R₂ was hydrogen or ethoxy, the spectra lacked the methylene hump and the methyl triplet. The ethoxy analog showed instead a carbinol hydrogen quartet at 212 cps (*J* = 7 cps) or at 217 cps (*J* = 7 cps)

(27) K. W. Bartz and N. F. Chamberlain, *Anal. Chem.*, **36**, 2151 (1964).

V. Characteristic Absorptions of S-Alkyls of Lincomycin Hydrochloride^a

substituent	Frequency, cps (<i>J</i> , cps)		
	S-CH	C-CH ₃	Anomeric H
ethyl	128	...	322 (5.5)
isopropyl	158 (7.5)	75	327 (5.5)
isobutyl	178 (7.0)	78	331 (5.5)

^a DMSO was the solvent.

is or *trans* configuration, and a methyl triplet and 72 cps, respectively. When the R₂ substituent was an alkyl group other than methyl, the spectrum showed minor changes. Absence of the S-methyl singlet and appearance of appropriate S-alkyl absorptions were noted, together with a small shift in the absorption frequency of the anomeric hydrogen (see Table IV).

When the 7-hydroxyl was replaced by a chlorine atom XV, profound changes were observed in the carbinol region of the spectrum (see Table II). It is important to note that the intramolecular hydrogen bond is also destroyed and the *J*_{5,6} and *J*_{6,7} coupling constants indicate a side-chain conformation similar to VIa.

Experimental Section

Nmr spectra were observed on a Varian A-60 spectrometer using solutions (ca. 0.4 ml, 0.3 *M*) of the samples in chloroform-*d* or deuterium oxide. Spectra were calibrated with internal tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (SDSS).⁹ Spectra are calibrated in cps at 60 Mc to allow discussion of portions of multiplets.²⁸ Spin-decoupling experiments were performed with a Varian HR-100 spectrometer using a V-3521 integrator for field-sweep decoupling.¹²

The preparation of degradation products, derivatives, and analogs used in this study is described elsewhere.^{2,5-7,21,22,26}

(28) G. Slomp, *J. Am. Chem. Soc.*, **84**, 673 (1962).

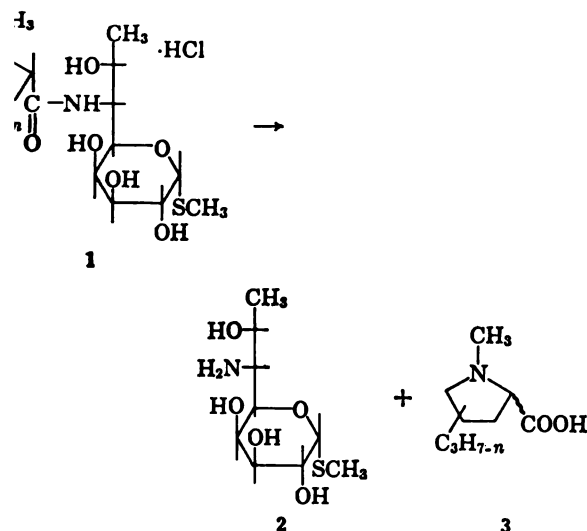
Lincomycin. V. Amino Acid Fragment¹

Barney J. Magerlein, Robert D. Birkenmeyer, Ross R. Herr, and Fred Kagan

Contribution from the Research Laboratories of the Upjohn Company, Kalamazoo, Michigan. Received December 20, 1966

Abstract: The amino acid derived from the cleavage of the antibiotic lincomycin is shown to be *trans*-1-methyl-4-*n*-propyl-L-proline. A partial synthesis of lincomycin is described.

Cleavage of the antibiotic lincomycin hydrochloride (1) into methyl thiolinecosaminide (2) and 1-methyl-*n*-propylproline (3) was described in previous papers in this series.^{2,3} The determination of the position of the *n*-propyl substituent and the configuration at carbon



presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964; Abstracts of Papers, p 6P. For a preliminary report cf. H. Hoeksema, B. Bannister, R. D. Birkenmeyer, and B. J. Magerlein, F. A. MacKellar, W. Schroeder, G. Slomp, R. Herr, *J. Am. Chem. Soc.*, **86**, 4223 (1964). R. Herr and G. Slomp, *J. Am. Chem. Soc.*, **89**, 2444 (1967). W. P. Schroeder, B. Bannister, and H. Hoeksema, *ibid.*, **89**, 2448

atoms C₂ and C₄ in the proline fragment is now reported.

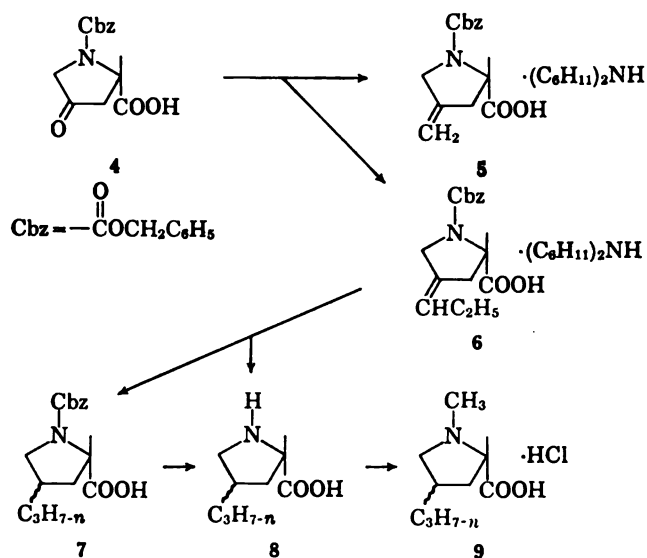
The over-all plan was to establish the position of the alkyl group and confirm the absolute stereochemistry of C-2 by synthesis of 3-, 4-, and 5-*n*-propyl-1-methylproline^{4a} and then to determine the absolute configuration of C₄ by degradation.

The synthesis of 1-carbobenzoxy-4-methylene-L-proline (5) resulting from the action of methylenetriphenylphosphorane on 1-carbobenzoxy-4-keto-L-proline (4) was recently described.^{4b} Under similar conditions *n*-propylidenetriphenylphosphorane failed to give the desired 4-propylidene compound 6. However, a modification of the recently described sodium methylsulfinylcarbanion-dimethyl sulfoxide procedure⁵ afforded 6 in 55% yield.

Although the double bond of 6 could be hydrogenated over a platinum catalyst to give 7, concomitant hydrogenation and hydrogenolysis of 6 to yield 8 was generally more convenient. Reductive methylation of 8 afforded the methylated amino acid 9 in high yield. The saturated amino acids 7, 8, and 9 were obtained as *cis-trans* isomers, but separation of these isomers could not be achieved through chromatography, electrophoresis, or fractional crystallization.

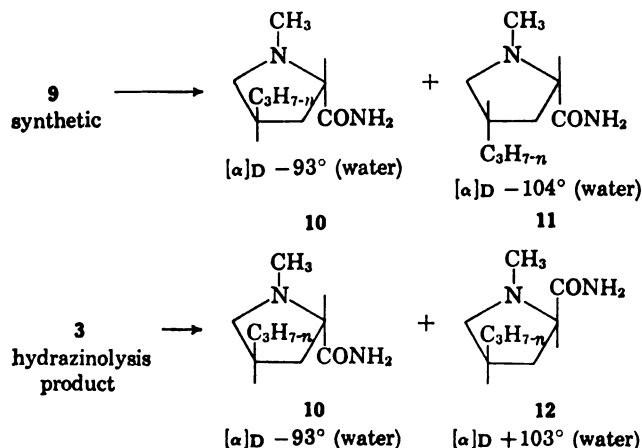
(4) (a) Rotational data suggested the L configuration for the carboxyl group. See ref 2. (b) M. Bethell, G. W. Kenner, and R. C. Sheppard, *Nature*, **194**, 864 (1962). The authors are indebted to Professor G. W. Kenner for experimental details of this reaction prior to publication.

(5) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).



Conversion of the acids **9** to the amides afforded a mixture of *cis* and *trans* isomers **10** and **11** which was readily separated by chromatography over silica gel. One of these compounds was identical with the amide prepared from naturally occurring propylhygric acid, thus establishing the position of the propyl group at C-4 and the absolute configuration of the C-2 carbon atom as L. The absolute configuration of C-4 was established by degradation.

The amino acid fragment obtained from the hydrazinolysis of lincomycin was frequently partially or completely epimerized at the α -carbon atom. After conversion to the amides, the D and L isomers, **10** and **12**, were separated by chromatography.

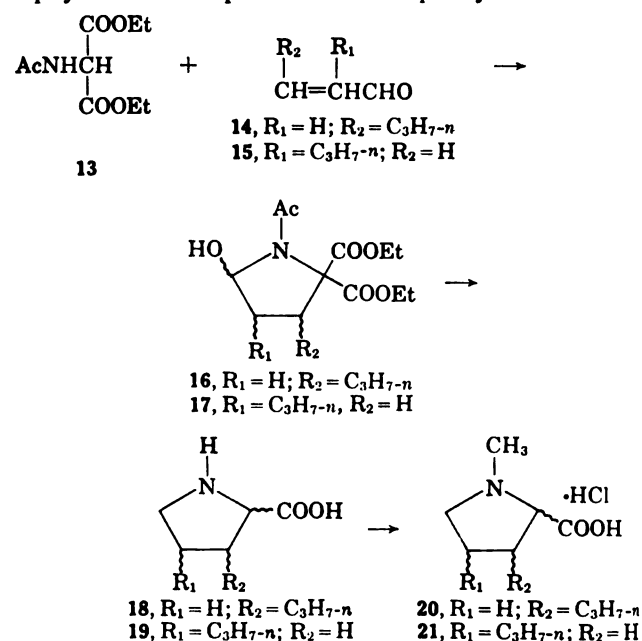


The nmr curves of diastereoisomers **10** and **11** (epimeric at the 4 position) differed from each other as did the curves of **10** and **12**. However, the curves of the mirror images **11** and **12** were identical as were those for **10** prepared from either synthetic amino acids **9** or natural amino acid **3**. Since the amides **10** prepared from either epimeric acids obtained by hydrazinolysis of lincomycin or from synthesis were identical, and since the synthetic amide was prepared from 4-keto-L-proline, we concluded that the *n*-propyl group was at position 4 and that the amino acid was in the L configuration. The isomers **11** and **12** which possessed identical nmr spectra, but optical rotations of opposite sign, were formulated as optical isomers though the absolute configuration of the propyl group was not as yet established. The absolute configuration of the

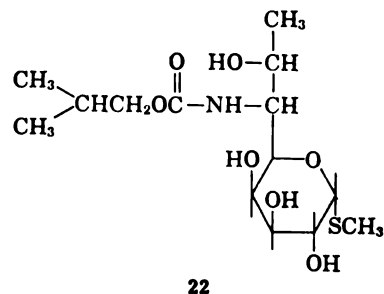
n-propyl group was determined by degradation as will be described later.

Concurrently with the synthesis of 1-methyl-4-*n*-propyl-L-proline from 1-carbobenzoxy-4-keto-L-proline, total syntheses of this amino acid and 1-methyl 3-*n*-propylproline were investigated. The method of synthesis was similar to that published for racemic 4-methylproline.⁶ Acetamidomalonic ester (**13**) was condensed with the appropriate aldehyde **14** or **15** to yield the cyclic intermediate **16** or **17**. This compound was not obtained pure, but was reduced and hydrolyzed to **18** or **19**. Reductive methylation of **18** and **19** gave racemic **20** and **21**. In neither case was racemic 3-*n*-propyl or 4-*n*-propyl-1-methylproline resolved though thin layer chromatography of the amide derivatives indicated that the *cis* and *trans* *dl* pairs could be separated by chromatography. The 4-substituted amides prepared from **21** showed two spots on thin layer chromatography which moved with the racemic acids obtained from lincomycin (**10** and **12**) and which separated from the 3-substituted amides prepared from **20**. This constituted additional evidence for 4 substitution in the hygric acid moiety of lincomycin.

The racemic acid **21** was coupled with the amine **2** using the mixed carbonic anhydride method. The crude product showed 12% of the activity of lincomycin when assayed microbiologically or by thin layer chromatography. No attempt was made to purify this material.

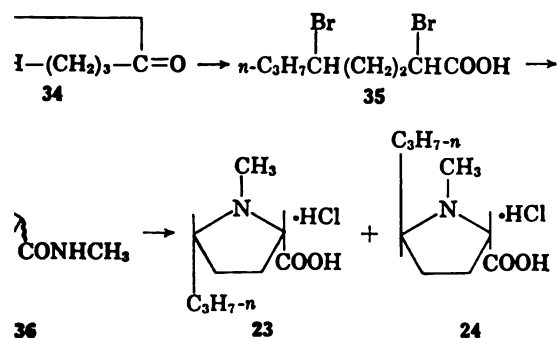


Under similar conditions racemic 1-methyl-3-*n*-propylproline (**20**) failed to condense with **2**, only the carbamate **22** being isolated from the reaction mixture.



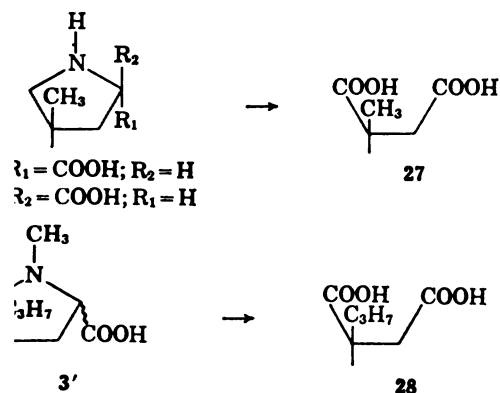
(6) J. S. Dalby, G. W. Kenner, and R. C. Sheppard, *J. Chem. Soc.*, 4387 (1962).

ic 1-methyl-5-*n*-propylproline was synthesized and separated into the racemic pairs 23

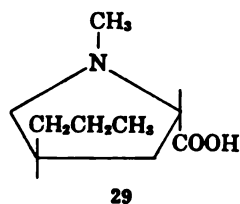


spectra of 23 and 24 differed sufficiently from the natural amino acid so as to exclude the -5-*n*-propylprolines (23 and 24) as lincomycin ion products.

tereochemistry at C-4 in 1-methyl-4-*n*-propyl- was determined by the use of a degradative introduced by Neuberger in his classical work stereochemistry of hydroxyproline.⁷ This was recently employed in the determination of lute configuration of the 4-methyl group in 4-roline (25 and 26).⁸ In this case the oxidation iastereoisomers 25 and 26 gave D-(+)-methyl- acid (27). Exhaustive oxidation of the race- imino acid fragment (3') from lincomycin D-(+)-*n*-propylsuccinic acid (28).⁹



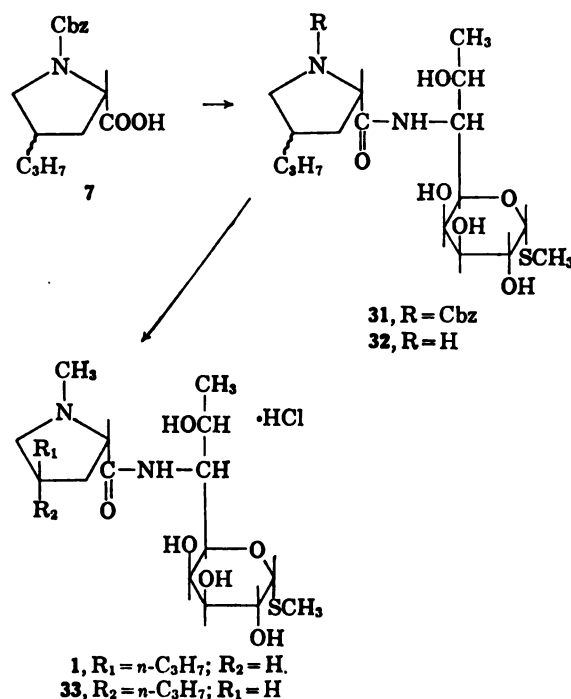
stereorelationship between D-(+)-methyl and propylsuccinic acid is known,¹⁰ we concluded propyl group of 3 is oriented similarly to the group of 25 and 26. That is, it is *trans* to the yl. Therefore, the amino acid fragment from in is *trans*-1-methyl-4-*n*-propyl-L-proline (29).



Neuberger, *J. Chem. Soc.*, 429 (1945).
Dalby, G. W. Kenner, and R. C. Sheppard, *ibid.*, 4387 (1962).
Clutterbuck, H. Raistrick, and F. Reuter, *Biochem. J.*, 31,

Abrahamsson, S. Stållberg-Stenhagen, and E. Stenhagen, in *The Chemistry of Fats and Other Lipids*, Vol. VII, Part 1, I. L. I. Ed., Pergamon Press, Oxford, 1963, p 24.

Two partial syntheses of lincomycin (1) from 4-hydroxy-L-proline were achieved. In the first the *cis-trans* mixture of 1-methyl-4-*n*-propyl-L-proline (9) was coupled with methyl thiolincosaminide (2) to give a mixture of lincomycin (1) and its *cis* isomer 33. In the first step of the second method, 1-carbobenzoxy-4-propylidene-L-proline (6) was hydrogenated to give 7, a *cis* and *trans* mixture. The hydrogenation of the exocyclic double bond in 1-carbobenzoxy-4-propylidene-L-proline (6) over platinum oxide or platinum or palladium on the usual supports led to mixtures containing only a small percentage of the desired *trans* isomer. The palladium catalysts invariably also caused hydrogenolysis of the carbobenzoxy group. The high ratio of the *cis* isomer indicated that the hydrogen atoms were approaching the molecule from the side opposite the carboxyl group. Therefore, if the amino acid could be attracted to the catalyst by its carboxyl group, the hydrogen atoms should then approach from the carboxyl side forming a greater proportion of *trans* isomer. Such a situation may exist if the catalyst were deposited on a basic ion-exchange resin. Therefore, the use of platinum on an ion-exchange resin¹¹ was investigated and the hydrogenation product found to contain considerably more of the desired *trans* isomer of 7 (25-35%) in which the carbobenzoxy group remained intact.



The blocked amino acid 7 was coupled with methyl thiolincosaminide (2) in high yield, forming 31. The blocking group was removed by hydrogenolysis and the resulting product 32 reductively methylated to yield a mixture of lincomycin (1) and its *cis* isomer 33. From this mixture pure lincomycin (1) was isolated by chromatography. This material was identical in both its physical and microbiological properties with the natural antibiotic. The *cis* isomer 33 was also isolated as a pure compound. It possessed about one-half the antibacterial activity of lincomycin. This semisynthetic

(11) F. J. McQuillin, W. O. Ord, and P. L. Simpson, *J. Chem. Soc.*, 5996 (1963).

preparation of lincomycin confirmed the structure of the amino acid portion of lincomycin.

The partial synthesis of lincomycin from 4-hydroxy-L-proline has been adapted to the preparation of lincomycin analogs having variations in both the amino acid and sugar moieties.¹²

Experimental Section¹³

1-Carbobenzoxy-4-propylidene-L-proline Dicyclohexylamine Salt (6). A sodium hydride suspension (3.8 g) was warmed with 75 ml of dimethyl sulfoxide at 70–75° until reaction was completed. After cooling to 20°, 30.8 g of propyltriphenylphosphonium bromide was added. The resulting red solution was stirred for 30 min to ensure complete reaction. A solution of 5.2 g of 4¹⁴ in 15 ml of dimethyl sulfoxide was added over a period of 15 min. The resulting mixture was stirred for 20 min at 26° and then at 70° for 4 hr. The cooled reaction mixture was treated with 100 ml of 5% potassium bicarbonate and 100 ml of water and filtered. The filtrate was washed twice with 150-ml portions of ether and the ether discarded after back-extracting with bicarbonate solution. The aqueous solution was diluted with 200 ml of water, acidified, and extracted with three 200-ml portions of ether. The combined ether solution was washed with three 50-ml portions of saturated sodium bisulfite solution, then with water, and dried. The residue, 5.7 g, obtained after evaporation of the solvent, was dissolved in 18 ml of acetonitrile and treated with 2.8 ml of dicyclohexylamine. The crystalline salt, 5.2 g (55% yield), melted at 154–157°. The analytical sample prepared by three recrystallizations from acetonitrile melted at 164–166° and showed $[\alpha]_D -8^\circ$ (chloroform).

Anal. Calcd for $C_{21}H_{27}N_3O_4$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.77; H, 9.39; N, 5.91.

trans- and cis-4-n-Propyl-L-proline (8). Ten grams of 6 was converted to the free base as described below in the preparation of 30.

This oil was dissolved in 250 ml of methanol and shaken under hydrogen over 2 g of platinum on Dowex¹⁵ for 4 hr. Palladium on carbon (2 g, 10%) was added and shaking continued for 2 hr. The catalyst was removed by filtration and the solvent distilled under reduced pressure. The residue was shaken with ether and 2.77 g (82.9%) of crystalline 8, mp 220–223° dec, deposited. Three recrystallizations from methanol–acetone afforded the analytical sample, mp 232–234°, $[\alpha]_D -63^\circ$ (water).

Anal. Calcd for $C_9H_{15}NO_2$: C, 61.12; H, 9.26; N, 8.91. Found: C, 61.06; H, 9.46; N, 8.94.

trans- and cis-1-Methyl-4-n-propyl-L-proline Hydrochloride (9). Formalin (4 ml) was added to 3.4 g of crude 8 from the previous step dissolved in 200 ml of methanol. The mixture was shaken under hydrogen for 2.5 hr at 45 psi pressure. The catalyst was removed by filtration and the solvent distilled. The residue was crystallized from methanol–ether–hydrogen chloride to afford 2.82 g of 9, mp 200–202°. After several recrystallizations from methanol–ether the hydrochloride melted at 201–206° and gave $[\alpha] -60^\circ$ (water).

Anal. Calcd for $C_9H_{15}NO_2Cl$: C, 52.04; H, 8.73; N, 6.75. Found: C, 51.72; H, 8.96; N, 6.44.

cis-Lincomycin Hydrochloride (33). A mixture of 2.47 g of 9 and 7.6 ml of *n*-tributylamine in 80 cc of distilled acetonitrile was stirred until all of the solid had dissolved. The solution was cooled in an ice bath and 1.64 g of isobutyl chloroformate slowly added. A solution of 3.0 g of methyl thiolincosaminide in 40 ml of water was added. The reaction mixture was stirred for 1 hr in the ice bath and 3 hr at 26°. The acetonitrile was distilled under vacuum. The residue was diluted with 20 ml of water and extracted twice with ether. The aqueous solution was lyophilized. The residue was triturated several times with chloroform and this solution chromatographed over Florisil,¹⁶ using an elution system of Skellysolve B¹⁴–ethyl

acetate with increasing amounts of methanol. The fractions which showed material in the lincomycin area by tlc were combined. This oil (0.86 g) was dissolved in dilute hydrochloric acid and the crude hydrochlorides 33 and 1 precipitated with acetone. The yield was 480 mg (9.04%). Tlc (ethyl acetate–acetone–water, 8:5:1) showed a major spot moving slightly slower than lincomycin and also a weak lincomycin spot. Bioassay indicated 37% lincomycin. Bioautography showed activity in the lincomycin area.

Several recrystallizations of the crude hydrochloride afforded an analytical sample, mp 147–150°, of *cis*-lincomycin hydrochloride (33) containing only a trace of lincomycin.

Anal. Calcd for $C_{18}H_{23}ClN_2O_4S$: C, 48.80; H, 7.96; N, 6.32. Found (corrected for 9.47% H₂O): C, 49.15; H, 7.80; N, 6.39.

cis-1-Methyl-4-n-propyl-L-proline Amide (11) and trans-1-Methyl-4-n-propyl-L-proline Amide (10). A mixture of 3.09 g of 9, 9.5 ml of tri-*n*-butylamine, 100 ml of acetonitrile, and 40 ml of acetone was stirred until solution was complete. To this solution, cooled to 10°, there was added 2.05 ml of isobutyl chloroformate. The reaction mixture was stirred for 30 min in an ice bath after which time 15 ml of ammonium hydroxide was added. Stirring was continued for 2 hr. The solvent was distilled under vacuum. The residue was acidified and extracted with ether. After neutralizing the aqueous solution, it was extracted with methylene chloride. Chromatography of this product over silica gel¹⁷ using 80% aqueous acetone as the eluent gave two fractions, one showing an enrichment of 10, the other almost pure 11. The 10 component-rich fraction (359 mg) was rechromatographed to yield a small fraction of fairly pure 10, the other fractions being mixtures of 10 and 11. The latter fractions were again rechromatographed and the resulting fractions recombined on the basis of tlc. The fractions containing the purest 10 were combined and recrystallized from Skellysolve B to give 10 mg of 10, estimated to be about 85% pure on the basis of tlc. This material showed $[\alpha]_D -93^\circ$ (water). Its nmr was almost identical with 10 isolated from natural 4-propylhygric acid.

In another experiment the original crystalline product was recrystallized for analysis from ethyl acetate–Skellysolve B. Tlc showed it to be almost pure 11, mp 113.5–115.5°, $[\alpha]_D -104^\circ$ (water).

Anal. Calcd for $C_9H_{15}O_2N$: C, 63.49; H, 10.66; N, 16.46. Found: C, 63.41; H, 10.76; N, 16.28.

trans-1-Methyl-4-n-propyl-L-proline Amide (10) and cis-1-Methyl-4-n-propyl-D-proline Amide (12) from Hydrazinolysis Cleavage Product. Partially racemic 1-methyl-4-n-propylproline was converted to the mixture of isomeric amides in the same manner as described for the preparation of racemic 1-methyl-3-n-propylproline amide. Recrystallization of the crude product from Skellysolve B gave a 65% yield of material, mp 86–86.5°, $[\alpha]_D +10^\circ$ (water).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.49; H, 10.66; N, 16.46. Found: C, 63.35; H, 10.92; N, 16.28.

A thin layer chromatograph of the above material on silica gel, using an acetone–water (8:2) irrigating system, disclosed the presence of two compounds of very similar mobility. Separation was effected *via* chromatography over silica gel using acetone–water (8:2) for elution. The faster moving component was identified as the *L-trans* amide and melted at 117–118° after recrystallization from Skellysolve B; $[\alpha]_D -93^\circ$ (water).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.49; H, 10.66; N, 16.46. Found: C, 63.57; H, 10.73; N, 16.71.

The more polar component, the *D-cis* amide, $[\alpha]_D +103^\circ$ (water), melted at 114–115° after recrystallization from Skellysolve B.

1-Acetoxy-2,2-carbethoxy-4-propyl-5-hydroxypyrrolidine (17). A mixture of 5.6 g of 2-propylacrolein (15),¹⁸ 10 g of diethyl acetamidomalonate, and 0.25 ml of 26% sodium methoxide–methanol solution in 150 ml of benzene was stirred for 3 hr at ambient temperature. The solution was neutralized with a few drops of acetic acid, clarified by filtration, and evaporated. This material did not crystallize and was used in the following step.

Racemic 4-n-Propylproline Hydrochloride (19). The pyrrolidine 17 from above was suspended in 127 ml of water and 127 ml of concentrated hydrochloric acid, and 22.8 g of granulated tin added.

(12) For a preliminary report, see B. J. Magerlein, Abstracts of Papers, 5th Interscience Conference on Antimicrobial Agents and Chemotherapy, and 11th International Congress of Chemotherapy, Washington, D. C., Oct 17–21, 1965, p 17.

(13) Melting points were taken in Pyrex capillaries and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics. Nuclear magnetic resonance spectra were run on a Varian, high-resolution, 60-Mc instrument; measurements are expressed in parts per million downfield from tetramethylsilane used as an internal standard.

(14) A. A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, **79**, 185 (1957).

(15) Synthetic magnesia–silica gel manufactured by the Floridin Co., Pittsburgh, Pa.

(16) A saturated hydrocarbon fraction, bp 60–71°, available from Skelly Oil Co., Kansas City, Mo.

(17) Silica gel 0.05–0.20 mm for chromatography, E. Merck A. G. Distributors, Brinkmann Instruments, Inc., Westbury, N. Y.

(18) M. B. Green and W. J. Hickinbottom, *J. Chem. Soc.*, 3262 (1957).

ing for 1 hr, the metal was removed by filtration and the evaporated under vacuum. The solution was saturated with hydrogen sulfide, and the precipitated solids were separated. The solution was treated repeatedly in this manner. The reaction mixture was lyophilized. The residue was dissolved in a small amount of water, extracted with ether, and again lyophilized. It was dried at 55° under vacuum. The residue, 14.7 g, was dried from acetonitrile affording 1.62 g of 19, mp 162–165°. Recrystallizations from methanol–ether of material prepared in a similar manner afforded an analytical sample, mp 165–

Calcd for $C_8H_{15}NO_2 \cdot HCl$: C, 49.61; H, 8.33; N, 7.23; Found: C, 49.24; H, 8.13; N, 7.53.

1-Methyl-4-propylproline Hydrochloride (21). In the manner described for the preparation of 20, 1.1 g of 19 was methylated with 620 mg of 21, mp 164–166°. Recrystallization from ether gave an analytical sample, mp 165–167°.

Calcd for $C_9H_{17}NO_2 \cdot HCl$: C, 52.04; H, 8.73; N, 7.13; Found: C, 51.74; H, 8.48; N, 7.13.

1-Methyl-4-n-propylprolylamide. In the manner described for the preparation of 10 and 12, 1.0 g of 21 was converted to the corresponding amide, mp 86–89°, in 90% yield. An analytical sample prepared from Skellysolve B melted at 84–85°.

Calcd for $C_9H_{17}NO_2$: C, 63.49; H, 10.66; N, 16.46; Found: C, 63.53; H, 10.64; N, 16.48.

Lincomycin. In the manner described for the preparation of racemic 21 was condensed with methyl thiolincosaminide to give a crude product which possessed 11% of the antibacterial activity of lincomycin and showed about the same amount of lincomycin thin layer chromatography.

2-Oxy-2,2-carbethoxy-3-propyl-5-hydroxypyrrolidine (16). In the manner described above, 2-hexenal¹⁹ (14) and diethyl acetoacetate were condensed to afford 16, mp 101–102°, in a 10% yield after recrystallization from acetone–ether.

Calcd for $C_{13}H_{21}NO_5$: C, 57.13; H, 7.99; N, 4.44; Found: C, 57.07; H, 8.02; N, 4.72.

3-n-Propylproline Hydrochloride (18·HCl). Acidic solution of 16, as described in the preparation of 17, afforded 18, mp 165–168°, after recrystallization from ether.

Calcd for $C_8H_{15}ClNO_2$: C, 49.61; H, 8.33; N, 7.23; Found: C, 49.84; H, 8.30; N, 7.49; Cl, 18.09.

3-n-Propylproline (18). A mixture of 880 mg of 3-n-propylproline hydrochloride (18·HCl), 2.0 g of silver carbonate, and 10 ml of water was stirred at 25° for 0.5 hr and then warmed on a water bath for 30 min and filtered. The filtrate was evaporated under vacuum and the residue recrystallized from ethanol–ethyl acetate to give 18, mp 229–230°. The yield of once recrystallized 18 was 600 mg (85% yield).

Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91; Found: C, 61.45; H, 9.60; N, 8.95.

1-Methyl-3-n-propylproline (20). A mixture of 14 g of 3-n-propylproline (18), 11.8 ml of formaldehyde, 200 ml of water, and 2.0 g of 10% Pd–C catalyst was hydrogenated on a hydrogenator at 35 psi hydrogen pressure. A yield of 11.6 g of product was obtained, melting at 202–203°, after recrystallization from ethanol–ethyl acetate.

Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18; Found: C, 63.12; H, 10.02; N, 8.42.

1-Methyl-3-n-propylprolylamide. To a stirred mixture of racemic 1-methyl-3-n-propylproline (20), 1.68 ml of triethylamine, and 69 ml of dry acetonitrile at 0° was added 0.58 g of isobutyl chloroformate. The reaction mixture was maintained for 0.5 hr and 6 ml of concentrated NH_4OH then added. After stirring 18 hr at 25°, the reaction mixture was evaporated under vacuum and the residue dissolved in 50 ml of water, with HCl, and extracted with four 50-ml portions of ether. The methylene chloride extracts were dried over anhydrous calcium chloride. The aqueous phase was neutralized and extracted with four 50-ml portions of methylene chloride. The methylene chloride extracts were combined and evaporated and the residue was recrystallized from Skellysolve B to a melting point of 99–100°. A 60% yield of product was obtained.

Calcd for $C_9H_{17}N_2O$: C, 63.49; H, 10.66; N, 16.46; Found: C, 63.60; H, 10.85; N, 16.22.

Material showed only one spot when chromatographed on

silica gel using a methyl ethyl ketone–acetone–water system (75:25:10).

Attempted Coupling of Racemic 1-Methyl-3-n-propylproline (20) with Methyl Thiolincosaminide. To a mixture of 60 ml of distilled acetonitrile, 1.68 ml of triethylamine, and 1.03 g of amino acid 20 cooled at 0° was added 0.87 ml of isobutyl chloroformate. After stirring at 0° for 0.5 hr, 1.52 g of methyl thiolincosaminide dissolved in 20 ml of water was added. Stirring was continued for a period of 60 hr at 25°. The reaction mixture was evaporated to dryness and the residue chromatographed over silica gel, eluting with acetone. The fast-moving material was isolated (140 mg) and recrystallized from acetone–Skellysolve B to a melting point of 186–187°. The infrared and nmr data support the carbamate structure 22.

Anal. Calcd for $C_{14}H_{27}NO_5$: C, 47.57; H, 7.70; N, 3.96; Found: C, 47.73; H, 7.84; N, 4.03; S, 9.25.

Ethyl 2,5-Dibromooctanoate (35). At 0° 13 g of 5-caprylo-lactone (34) was added to 10.5 ml of phosphorus tribromide followed by 7.1 ml of bromine. After stirring at ambient temperature for 18 hr, 1 ml of phosphorus tribromide and 6 ml of bromine were added. The reaction mixture was heated at reflux for 24 hr. To the cooled solution was added 30 ml of absolute ethanol and the mixture heated at reflux for 1.5 hr. The solvents were removed under vacuum and the residue was dissolved in benzene. This solution was washed free of bromide ion, dried, and concentrated. The yield of 35, bp 125–135° (0.8 mm), was 15–20 g (43–57% yield).

Anal. Calcd for $C_{10}H_{18}Br_2O_4$: C, 36.38; H, 5.49; Br, 48.43; Found: C, 35.43; H, 5.37; Br, 48.75; O, 9.81.

Racemic 1-Methyl-5-n-propylproline N-Methylamides (36). A 14.85-g quantity of ethyl 2,5-dibromooctanoate (35) was condensed with 17.4 g of methylamine in 85 ml of methanol by heating at 140° for 4 hr in an autoclave. The reaction mixture was filtered and evaporated *in vacuo* to dryness. The residue was dissolved in chloroform and filtered to remove methylamine hydrobromide. The filtrate was evaporated to dryness, and the residue was distributed countercurrently for 200 transfers using the solvent system ethyl acetate–ethanol–cyclohexane–water (1:1:1:1). Two main peaks were noted on analysis by determination of solids. The first, in tubes 80–107, was pooled and evaporated to dryness. The partially crystalline residue was recrystallized from Skellysolve B to give 1.8 g of product.

Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.21; Found: C, 65.86; H, 11.27; N, 14.54.

The second peak in tubes 118–150 was pooled and evaporated to dryness. The residue crystallized in the refrigerator, but melted at room temperature. No suitable solvent for recrystallization was found, so this material was used directly in the next step.

cis- and trans-1-Methyl-5-n-propylproline Hydrochloride (23 and 24). A 250-mg sample of the crystalline methylamide of 1-methyl-5-n-propylproline (36) was heated at reflux with 10 ml of 6 N HCl for 4 hr. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in water and Dowex 2 (OH^-) was added to about pH 10. The resin was collected and eluted with dilute hydrochloric acid. The eluate was evaporated to dryness, and the residue was dissolved in a small amount of anhydrous ethanol. Ether was added until the solution was cloudy, and the mixture was cooled. A small amount of yellow oil separated. The supernatant was decanted and diluted with several volumes of ether. Crystals formed slowly on cooling. From two such runs, 143 mg of crystalline material was obtained. Recrystallization from acetonitrile–ether gave 95 mg of hydrochloride.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 52.04; H, 8.73; N, 6.74; Found: C, 51.12; H, 8.45; N, 7.03; O, 14.85; Cl, 16.55.

About 800 mg of the lower melting isomer was hydrolyzed by heating under reflux with 40 ml of 6 N HCl for 4 hr. The product was isolated as described above to give 107 mg of recrystallized amino acid hydrochloride.

Anal. Found: C, 51.82; H, 9.33; N, 7.08; O, 18.5; Cl, 16.90.

D-(+)-n-Propylsuccinic Acid (27) from Oxidation of Partially Racemized 1-Methyl-4-n-propylproline. A solution of 7.44 g of partially racemized 1-methyl-4-n-propylproline hydrochloride in 100 ml of water containing 36 ml of 1 N sodium hydroxide was added slowly with vigorous stirring to 28 g of potassium permanganate in 550 ml of water. The temperature of the mixture was maintained at $25 \pm 2^\circ$ by occasional cooling. When most of the acid was added the permanganate color was no longer present. Therefore, 2 g of the additional permanganate was added. The reaction mixture was filtered after the addition of filter aid. The purple color of the filtrate was discharged with excess sodium bisulfite and

the solution refiltered. The clear filtrate was acidified and lyophilized. The residue from lyophilization was shaken with absolute alcohol-ether (3:1) and filtered. The filtrate was evaporated to yield 4.4 g of oil. This oil was chromatographed over 125 g of silica gel using a mixture of solvents for elution made up of benzene-methanol-acetic acid (10:2:1). The fractions thus obtained were checked by thin layer chromatography (same system) using *dl*-propylsuccinic acid²⁰ as the control. Those fractions showing only material moving with the control were combined (1.83 g) and crystallized from benzene-Skellysolve B several times. The crystalline product, 280 mg, melted at 101.5–103.5° and rotated at +23° (water).

Anal. Calcd for $C_7H_{11}O_4$: C, 52.49; H, 7.55. Found: C, 52.48; H, 7.67.

cis- and *trans*-1-Carbobenzoxy-4-*n*-propyl-L-proline (30). The amine salt (6, 10 g) was shaken with ether and 2% potassium hydroxide. The aqueous layer was separated and acidified. Extraction with methylene chloride led to the isolation of 6 g of oily acid. A mixture of 2 g of this oil and 800 mg of platinum on Dowex-1 catalyst¹⁰ in 50 ml of methanol was shaken under 40 psi hydrogen pressure for 17 hr. The catalyst was removed by filtration and the solvent distilled *in vacuo*, leaving a residue of 2 g of oily 30. Thin layer chromatography, using a methanol-5% ammonium hydroxide system and permanganate-periodate indicator spray, indicated that the double bond was hydrogenated. Ninhydrin gave a negative test. This product resisted crystallization and was used without purification in the next step.

cis- and *trans*-Methyl N-(1'-Carbobenzoxy-4'-*n*-propyl-L-prolyl)-thiolincosaminide (31). To a solution of 7.5 g of 30 and 4.25 ml of triethylamine in 700 ml of distilled acetonitrile cooled to 0° there was added 4.16 ml of isobutyl chloroformate in 5 ml of acetonitrile. The mixture was stirred at 0° ($\pm 5^\circ$) for 15 min. A solution of 7 g of methyl thiolincosaminide (2) in 100 ml of water was added rapidly. The resulting solution was stirred at 0° for 1 hr, the cooling bath removed, and stirring continued for another hour. The acetonitrile was removed by distillation under vacuum leaving a partially crystalline residue. The mixture was cooled to 10° and filtered. After drying at 55° under vacuum the crystalline product weighed 10.5 g and melted at 191–194°. *In vitro* assay *vs. S. lutea* showed <1% the antibacterial activity of lincomycin. This

material was recrystallized twice from ethyl acetate containing a few drops of water to afford the analytical sample, mp 197–203°, $[\alpha]_D^{25} +111^\circ$ (MeOH).

Anal. Calcd for $C_{25}H_{38}N_2O_8S$: C, 57.01; H, 7.27; N, 5.32; S, 6.09. Found: C, 56.93; H, 7.45; N, 5.35; S, 6.03.

cis- and *trans*-Methyl N-(4-Propyl-L-prolyl)thiolincosaminide Hydrochloride (32·HCl). A solution of 8.95 g of 31 in 200 ml of methanol was shaken over 2 g of 10% Pd-C under 40 psi hydrogen pressure for 6 hr. The catalyst was removed by filtration and the solution concentrated under vacuum. The residue was dissolved in 75 ml of 0.5 *N* hydrochloric acid and 250 ml of water with warming to about 35°. Dilution with 1500 ml of acetone precipitated 32·HCl which was collected by filtration. The crystals, dried at 55° under vacuum, weighed 6.0 g (82.3% yield) and melted at 202–205°. The rotation was +151° (H_2O).

Anal. Calcd for $C_{17}H_{27}N_2O_8S \cdot HCl$: C, 47.57; H, 7.75; N, 6.57; S, 7.47. Found (corrected for 3.31% water): C, 47.67; H, 7.72; N, 6.53; S, 7.14.

In one experiment the free base crystallized from acetone. It melted at 178–180°.

Anal. Calcd for $C_{17}H_{27}N_2O_8S$: C, 52.02; H, 8.22; N, 7.14. Found: C, 51.97; H, 8.01; N, 7.00.

Lincomycin Hydrochloride (1) and *cis*-Lincomycin Hydrochloride (33). Two grams of 32·HCl, 2.4 ml of formalin, and 800 mg of 10% palladium on carbon in 200 ml of methanol was shaken under 40 psi hydrogen pressure for 5 hr. The catalyst was removed by filtration. Triethylamine (1 ml) was added and the solution evaporated. The residue was chromatographed twice over silica gel using for elution a solvent mixture of ethyl acetate-acetone-water (8:5:1). The various fractions were monitored by thin layer chromatography on silica gel using the same solvent system and fractions showing only 1 and 33 combined. The crude 1 (free base) fraction weighed 320 mg. It was dissolved in dilute hydrochloric acid and 1·HCl precipitated by the addition of acetone. The yield of 1·HCl was 290 mg. After two recrystallizations from the same solvent it melted at 155–157° dec. This material had identical spectra with lincomycin hydrochloride by infrared and nmr. It possessed full antibacterial activity when compared with lincomycin hydrochloride.

The slower moving fraction, 570 mg, from above was similarly converted to its hydrochloride. After recrystallization from acetone-water it melted at 138–145° dec and was identical in the infrared and nmr with *cis*-lincomycin hydrochloride (33) prepared as described above.

(20) P. A. S. Smith and J. P. Horwitz, *J. Am. Chem. Soc.*, **71**, 3418 (1949).

The Morphine-Thebaine Group of Alkaloids. IX.¹ The Reaction of Thebaine with Magnesium Iodide

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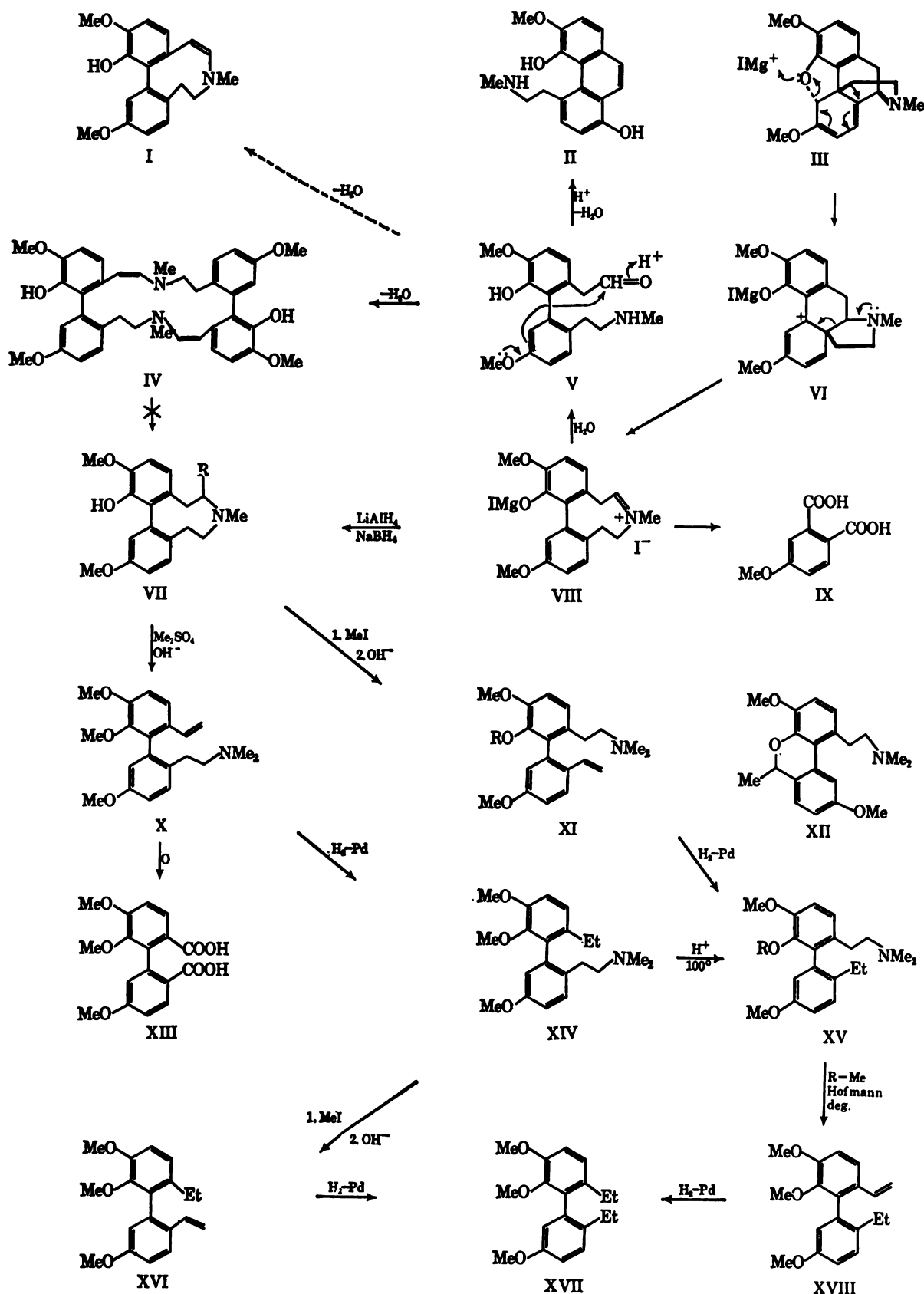
Abstract: The reaction of thebaine with anhydrous magnesium iodide has been shown to give the iminium salt VIII, the structure of which has been deduced from its oxidation to 4-methoxyphthalic acid, its hydrolysis and cyclodehydration to thebenine (II), and its reduction to neodihydrothebaine (VII, R = H). The structure of neodihydrothebaine has been confirmed by degradation and spectral studies. Hydrolysis and recyclization of the iminium salt VIII has been found to give an enamine, kryptothebaine, which is clearly not the enamine I and is assigned structure IV.

The reaction of thebaine (III) with anhydrous magnesium iodide in ether and benzene has previously been shown² to give a product containing magnesium

(1) Part VII: K. W. Bentley, J. C. Ball, and J. P. Ringe, *J. Chem. Soc.*, 1963 (1956); the paper by K. W. Bentley and S. F. Dyke, *ibid.*, 2574 (1959), is now regarded as part VIII of this series.

(2) K. W. Bentley and R. Robinson, *ibid.*, 947 (1952).

and iodine, to which the iminium salt structure VIII was assigned on the basis of its conversion into phenyldihydrothebaine (VII, R = Ph) on treatment with phenylmagnesium bromide. This assignment of structure is now supported by the reduction of the salt to neodihydrothebaine (VII, R = H), by its oxidation to 4-



methoxyphthalic acid (IX),³ and by its conversion into thebenine (II).

(3) In an earlier report of this reaction,³ it was stated that 4-methoxyphthalic acid could not be isolated from the products of the oxidation under the conditions used for the oxidation of phenyldihydrothebaine. This acid has now been isolated after oxidation of the iminium salt with very much larger quantities of permanganate than previously used, and it seems probable that in the earlier work oxidation was incomplete probably not progressing even to the production of a homophthalic acid.

Reduction of the iminium salt VIII with lithium aluminum hydride in ether or with sodium borohydride in ethanol takes place very rapidly and affords a very good yield of (+)-neodihydrothebaine (VII, R = H);⁴ the

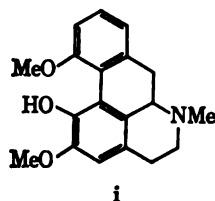
(4) This reaction was previously reported³ to give a noncrystalline uncharacterizable product. It is now known that the lithium aluminum hydride used in the earlier work was seriously contaminated with aluminum chloride, which is known to affect the course of reductions with

mild conditions involved in the formation and reduction of the salt were insufficient to cause racemization of the diphenyl system, which is generated in one configuration only. The structure assigned to neodihydrothebaine (VII, R = H) has been confirmed by degradation of the base and its methyl ether. Hofmann degradation of neodihydrothebaine methiodide occurs readily in aqueous potassium hydroxide to give the isomethine XI (R = H) only, the structure of the product being demonstrated by its easy cyclization to the nonphenolic base XII on heating with concentrated hydrochloric acid. The phenolic nucleus apparently inhibits Hofmann degradation on one side of the nitrogen since only the isomethine XI (R = H) is produced during this reaction, and the methiodide of the isomethine is resistant to further degradation in refluxing 40% aqueous potassium hydroxide. By contrast, however, the isomethine methyl ether (XI, R = Me) methiodide can be degraded in aqueous solution to a neutral product, which is presumably the olefin XVIII (Et = CH=CH₂), but which could not be adequately characterized owing to the speed with which it polymerized. Catalytic reduction of the isomethine XI (R = H) proceeded very rapidly and gave the dihydro base XV (R = H). The methiodide of this base, like that of the parent phenol XI (R = H) resists further Hofmann degradation in aqueous solution, though the methiodide of the methyl ether XV (R = Me) can be easily degraded to the olefin XVIII.

Hofmann degradation of neodihydrothebaine methyl ether methiodide, unlike the degradation of the parent phenol, affords a mixture of two products, readily separated as the methiodides. The minor component is identical with the isomethine methyl ether (XI, R = Me) and hence the major product, which is isomeric with this base, may be assigned the structure X of the methine base. Evidently in the absence of the stabilizing effect of the phenolic hydroxyl degradation can occur with ring fission on either side of the nitrogen atom.⁵ Oxidation of the mixture of methine and isomethine bases obtained in this way with alkaline potassium permanganate afforded an uncrystallizable yellow acid, which is presumably a mixture of α -keto acids since on further oxidation with alkaline hydrogen peroxide it gave a good yield of 5,6,5'-trimethoxydiphenic acid (XIII), identical with material prepared from phenyldihydrothebaine (VII, R = Ph) and from acetylthebaol. The structure of this acid was further confirmed by its cyclization to 1,5,6-trimethoxyfluorenone-4-carboxylic acid.

this reagent. It may be noted that the characteristics of the reduction product described in the earlier communication bear a striking resemblance to those of the product of reduction of kryptothebaine (IV) reported in this paper.

(5) A similar difference in behavior on Hofmann degradation has been observed between methylidihydrothebaine (VII, R = Me) and its O-acetyl derivative [L. F. Small and E. M. Fry, *J. Org. Chem.*, **3**, 509 (1939)], and between isothebaine (i) methiodide and methyl ether methiodide [V. V. Kiselev and R. A. Kononova, *J. Gen. Chem. USSR*, **19**, 148 (1949)].



Further Hofmann degradation of the methine base X methiodide proceeds readily with the formation of the same readily polymerized olefin XVIII (Et = CH=CH₂) as is obtained by the degradation of the isomethine methyl ether (XI, R = Me) methiodide. Hydrogenation of the methine base X proceeds rapidly and gives the dihydromethine XIV, the methiodide of which can be degraded to a nitrogen-free product XVI isomeric with that XVIII obtained by the degradation of the dihydroisomethine methyl ether (XV, R = Me) methiodide. These two nitrogen-free products afford the same 2,2'-diethyl-5,6,5'-trimethoxydiphenyl (XVII) on catalytic reduction.

The spectra of the various compounds in this series are in accord with the assigned structures. The ultraviolet spectra of the bases X and XI, R = H, and the nitrogen-free products XVI and XVIII are styrenoid, and the infrared spectra of all four compounds show bands at 10.77–10.83 μ attributed to the vinyl group, whereas the spectra of the bases VII (R = H), XV (R = H), XV (R = Me), XIV, XII, and the nitrogen-free product XVII, from which the vinyl compounds are derived or into which they have been converted, show no absorption bands in this region.

The nmr spectrum of neodihydrothebaine (VII, R = H) shows a complex signal at δ 7.4–6.6 (5 aromatic H) and signals at δ 5.25 (OH), 3.86 (OCH₃), 3.75 (OCH₃), approximately 2.5, complex (8 H as CH₂), and 2.25 (NCH₃). The spectrum of the isomethine XI (R = H) shows a complex signal at δ 7.8–6.6 (5 aromatic H) and signals at δ 5.69 and 5.25 (double doublet, C-16 H, $J_{15,16} \text{ trans} = 18$ cps; $J_{16,18} = \text{ca. } 3$ cps), δ 5.09 and 4.82 (double doublet, C-16 H, $J_{15,16} \text{ cis} = 10$ cps; $J_{16,18} = \text{ca. } 3$ cps), δ 5.90 (OH), 3.85 (OCH₃), 3.76 (OCH₃), $\text{ca. } 2.35$ (4 H as CH₂), and 2.0 (6 H as NMe₂). In dimethyl sulfoxide the hydroxyl proton of the isomethine gave a signal at δ 7.95, and the signal due to the C-15 proton, which was obscured in the spectrum of the base in deuteriochloroform by the aromatic and hydroxyl proton signals, appeared as a double doublet with centers at δ 6.17 and 5.77 ($J_{15,16} \text{ trans} = 18$ cps; $J_{15,16} \text{ cis} = 10$ cps). The spectrum of 2,2'-diethyl-5,6,5'-trimethoxydiphenyl (XVII) showed signals at δ 7.6–6.6 (5 aromatic H), 3.9, 3.8, and 3.59 (3OCH₃), 2.3 (quartet, 4 H), and 1.02 (triplet 6H), the latter two signals being attributable to two ethyl groups in virtually identical environments.

The iminium salt VIII is very rapidly decomposed by dilute acids and even by water, and the product may be assumed to be the amino aldehyde V, since on warming with mineral acid the iminium salt is converted into thebenine (II), which is the product of cyclodehydration of the aldehyde V.⁶ From the mechanism of this cyclodehydration thebenine, not its O-methyl ether, would be expected to be the product of this reaction.

Attempts to isolate the amino aldehyde V were all unsuccessful and led to the recovery of a new base isomeric with thebaine in empirical formula and showing an infrared absorption band at 1645 cm⁻¹ indicating that the base is an enamine. This base, like the iminium salt VIII is very rapidly converted by hot 2 N

(6) In the earlier communication² thebenine was not clearly identified as the product of this reaction. The iminium salt used in that work was not freshly isolated, and the use of partially autoxidized material has a profound effect on the fluorescence of the resulting thebenine in alkaline solution, though not in acids.

hydrochloric acid into thebenine (II), presumably by way of its hydrolysis product, the amino aldehyde V. The simplest structure for this enamine would be that shown in formula I, which could be formed from the amino aldehyde V or directly by deprotonation of the iminium salt VIII, and the nmr spectrum of the base is compatible with such a structure. The spectrum shows signals at δ 6.9–6.6 (5 aromatic H), 6.2 (doublet, C-10 H, $J_{10,9 \text{ cis}} = \text{ca. } 13 \text{ cps}$), 4.55 (doublet, C-9 H, $J_{9,10 \text{ cis}} = \text{ca. } 13 \text{ cps}$), 4.65 (OH), 3.9 (OCH_3), 3.81 (OCH_3), *ca.* 2.6 (4 H as CH_2), and 2.35 (NCH_3). This structure for the product is untenable, however, since on reduction catalytically or with sodium borohydride the enamine is reduced to an uncharacterizable base, which is clearly different in solubility, R_f value, and sign of optical rotation from neodihydrothebaine (VII, $R = \text{H}$), although the two bases have virtually identical infrared absorption spectra. The only rational explanation of these results is that the enamine has the dimeric structure IV, the 18-membered ring of which might be expected to be formed from the amino aldehyde V more readily than the nine-membered ring of the simpler base I, since rings of the latter size are notoriously difficult to close. The nmr spectrum of the enamine is equally compatible with the structures IV and I in which the environments of the protons are virtually identical. Similarly, the environments of all of the atoms in neodihydrothebaine (VII, $R = \text{H}$) and the base that would result from the reduction of the enamine IV are virtually identical, and it is reasonable to assume that the infrared absorption spectra of the two bases would be almost indistinguishable. The sign of optical rotation of the reduced enamine is the same as that of the isomethine XI ($R = \text{H}$), in which the relatively rigid nine-membered ring of neodihydrothebaine (VII, $R = \text{H}$) has been cleaved. Hydrolysis of the enamine IV would, of course, afford the amino aldehyde V, convertible by acids to thebenine (II). Formation of the enamine IV from the amino aldehyde V would be expected to be accompanied by the formation of a small amount of the enamine I and a considerable quantity of a linear polymeric enamine, and indeed a very good yield of crude enamine can be obtained but only about 25–30% of this is recoverable as a crystalline solid from 2-ethoxyethanol, and material recovered from the mother liquors defies all attempts at crystallization. Catalytic reduction of the crude enamine, however, affords about 5–8% of neodihydrothebaine, readily separable from other products by virtue of its solubility in ether. A good yield of thebenine is, however, obtained from the crude enamine on boiling with 2 *N* hydrochloric acid, as would be expected, since all three possible enamines would give the amino aldehyde V on hydrolysis. These results suggest that the crude enamine consists of about 5% of the simple base I, 30% of the dimeric base IV, and 65% of a mixture of polymeric enamines.

Experimental Section

Reaction of Thebaine with Anhydrous Magnesium Iodide. A solution of anhydrous magnesium iodide (28 g, 0.1 mole) prepared from iodine (25.6 g) and excess (8 g) of magnesium in dry ether (200 ml) and dry benzene (300 ml) was added over 45 min to a vigorously stirred boiling solution of thebaine (31.1 g, 0.1 mole) in dry benzene (250 ml) under nitrogen. A light green-brown precipitate rapidly formed. The mixture was stirred under reflux for another 45 min. For most purposes this mixture was used

directly without isolation of the product. Isolation of the product by filtration of the mixture afforded a solid which, on washing well with ether and rapid drying in air, was obtained as an off-white powder that rapidly became green and degenerated to a sticky dark product in moist air.

Oxidation of the Thebaine-Magnesium Iodide Reaction Product VIII. The product of the above reaction, isolated as above (30 g) was vigorously stirred on the boiling water bath with water (350 ml), potassium hydroxide (50 g), and potassium permanganate (300 g) over a period of 4 hr, the oxidizing agent being added in portions of 50 g. The mixture was filtered, and the residue was washed with three 100-ml portions of boiling water. The filtrate was heavily contaminated with colloidal manganese dioxide which was coagulated by passing sulfur dioxide through the solution, which was filtered, concentrated to 300 ml, and acidified by the cautious addition of concentrated hydrochloric acid. Continuous ether extraction of the resulting mixture over 2 days afforded, on evaporation of the dried extract, a solid product that gave a derivative of fluorescein on fusion with resorcinol and concentrated sulfuric acid. A portion of this material was dissolved in aqueous methylamine, and the solution was evaporated. The residue was heated strongly and the volatile matter evolved was condensed and recrystallized from ethanol, when 4-methoxy-N-methylphthalimide was obtained as very pale yellow needles, mp 156° alone or mixed with an authentic specimen. A further portion of the oxidation product was heated alone and the volatile matter was condensed and recrystallized from a 1:1 mixture of benzene and light petroleum (bp $60\text{--}80^\circ$); 4-methoxyphthalic anhydride was obtained as pale yellow needles, mp 94° alone or mixed with an authentic specimen.

Action of Hydrochloric Acid on the Thebaine-Magnesium Iodide Reaction Product VIII. The freshly isolated reaction product (4 g) was boiled with 2 *N* hydrochloric acid (20 ml) for 5 min. The mixture was cooled and basified with ammonia, and the amorphous product was collected and washed well with water. Comparative chromatographic studies on thin layer plates indicated that this product was thebenine (II). It was dissolved in hot 2 *N* hydrochloric acid (15 ml), and the solution was cooled in ice when a viscous hydrochloride separated. This crystallized on trituration with ice-water and was obtained as pale yellow needles, mp $234\text{--}236^\circ$, identical in melting point, mixture melting point, infrared absorption, and R_f value with thebenine hydrochloride.

Neodihydrothebaine (VII, $R = \text{H}$). a. A solution of lithium aluminum hydride (4.5 g) in anhydrous ether (200 ml) was added to a vigorously stirred suspension of the product of reaction of thebaine (31.1 g) with anhydrous magnesium iodide (28 g) in ether-benzene. A vigorous reaction ensued and the light green-brown suspended material became white. The mixture was stirred for 1 hr; the excess of hydride was cautiously decomposed by the addition of water, and the product was dissolved by the addition of 2 *N* hydrochloric acid. The organic layer was discarded, and the aqueous layer, after extraction once with ether to remove all of the benzene, was diluted with saturated sodium potassium tartrate and ammonium chloride, covered with a layer of ether, and basified with ammonia. The precipitated base dissolved rapidly in the ether, which was separated, dried, and passed through a column of Florisil (60–100 mesh) (30 g) to remove a small amount of purple material. Evaporation of the ether then afforded neodihydrothebaine (VII, $R = \text{H}$) as a very pale brown oil that slowly crystallized on standing. The base was recrystallized with difficulty from 90% methanol below 0° , when it was obtained as almost colorless prisms, mp $98\text{--}100^\circ$, $[\alpha]_D^{20} +63.7^\circ$ (*c* 2.0, CHCl_3).

Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: C, 73.3; H, 7.4. Found: C, 73.6; H, 7.5.

The base was readily soluble in aqueous alkalis, and the solution coupled instantaneously with diazotized sulfanilic acid to give a blood red dye.

The **methiodide** formed rapidly in ethanol and was obtained as pale cream prisms, mp $249\text{--}250^\circ$ from ethanol.

Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2 \cdot \text{CH}_3\text{I}$: C, 53.1; H, 5.6. Found: C, 52.8; H, 5.8.

The **methyl ether methiodide** was prepared by the addition of methyl sulfate to a solution of the phenol in aqueous potassium hydroxide, when the initial precipitate of the methyl ether rapidly dissolved, followed by the addition of potassium iodide. The precipitated salt crystallized rapidly and was collected and recrystallized from water as white plates, mp $260\text{--}261^\circ$.

Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_2 \cdot \text{CH}_3\text{I} \cdot 0.5\text{H}_2\text{O}$: C, 52.7; H, 6.1. Found: C, 52.8; H, 6.0.

b. The same base was obtained by reduction of the suspension of the iminium salt VIII in ether-benzene by the addition of

sodium borohydride (8.0 g) in hot ethanol (200 ml). The finely divided suspension rapidly coagulated to a sticky green mass that dissolved quickly as the reduction proceeded. The mixture was finally diluted with aqueous ammonium chloride, and the ether-benzene layer was removed, washed twice with water, dried, passed through Florisil as in part a above, and evaporated *in vacuo*. The residual base was identified with that produced in part by a thin layer chromatography and by conversion into the methiodide and methyl ether methiodide.

Identical results were obtained when the iminium salt VIII was isolated, washed with dry ether, and added to a vigorously stirred solution of sodium borohydride in ethanol, with isolation of the product by the addition of aqueous ammonium chloride and ether extraction.

Neodihydrothebaine Isomethine (XI, R = H). Potassium hydroxide was added to a boiling solution of neodihydrothebaine methiodide (4 g) in water (50 ml) until the solution became turbid due to the separation of a potassium salt. The solution was clarified by the addition of a small volume of water and then boiled for 30 min, during which time a viscous oil separated. The mixture was cooled in ice-salt and the liquid decanted from the hard brown glass, which was then dissolved in 2 *N* hydrochloric acid (50 ml) and methanol (30 ml). The base was precipitated as a crystalline solid by the slow addition of aqueous ammonia to the vigorously stirred acid solution, and was collected, washed with water, and recrystallized from aqueous methanol, and obtained as off-white prisms, mp 128–129°, $[\alpha]_D^{20} -24.5^\circ$ (c 2.0, CHCl₃).

Anal. Calcd for C₂₀H₂₃NO₂: C, 73.5; H, 7.7. Found: C, 73.7; H, 7.1.

The methiodide was obtained from ethanol as off-white prisms, mp 268–269°.

Anal. Calcd for C₂₀H₂₃NO₂·CH₃I: C, 53.8; H, 6.0. Found: C, 53.8; H, 5.9.

The methyl ether methiodide was obtained by the addition of aqueous potassium iodide to the aqueous solution finally resulting from the methylation of the base in aqueous potassium hydroxide with methyl sulfate. It was readily recrystallized from water and obtained as white needles, mp 205°.

Anal. Calcd for C₂₁H₂₇NO₂·CH₃I: C, 54.6; H, 6.2. Found: C, 54.4; H, 6.0.

The methyl ether methoperchlorate was prepared by the addition of perchloric acid to a solution of the methyl ether methiodide in aqueous ethanol. On recrystallization from aqueous ethanol it was obtained as white elongated plates, mp 161–162°.

Anal. Calcd for C₂₁H₂₇NO₂·CH₃ClO₄: C, 58.1; H, 6.65. Found: C, 57.9; H, 6.6.

Cyclization of Neodihydrothebaine Isomethine (XI, R = H). Neodihydrothebaine isomethine (0.5 g) was boiled with concentrated hydrochloric acid (5 ml) for 3 min. The solution was diluted with water and poured into an excess of aqueous potassium hydroxide. The precipitated nonphenolic base XII was isolated by ether extraction, but could not be induced to crystallize, and was characterized as the picrate, yellow prisms, mp 208–210°.

Anal. Calcd for C₂₀H₂₃NO₂·C₆H₅N₂O₇: C, 56.2; H, 5.1. Found: C, 56.4; H, 5.4.

Neodihydrothebaine Dihydroisomethine (XV, R = H). Neodihydrothebaine isomethine (XI, R = H) (1 g) was shaken under hydrogen at 20° (750 mm) in the presence of 10% palladium-on-charcoal catalyst (0.25 g). Hydrogen (70 ml) was absorbed over 15 min. Filtration and evaporation of the solution afforded the dihydroisomethine (XV, R = H) as a colorless oil, $[\alpha]_D^{20} -10.0^\circ$ (c 2.1, CHCl₃), that could not be crystallized.

The methiodide was obtained readily as white prisms, mp 286–288° from ethanol.

Anal. Calcd for C₂₀H₂₇NO₂·CH₃I: C, 53.55; H, 6.4. Found: C, 53.6; H, 6.7.

The methyl ether methiodide was obtained as white prisms, mp 228–230° from water.

Anal. Calcd for C₂₁H₂₇NO₂·CH₃I: C, 54.5; H, 6.6. Found: C, 54.6; H, 6.6.

Hofmann Degradation of Neodihydrothebaine Isomethine Methyl Ether (XI, R = Me) Methiodide. Potassium hydroxide was added to a boiling solution of neodihydrothebaine isomethine methyl ether methiodide (1 g) in water (25 ml) until separation of an oil began. The mixture was then boiled for 1 hr, during which time a base (trimethylamine) was evolved, and an insoluble oil separated. The mixture was cooled and extracted with ether, and the ether extract was shaken twice with 2 *N* hydrochloric acid and evaporated, to leave an uncrystallizable fluorescent (blue) neutral oil that was rapidly converted into a rubbery solid on attempted distillation or

(more slowly) on standing. Thin layer chromatographic studies indicated that this product, presumably the divinylidiphenyl XVIII (Et = CH=CH₂), was identical with the product of degradation of neodihydrothebaine methine methyl ether (X) methiodide.

Hofmann Degradation of Neodihydrothebaine Dihydroisomethine Methyl Ether (XV, R = Me) Methiodide. Neodihydrothebaine dihydroisomethine methyl ether methiodide (2 g) was degraded by the process given above to yield 2'-ethyl-5,6,5'-trimethoxy-2-vinylidiphenyl (XVIII) as a pale brown oil which was distilled under high vacuum, and was obtained as a colorless oil, bp 190–200° (bath temp) (0.05 mm).

Anal. Calcd for C₁₉H₂₁O₃: C, 76.5; H, 7.6. Found: C, 76.4; H, 7.7.

2,2'-Diethyl-5,6,5'-trimethoxydiphenyl (XVII). 2'-Ethyl-5,6,5'-trimethoxy-2-vinylidiphenyl (XVIII) (0.8 g) in ethanol (25 ml) was shaken under hydrogen at 20° (760 mm) in the presence of 10% palladium-on-charcoal catalyst (0.25 g). Hydrogen (66 ml) was absorbed over 10 min. The solution was filtered and evaporated, and the residual oil was distilled when the diphenyl XVII was obtained as a colorless oil, bp 190–200° (bath temperature) (0.05 mm).

Anal. Calcd for C₁₉H₂₁O₃: C, 76.1; H, 8.1. Found: C, 76.2; H, 8.1.

The same product, identical in behavior with the above on thin layer chromatography, was obtained by the hydrogenation of 2-ethyl-5,6,5'-trimethoxy-2'-vinylidiphenyl (XVI), obtained by the degradation of the methiodide of neodihydrothebaine dihydro-methine methyl ether (XVI).

Neodihydrothebaine Methine Methyl Ether (X). Neodihydrothebaine methyl ether methiodide (5 g) was dissolved in boiling water (50 ml), and potassium hydroxide was added to the solution until separation of an oil began. The mixture was then boiled for 30 min, cooled, and diluted, and the product was isolated by ether extraction. Thin layer chromatographic studies showed that the uncrystallizable oil contained two bases. It was converted into the methiodide by heating with methyl iodide and ethanol, and on cooling the solution slowly deposited neodihydrothebaine isomethine methyl ether methiodide (0.5 g), mp 205°, identical with the salt prepared from the isomethine (see above). Evaporation of the mother liquors after removal of this salt afforded material that could not be obtained crystalline from ethanol or from water. It was converted into neodihydrothebaine methine methyl ether methoperchlorate by the addition of perchloric acid to a solution of the methiodide in water. The methoperchlorate was obtained as white needles, mp 150–151°, on recrystallization from water.

Anal. Calcd for C₂₁H₂₇NO₂·CH₃·CH₂ClO₄: C, 58.1; H, 6.65. Found: C, 58.1; H, 6.55.

Oxidation of Neodihydrothebaine Methine Methyl Ether. Neodihydrothebaine methine methyl ether, containing some of the isomethine methyl ether (1.8 g), was stirred on the boiling water with potassium hydroxide (2.0 g), potassium permanganate (4.0 g), and water (50 ml) for 4 hr. The mixture was filtered, and the yellow filtrate was acidified with hydrochloric acid; the precipitated product was isolated by ether extraction and obtained as a viscous yellow oil. Thin layer chromatographic studies showed this material to consist of two yellow products and about 10% 5,6,5'-trimethoxydiphenic acid. The material was dissolved in 2 *N* potassium hydroxide solution (50 ml), and the solution was warmed on the water bath for 10 min with 30% hydrogen peroxide (1 ml). Acidification of the solution then afforded 5,6,5'-trimethoxydiphenic acid (1.2 g) as white prisms, mp 215°, from aqueous methanol; the melting point was undepressed on mixing with authentic specimens prepared from acetylthebaol and phenyldihydrothebaine.

The trimethoxydiphenic acid was warmed with concentrated sulfuric acid at 50° for 15 min. Dilution of the solution with water precipitated 1,5,6-trimethoxyfluorenone-4-carboxylic acid as yellow needles from 50% acetic acid, mp 256° alone or mixed with an authentic specimen.

Hofmann Degradation of Neodihydrothebaine Methine Methyl Ether (X) Methiodide. Degradation of the methiodide of the base X by the process described above for the degradation of neodihydrothebaine isomethine methyl ether methiodide afforded a neutral product identical with that obtained in that degradation.

Neodihydrothebaine Dihydromethine Methyl Ether (XIV). Neodihydrothebaine methine methyl ether (containing about 10% of the isomethine methyl ether) (5.4 g) was shaken in ethanol (50 ml) with 10% palladium on charcoal (0.25 g) under hydrogen at 20° (760 mm). Hydrogen (348 ml) was absorbed over 40 min. Filtration and evaporation afforded a noncrystalline gum, which was converted into the methiodide. Two recrystallizations of the methiodide afforded the dihydromethine methyl ether methiodide

be isomethine derivative (tlc) as white prisms, mp 200–

Calcd for $C_{21}H_{21}NO_3 \cdot CH_3I$: C, 54.5; H, 6.6. Found: H, 6.6.

nm Degradation of Neodihydrothebaine Dihydromethine Ether (XIV) Methiodide. The methiodide (2.0 g) was de- boiling aqueous potassium hydroxide, when trimethyl- as evolved and 2-ethyl-5,6,5'-trimethoxy-2'-vinylidiphenyl s isolated by ether extraction and distillation and obtained less oil, bp 190–200° (bath temperature) (0.05 mm).

Calcd for $C_{19}H_{25}O_3$: C, 76.5; H, 7.6. Found: C, 7.4.

tic reduction of this compound proceeded readily in ver 10% palladium on charcoal, and gave 2,2'-diethyl- methoxydiphenyl (XVII), identical in thin layer chromato- behavior with material prepared by the reduction of 2'- 5'-trimethoxy-2-vinylidiphenyl (XVIII) described above.

thebaine (IV). The product of reaction of thebaine (31.1 nhydrous magnesium iodide in ether–benzene suspension ed with 2 N hydrochloric acid. A sticky insoluble mass bly a hydriodide) was obtained, and the aqueous and solutions were poured off. After the material was in methanol, the solution was diluted with ice water and / basified with ammonia. A further quantity of base ined by adding ammonia to the aqueous acid layer sep- above. The precipitated solid was collected and red- from ethanol and from aqueous 2-ethoxyethanol; product, kryptothebaine (IV), was obtained in each case gray prisms, mp 274° (8.5 g). Recrystallization from 2-ethoxyethanol with the addition of a drop of aqueous

sodium dithionite gave the enamine as pale cream prisms, mp 274°, but these rapidly became green on standing, the color darkening to almost black after several days.

Anal. Calcd for $C_{20}H_{23}N_2O_4$: C, 73.3; H, 6.75; mol wt, 622. Found: C, 73.3; H, 6.8; mol wt (Rast in camphor), 586.

Reduction of this base catalytically over 10% palladium on char- coal was sluggish and was only complete after 10 hr, and reduction with sodium borohydride was slow even in boiling 2-ethoxyethanol. The same base was obtained in each case, and unlike neodihydro- thebaine (which it closely resembled in infrared absorption), it was completely insoluble in ether. No crystalline salts of this un- crystallizable base could be prepared.

Catalytic reduction of the crude product (2 g) obtained on basi- fication of the aqueous methanolic solution of the hydriodide, however, gave, slowly, a product part of which dissolved in ether. Evaporation of the ether gave neodihydrothebaine (0.16 g) identi- fied as its methiodide, mp 249–250° from ethanol.

Reaction of Kryptothebaine (IV) with Hydrochloric Acid. Kryp- tothebaine (IV), prepared as above (2 g), was boiled with 2 N hy- drochloric acid (10 ml) for 5 min. The solution, on cooling, de- posited a viscous gum (2.0 g), which crystallized from water at 0° as yellow needles, mp 234–236°, identical in melting point, mixture melting point, infrared absorption, and R_f value with thebenine (II) hydrochloride prepared in the same way from thebaine.

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The Structures of Deserpideine and Raujemidine¹

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Contribution from S. B. Penick and Company, New York, New York, and the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania. Received December 10, 1966

Abstract: The indole alkaloids deserpidine and raujemidine correspond to expressions I and Ia, respectively. The most interesting transformation of deserpidine is its hydrogenation and hydrogenolysis with Adams catalyst to eld products II, III, X, and XII.

initial investigation of the alkaloids of *Rauwolfia la Jacq.* by Salkin and his group⁴ led to the isolation of isoreserpinine, isoreserpinine, raunititidine, reserpiline, and reserpine.

ave now found that the weakly basic alkaloid from certain samples of *R. nitida* yields, in 1 to the known alkaloid deserpidine (II), a stalline alkaloid, deserpidine (I), $C_{22}H_{28}N_2O_8$, -152° , $[\alpha]^{25}_D -133^\circ$ (pyridine), whose ultra- spectrum is identical with its companion de- ie. The infrared spectrum of deserpidine is ry similar to that of deserpidine, but varies

iminary communications of some of these results appeared in th, R. S. Jaret, M. Shamma, and R. J. Shine, *J. Am. Chem.* 1083 (1964); (b) M. Shamma and R. J. Shine, *Tetrahedron* 177 (1964); and (c) E. Smith, R. S. Jaret, M. Shamma, and e, *Lloydia*, 27, 440 (1964).

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Salkin, N. Hosansky, and R. Jaret, *J. Pharm. Sci.*, 50, 1038

slightly from the latter in the fingerprint region. In analogy with deserpidine (II), the Bohlmann bands between 3.4 and 3.6 μ were missing in deserpidine (I), indicating a *cis* C–D ring fusion.

The chemistry of deserpidine (I) initially indicated a behavior that somewhat paralleled the chemistry of deserpidine (II). The reaction of deserpidine (I) with sodium methoxide at room temperature gave the expected methyl 3,4,5-trimethoxybenzoate (IIIa) and methyl deserpideate (IV), $C_{22}H_{28}N_2O_4 \cdot H_2O$, mp 159–162°, $[\alpha]^{25}_D +8^\circ$ (pyridine). Hydrolysis of either deserpidine or methyl deserpideate with potassium hydroxide in aqueous methanol gave deserpideic acid (V), $C_{21}H_{24}N_2O_4$, mp 224–226°, $[\alpha]^{25}_D -29^\circ$ (50% methanol–water), which could be converted to deserpideic acid lactone (VI), $C_{21}H_{22}N_2O_3$, mp 159–161°, $[\alpha]^{25}_D -58^\circ$ (50% methanol–water), on treatment with acetic anhydride in pyridine. When deserpideic acid lactone was allowed to stand at 0° in sodium methoxide in methanol, methyl deserpideate (IV) was obtained. Deserpideine (I) itself could be reconstituted by treat- ment of methyl deserpideate with 3,4,5-trimethoxy-

benzoyl chloride. The reaction cycle was completed by converting deserpideic acid (V) to methyl deserpideate (IV). This esterification could be accomplished by either of two methods. The reaction of deserpideic acid with diazomethane proceeded poorly giving only a 25% yield of methyl deserpideate, the remainder of the product being unreacted starting material. The Fischer esterification, however, went smoothly at room temperature giving an 88% yield of methyl deserpideate.

Oxidation of deserpideine with 2 molar equiv of lead tetraacetate and reduction of the crude reaction product with borohydride gave a new compound, 3-isodeserpideine (VII), crystallized as the nitrate and the methiodide salts.

On the other hand, if the methanolysis of deserpideine with sodium methoxide were allowed to proceed in refluxing methanol, a considerable amount of a new compound was obtained. This material, mp 174–176°, analyzes for $C_{21}H_{20}N_2O_2 \cdot 0.5C_2H_5OH$, has a very high dextrorotation, $[\alpha]^{25D} +288^\circ$ (pyridine), and an infrared spectrum exhibiting only one carbonyl band which appears at 5.83μ . The nmr spectrum shows one methoxyl singlet at δ 3.88 due to three protons, and the mass spectrum has a molecular ion peak at m/e 332. From these data, structure VIII was considered for this new compound.

To ascertain this structural assignment, our highly dextrorotatory compound, presumed to be VIII, was converted to the alcohol IX by means of lithium aluminum hydride and compared with authentic IX that we had synthesized by a route developed by Elderfield and Fischer.⁵ Comparison of the two alcohols (IX) as their hydrobromide salts showed the two salts to be identical. They both had identical infrared spectra taken as KBr pellets and they showed the same characteristics on melting. Paper chromatography R_f values in a number of solvent systems further showed the identity of the two materials. The structure of the highly dextrorotatory compound was thus shown to be 11-demethoxytetrahydroalstoniline (VIII), and its formation has no analogy in the reserpine series.

Significant information about the stereochemistry of the new alkaloid could be derived from a study of its rate of quaternization with methyl iodide. Rates of methiodide formation had previously proven to be a useful tool in the study of the stereochemistry of the yohimbinoind alkaloids.⁶ These rates were determined in acetonitrile solution using pseudo-first-order kinetics, a large excess of methyl iodide being present. The pseudo-first-order rate constants for deserpideine and its derivatives and a variety of other indole alkaloids are given in Table I. In the yohimbine series, such a very fast rate as that exhibited by deserpideine (I) and its derivatives IV and VI is associated with the pseudo-configuration, but in the present case a more specific statement is desired; namely, that in deserpideine and its derivatives the basic nitrogen is unhindered.

A second piece of data of great utility was supplied by mass spectrometry. Since deserpideine free base is rather unstable, the mass spectra were run on its more stable crystalline derivatives, methyl deserpideate (IV) and deserpideic acid lactone (VI). The molecular ion peaks of methyl deserpideate and the lactone, at m/e

Table I. Pseudo-First-Order Rates of Methiodide Form.

Alkaloids and derivatives	$k \times 10^4$, sec ⁻¹	S ch
Deserpideine (I)	300	
Methyl deserpideate (IV)	350	
Deserpideic acid lactone (VI)	220	
3-Isodeserpideine (VII)	31	
Deserpidine (II)	7.2	E
16-Methyl-19-methoxyalloyohimbane (XI)	2.5	A
α -Yohimbine methyl ether (XII)	1.1	A
3-Isodeserpidine	1.0	A
Yohimbine	48.7	N

382 ($C_{22}H_{28}N_2O_4$) and m/e 350 ($C_{21}H_{22}N_2O_3$), respectively were two mass units less than for the corresponding compounds in the deserpideine series. These results immediately indicated the presence of either an unsaturation or an additional ring in compounds of the deserpideine series, and further confirmed the assignment $C_{22}H_{28}N_2O_4$ formulation to deserpideine, which has mass units less than that for deserpideine. The difference between an unsaturation and an extra ring was decided by the study of a third piece of data, the nmr spectra. Spectra of deserpideine and its derivatives show absorption at δ 5.55 corresponding to one proton. This absorption is in the region of vinylic absorption, deserpideine possesses a trisubstituted double bond which is not conjugated to the chromophoric system. The most likely positions for such a double bond were C-14(15) or C-19(20).

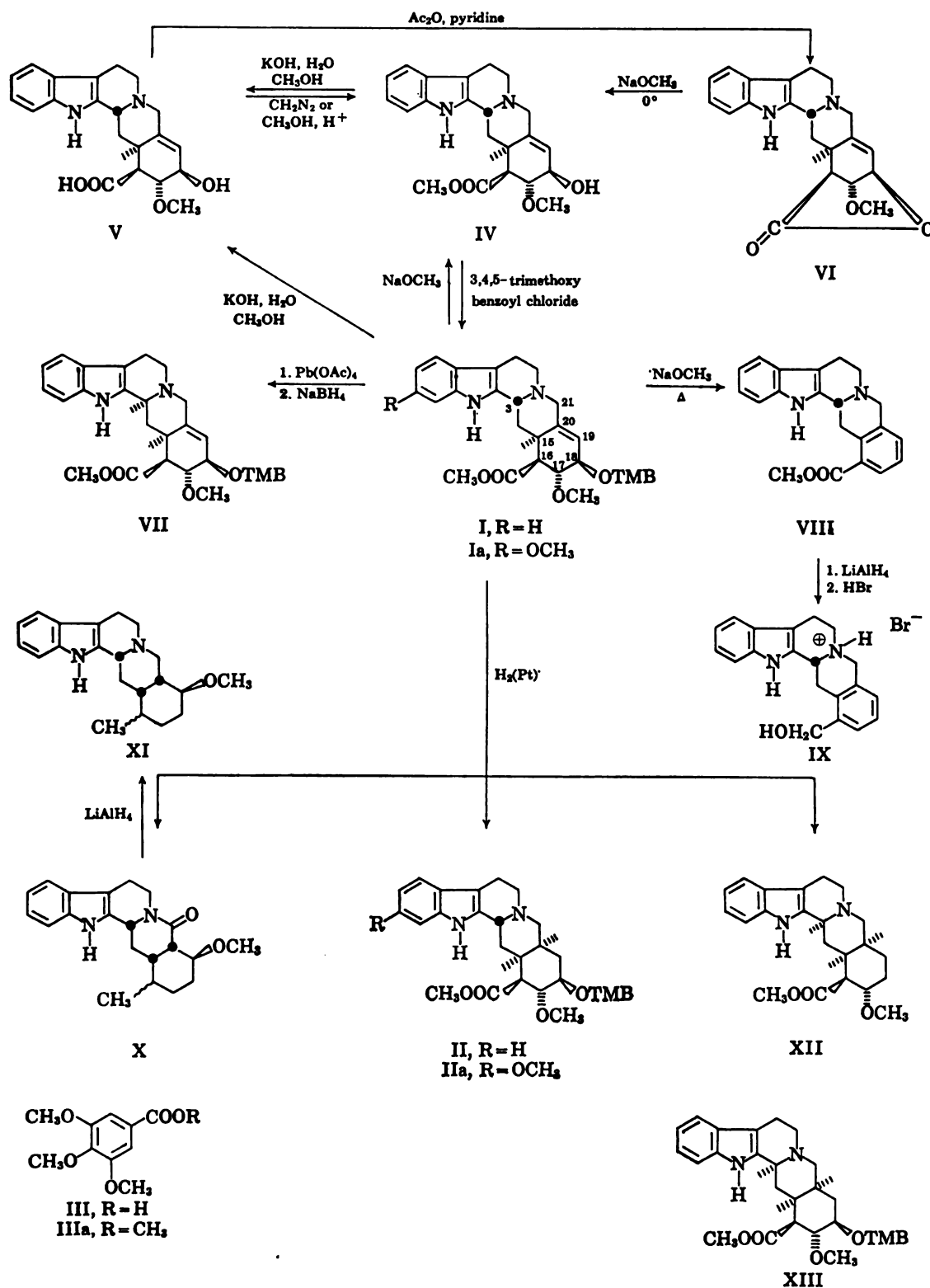
In an attempt to reduce this isolated double bond in deserpideine was hydrogenated using Adams catalyst in ethanol at room temperature. The alkaloid did not take up hydrogen, but only slowly. If the reaction was allowed to proceed for 12 hr, a complex mixture of products ensued.

A thin layer chromatogram of the reduction product showed at least ten spots. The crude hydrogenation mixture was, therefore, separated into an acidic, a basic, and a neutral fraction by classical extraction techniques. A crystalline compound was obtained in 68% yield from the acidic fraction which was characterized as 3,4,5-trimethoxybenzoic acid (III). Identification of this material strongly indicated the position of the double bond to be at C-19(20), and hydrogenolysis of the allylic 3,4,5-trimethoxybenzyl group can then occur.

Following removal of the acidic and neutral components, crystallization of the basic fraction was possible, and a white crystalline compound was obtained. This compound was shown to be identical with authentic deserpidine (II) in a number of ways. The two compounds had the same infrared spectra in chloroform and in acetonitrile solution, and their nmr spectra were also identical. Thin layer chromatograms in a number of solvent systems always resulted in the two compounds having the same R_f values. A methiodide rate study showed the synthetic material to have a rate of 10^{-4} sec⁻¹, characteristic of the expected epiallonyl configuration. Finally, the melting points (224–225°) were the same and a mixture melting point was pressed. As a precautionary measure, rotation was determined and found to be the same, $[\alpha]^{25D} +288^\circ$ in chloroform. This shows that the deserpideine isolated from the hydrogenation reaction has the same

(5) R. Elderfield and B. Fischer, *J. Org. Chem.*, **23**, 949 (1958).

(6) M. Shamma and J. Moss, *J. Am. Chem. Soc.*, **83**, 5038 (1961); M. Shamma and J. Richey, *ibid.*, **85**, 2507 (1963).



absolute configuration as natural deserpidine. Thus, the identity of the two compounds was clearly established, and this transformation proves the stereochemistry of deserpidine to be as indicated in I.

The neutral fraction readily crystallized into a colorless compound which contained no carbonyl band between 5 and 6 μ , but possessed a very intense absorption at 6.13 μ . The loss of basicity of the nitrogen and the disappearance of the ester carbonyl bands accompanied by the presence of the 6.13- μ peak clearly point to allylic hydrogenolysis of the C-21(N-4) bond followed by intramolecular ester-amide conversion to

form lactam X.⁷ Further evidence for the structural assignment for the neutral compound is seen in the nmr and mass spectra of the material. The mass spectrum shows a molecular ion peak at m/e 338 which is the correct molecular weight calculated for 16-methyl-19-methoxy-21-oxoyohimbane (X). The nmr spectrum shows only one methoxyl absorption at δ 3.25 and shows a C-CH₃ doublet at δ 1.03. The absence of a vinylic absorption and the presence of the C-CH₃ doublet clearly indicate reduction of the double bond

(7) F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **78**, 2021 (1956).

originally present in I. The stereochemistry of the asymmetric centers at C-3, C-15, C-19, and C-20 in lactam X must be as indicated from our knowledge of the stereochemistry of deserpidine. Upon reduction of lactam X with lithium aluminum hydride, 16-methyl-19-methoxyalloyohimbane (XI) was obtained which showed a molecular ion peak at m/e 324 in accordance with the formula $C_{21}H_{28}N_2O$. The infrared spectrum showed no carbonyl absorption and specifically the band at 6.13μ had disappeared. The rate of methiodide formation for compound XI was found to be $2.5 \times 10^{-4} \text{ sec}^{-1}$ which is a slow rate strongly characteristic of an allo configuration.

After removing the crystalline deserpidine, the basic fraction of the hydrogenation product still contained several minor components as monitored by thin layer chromatography, and it was found possible to separate one additional basic component. The infrared spectrum of this compound showed the absence of the band at 6.3μ , characteristic of the 3,4,5-trimethoxybenzoyl group, and the presence of Bohlmann bands at $3.4\text{--}3.6 \mu$. It was, therefore, assumed that this compound had lost the 3,4,5-trimethoxybenzoyl group *via* hydrogenolysis, and that the proton at C-3 had epimerized to the α configuration. A rate of methiodide formation was needed to decide from which side of the molecule hydrogenation had occurred, and a choice had to be made between the normal and the allo configuration for the new base. The rate was found to be extremely slow, $1.1 \times 10^{-4} \text{ sec}^{-1}$, indicating an allo configuration and α hydrogenation, so that the compound had to be the known α -yohimbine methyl ether (XII).⁸ Indeed, when the two compounds were compared, they were found to be identical. The isolation of this product further supports the assignment of stereochemistry of the asymmetric centers at C-15, C-16, and C-17 in deserpidine (I). The isomerization of C-3 in this reaction is not surprising since it is known that reserpine is converted to 3-isoreserpine under these reducing conditions.⁹

Catalytic hydrogenation of 3-isodeserpideine (VII) under the same conditions as for deserpidine also led to a complex mixture of products. Extraction of the acidic material gave a 65% yield of 3,4,5-trimethoxybenzoic acid, the same yield as obtained from the hydrogenation of deserpidine. Addition of methanol to the amorphous material obtained after extraction of the acidic material caused it to crystallize. The crystalline material, obtained in a 28% yield, was shown to be a α -yohimbine methyl ether (XII) by comparison with an authentic sample. The yield of this compound is significantly greater than in the hydrogenation of deserpidine which gave a 12% yield, and this would be expected since the hydrogen at C-3 is already in the α configuration in 3-isodeserpideine (VII). A small amount of 3-isodeserpideine (XIII) also could be obtained from the hydrogenation.

Hydrogenation of methyl deserpideate (IV) with Adams catalyst led to a complex mixture of products. This reaction mixture was separated into a neutral lactam fraction and a basic fraction. Preparative thin layer chromatography of the basic fraction yielded

pure methyl deserpidate (XIV) which was shown identical with authentic material.

These data give compelling evidence that deserpi must have structure I and is, therefore, 19-deh deserpidine. The position of the double bond is onstrated by the results of the hydrogenation e ments, the rate studies, and the formation of 1 methoxytetrahydroalstoniline (VIII). All asymr centers were shown to have the same stereochemis deserpidine.

Application of Hudson's lactone rule¹⁰ to the serpidine series to determine the absolute configur led to ambiguous results. When the rotations measured in methanol, the change in the molecular ation from deserpideic acid, $[M]^{25}_D -107^\circ$, to serpideic acid lactone, $[M]^{25}_D -206^\circ$, was found -99° , indicating that the hydroxyl group at C-18 This configuration is opposite to that assigned o basis of the isolation of (–)-deserpideine from th drogenation reaction. However, when the rota were measured in pyridine, the change in mole rotation was found to be $+73.3^\circ$, indicating a β figuration for the C-18 hydroxyl. Thus, the abs configuration that may be assigned by use of Hud lactone rule is shown to be solvent dependent in present case. This finding along with other k exceptions^{11–14} shows that assignments of abs configuration on the basis of Hudson's lactone should be done with extreme caution.

11-Demethoxytetrahydroalstoniline (VIII) has asymmetric center and the compound is dextro tory, so that the contribution of C-3 to the assymr of the molecule must be dextrorotatory. method of rotational differences had previ been applied to the C-3 hydrogen in the rese series.¹⁵ It was found that when the hydrogen at was α , this center made a large negative contributi the molecular rotation. In the case of 11-demeth tetrahydroalstoniline, the asymmetric center at makes a large positive contribution to the mol rotation, and therefore the C-3 proton should l This is in agreement with the absolute configur presently assigned to deserpidine on the basis of the lation of (–)-deserpideine from the hydrogenation ture.

It is fitting at this point to turn our attention to alkaloid raujemidine obtained from *R. canescen* 1956. This base had been reported to give an elem analysis nearly identical with that of reserpine, and treatment with sodium methoxide yielded methyl 3 trimethoxybenzoate.¹⁶ A rate of methiodide forma was, therefore, determined for raujemidine and found to be $3.0 \times 10^{-2} \text{ sec}^{-1}$. This very fast rate cated that the molecule possesses an unhindered nitrogen. The nmr spectrum of raujemidine was to that of reserpine, but it possessed an additional vi absorption at δ 5.50. The relationship between alkaloid and deserpidine seemed obvious; it appe

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raujemidine was 19-dehydroreserpine (Ia), so that nidine stands to reserpine in the same relationship deserpideine is related to deserpidine.

test this hypothesis, raujemidine was hydrogenated the same conditions as deserpideine. It was found the two compounds behaved similarly in the presence of platinum and hydrogen. Raujemidine hydrogenated slowly and gave a complex mixture of products. 3,4,5-trimethoxybenzoic acid (III) was extracted from the product and was shown to be identical with authentic material. This settled the position of the ester bond at C-19. An infrared spectrum of the hydrolyzed residue showed an increased absorption at 6.13 μ due to the formation of a lactam. The residue was purified by preparative scale thin layer chromatography. The band that possessed the same R_f value as reserpine (IIa) was examined in detail. This compound was eluted from the silica gel and crystallized from ethanol. The crystalline compound was shown to be identical with authentic reserpine by comparing physical properties. They both had identical infrared spectra in chloroform and acetonitrile. The nmr spectra were practically superimposable, the melting points were identical, and a mixture melting point was undepressed. The R_f values in a number of solvent systems were identical.

The structure of raujemidine was therefore settled as Ia, with a molecular formula $C_{23}H_{28}N_2O_9$. Raujemidine is the second member of the 19-dehydroyohimbinol series to be characterized. Further investigation with raujemidine was precluded by its instability, also by lack of sample. Very recently, Arndt and Djerassi isolated 19-dehydroyohimbine from *Aspidosiphon pyricollum* which represents the third member of the rare 19-dehydroyohimbine alkaloids.¹⁷

Experimental Section

Standard Experimental Procedures. All microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and by Zkopff Microanalytical Laboratory, Woodside, N. J. The melting points were taken either on a Nalge melting point apparatus or in a sealed capillary and are uncorrected. The nmr spectra were measured on a Varian Associates A-60 spectrometer with microcells purchased from Varian Associates, with deuteriochloroform as the solvent and tetramethylsilane as the internal standard. The mass spectra of a few derivatives were graciously obtained in the laboratories of Professor Carl Djerassi or Professor Klaus Biemann. The remainder of the mass spectra were obtained on a Nuclide 12-90-G1.1 mass spectrometer. Adsorbents purchased from Applied Science Laboratories of State College, Pa., were used to prepare the thin layer chromatography plates for this study. The spots were visualized by placing the plates in a fuming sulfuric acid vapor or by shining an ultraviolet light.

Deserpideine (I). The milled root of *R. nitida*, originally collected from the island of Hispaniola, was moistened with saturated potassium carbonate solution and extracted with benzene. The benzene extract was shaken with 0.5 M phosphoric acid. The acid solution was extracted at pH 2 with chloroform, and the chloroform layer was washed with potassium carbonate solution. Evaporation of the solvent left the weakly basic alkaloid fraction behind. The alkaloids were precipitated from ethanol solution as their picrate salts. The crude nitrate salts were placed in chloroform solution and washed with aqueous sodium carbonate solution. The chloroform layer was then separated and the solvent evaporated. The residue was taken up in methanol, and the reserpine which had been removed by filtration. After concentration to dryness, the mother liquors were taken up in ethyl acetate to give a mixture of deserpideine and deserpidine. Crystallization of the hydrochloride salts from acetone gave deserpideine hydro-

chloride, which after recrystallization from methanol melted at 277° dec, $[\alpha]^{25}_D -98.5^\circ$ (c 0.5, chloroform).

Anal. Calcd for $C_{23}H_{27}ClN_2O_8$: C, 62.68; H, 6.09; Cl, 5.78; N, 4.57; O, 20.87. Found: C, 62.49; H, 6.23; Cl, 5.76; N, 4.56; O, 20.81.

The free base was liberated from a chloroform solution of the hydrochloride with sodium carbonate and crystallized from ether, mp 149–152° dec, $[\alpha]^{25}_D -133^\circ$ (c 1, pyridine), $[\alpha]^{25}_D -108^\circ$ (chloroform).

Anal. Calcd for $C_{23}H_{28}N_2O_8$: C, 66.64; H, 6.29; N, 4.86; O, 22.20; $5OCH_3$, 26.87. Found: C, 66.62; H, 6.60; N, 4.91; O, 22.30; OCH_3 , 26.30.

Deserpideine Methiodide. A solution of 100 mg (0.174 mmole) of deserpideine in 1.5 ml of ethyl acetate was prepared and cooled to 0°. To this slightly yellow solution, 1.0 ml of pure methyl iodide was added. The flask was flushed with nitrogen, stoppered, and allowed to stand at 0° for 4 hr. Evaporation of the excess methyl iodide caused an insoluble residue to form. Crystallization of this residue was effected by adding three drops of methanol to the ethyl acetate mixture and heating. Filtration and recrystallization from methanol gave 112 mg (0.156 mmole, 90%) of the white crystalline methiodide. Recrystallization from methanol for an analytical sample gave a compound that melted 246–248° dec.

Anal. Calcd for $C_{23}H_{29}IN_2O_8$: C, 54.70; H, 5.43. Found: C, 54.89; H, 5.47.

Methyl Deserpideate (IV). About 100 mg of clean sodium metal was placed into 10 ml of anhydrous methanol. The solution was allowed to stand in ice for 1 hr. Then, 921 mg (1.60 mmoles) of deserpideine in 10 ml of dry methanol was added. The flask was flushed with nitrogen, stoppered, and allowed to stand in the dark at room temperature for 24 hr. The solution had acquired a yellow color. After adding 20 g of ice, the solution was adjusted to pH 6 (Hydriol paper) with dilute hydrochloric acid. The solution was then extracted with three 10-ml portions of ether to remove the methyl 3,4,5-trimethoxybenzoate. The aqueous layer was made basic by adding 5% sodium carbonate and was then extracted with three 10-ml portions of chloroform. The chloroform solution was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The residue that remained weighed 612 mg. This was dissolved in 2 ml of 95% ethanol, and the solution was made acidic by adding hydrochloric acid in ethanol. Crystallization proceeded very slowly. Filtration gave 400 mg (0.96 mmole, 60%) of white crystalline methyl deserpideate hydrochloride, mp 246–247° dec, λ^{25}_D 221 and 278 $m\mu$ (log ϵ 4.59 and 3.94).

Anal. Calcd for $C_{23}H_{27}ClN_2O_8$: C, 63.07; H, 6.50; Cl, 8.46; N, 6.69; O, 15.27; $2OCH_3$, 14.97. Found: C, 63.30; H, 6.40; Cl, 8.81; N, 6.55; O, 15.45; OCH_3 , 14.67.

The free base melted at 159–161° dec, $[\alpha]^{25}_D +8.4^\circ$ (c 1, pyridine), λ^{25}_D 225 and 280 $m\mu$ (log ϵ 4.53 and 3.91).

Anal. Calcd for $C_{23}H_{28}N_2O_8 \cdot 0.5 H_2O$: C, 67.50; H, 6.95; N, 7.16. Found: C, 67.38; H, 6.76; N, 7.36.

Treatment of methyl deserpideate with 3,4,5-trimethoxybenzoyl chloride in pyridine resulted in the formation of deserpideine with unchanged specific rotation and melting point.

11-Desmethoxytetrahydroalstonine (VIII). Deserpideine (2 g, 3.46 mmoles) was refluxed in 90 ml of absolute methanol and 0.2 g of sodium under nitrogen for 2 hr. The solution was acidified with glacial acetic acid and concentrated *in vacuo* to 10 ml, poured into ice water, acidified with HCl, and extracted with ether. From the ether layer, 0.7 g of 3,4,5-trimethoxybenzoic acid methyl ester was obtained. Basification with potassium carbonate and extraction with ether gave 1.2 g of crude product. Crystallization from alcoholic HCl gave 0.7 g (49%) of methyl deserpideate hydrochloride, mp 246–247° dec, $[\alpha]^{25}_D -46^\circ$ (c 1, methanol).

The mother liquors of the methyl ester hydrochloride crystallization after conversion to the free base were chromatographed over alumina (Merck acid washed) and eluted with benzene followed by benzene with increasing amounts of chloroform. A 50:50 mixture eluted a substance which crystallized as the hydrochloride from absolute alcohol and had a melting point of 237–239° dec, $[\alpha]^{25}_D +249^\circ$ (50% ethanol-water), λ^{25}_D 223 and 282 $m\mu$ (log ϵ 4.70 and 4.02).

Anal. Calcd for $C_{21}H_{21}ClN_2O_7$: C, 68.38; H, 5.74; Cl, 9.61; N, 7.59; O, 8.68. Found: C, 68.37; H, 5.76; Cl, 9.32; N, 7.40; O, 8.66.

The free base VIII crystallized from ethanol, mp 174–176° dec, $[\alpha]^{25}_D +288^\circ$ (c 0.5, pyridine), and was susceptible to air oxidation.

Anal. Calcd for $C_{21}H_{22}N_2O_7 \cdot 0.5 C_2H_5OH$: C, 74.34; H, 6.52; N, 7.88; O, 11.25; OCH_3 , 8.73. Found: C, 74.84; H, 6.52; N, 7.70; O, 11.14; OCH_3 , 9.07.

R. R. Arndt and C. Djerassi, *Experientia*, 21, 566 (1965).

Deserpideic Acid (V). Deserpideine hydrochloride (1.2 g, 1.96 mmoles) in 12 ml of methanol and 6 ml of 10 *N* sodium hydroxide was kept at 45° for 5 hr. The alcohol was then removed under slight vacuum, and the solution was carefully adjusted to pH 4.8 giving 3,4,5-trimethoxybenzoic acid (0.43 g). Acidification to pH 2 with concentrated HCl gave crystals of deserpideic acid hydrochloride (0.5 g, 63%). The salt was recrystallized from water, mp 282° dec, $[\alpha]^{25}_D - 32.5^\circ$ (methanol). The melting point of deserpideic acid was 224–226° dec, $[\alpha]^{25}_D - 29^\circ$ (50% methanol–water).

Anal. Calcd for $C_{21}H_{23}ClN_2O_5$: C, 62.30; H, 6.22; Cl, 8.76; N, 6.92. Found: C, 62.39; H, 6.69; Cl, 8.42; N, 6.84.

Deserpideic acid Lactone (VI). Deserpideic acid (2 g, 5.43 mmoles) was kept at room temperature for 24 hr in 25 ml of pyridine and 20 ml of acetic anhydride. The solution was then concentrated *in vacuo* and poured onto ice. The clear solution was made basic with sodium bicarbonate and extracted with chloroform, and the chloroform solution concentrated to incipient crystallization. Filtration and recrystallization from methanol gave deserpideic acid lactone (1.1 g, 58%), mp 159–161° dec, $[\alpha]^{25}_D - 58^\circ$ (methanol).

Anal. Calcd for $C_{21}H_{21}N_2O_5$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.81; H, 6.73; N, 8.24.

Preparation of Methyl Deserpideate (IV) from Deserpideic Acid (V) and Diazomethane. A solution of diazomethane in ether was prepared by stirring 1.0 g of Du Pont's EXR-101 (70:30 *N,N'*-dimethylterephthalamide:white mineral oil) in 10 ml of 50% sodium hydroxide and 50 ml of ether and codistilling the diazomethane with ether. To this ethereal diazomethane solution, a solution of 340 mg (0.924 mmole) of deserpideic acid in 15 ml of ether and 45 ml of methanol was added. The yellow solution was allowed to stand at 0° overnight in a hood. After evaporating the solvent, the methyl deserpideate was removed by adding chloroform to the residue and filtering. The starting acid is insoluble in chloroform. The yield of methyl deserpideate was 87 mg (0.228 mmole, 25%).

Preparation of Methyl Deserpideate (IV) from Deserpideic Acid (V) and Methanolic Hydrogen Chloride. To a solution of dry hydrogen chloride in 15 ml of anhydrous methanol 202 mg (0.544 mmole) of deserpideic acid was added. The flask was flushed with nitrogen, stoppered, and allowed to stand at room temperature in the dark for 48 hr. The methanol was evaporated *in vacuo* giving a yellow viscous oil. This oil was extracted with 5% sodium carbonate and chloroform. The chloroform layer was dried, and the solvent was removed giving 185 mg (0.484 mmole, 88%) of an off-white solid whose infrared spectrum and nmr spectrum were identical with those of authentic methyl deserpideate. This product was recrystallized from methanol, mp 159–161° dec.

Preparation of Methyl Deserpideate (IV) from Deserpideic Acid Lactone (VI). About 25 mg of fresh sodium was placed into 3 ml of anhydrous methanol. After the sodium had reacted, the solution was cooled to 0°, and 15 mg (0.0428 mmole) of deserpideic acid lactone was added. The flask was flushed with nitrogen, stoppered, and allowed to stand in the dark at 0° for 45 hr. Dry methanolic hydrogen chloride was slowly added to bring the solution to pH 5, sodium chloride precipitating out. The solvent was removed by passing a stream of dry nitrogen over the solution. Chloroform was added to the residue, and the inorganic salts were filtered. The chloroform was evaporated under reduced pressure; the residue was taken up into 5 ml of chloroform, and the solution was washed with two 5-ml portions of 5% sodium carbonate solution. The chloroform layer was dried with anhydrous sodium sulfate and filtered and the solvent removed under reduced pressure. The product from this treatment had melting point and infrared and nmr spectra that were identical with those of authentic methyl deserpideate.

Hydrogenation of Deserpideine (I). Exactly 2.86 g (4.96 mmoles) of deserpideine was dissolved in 250 ml of 95% ethanol and added to a mixture of 565 mg of platinum oxide in 10 ml of 95% ethanol. The hydrogenation bottle was flushed with nitrogen and placed on a Parr hydrogenation apparatus and was then charged with 36 lb of hydrogen. Shaking was started and continued for 2 days. The bottle was then removed and thoroughly flushed with nitrogen. The catalyst was filtered from the solution by repeatedly passing the mixture through very retentive, quantitative filter paper (Schleicher and Schuell, Analytical Filter Paper No. 576) until no catalyst was seen on the filter paper; four times were sufficient. The solvent was removed under reduced pressure giving 2.69 g of yellowish amorphous solid. The hydrogenation product was extracted with aqueous sodium carbonate and chloroform. The aqueous extracts were acidified by the addition of concentrated hydrochloric acid. A white crystalline precipitate formed, which was filtered from the cold

solution giving 723 mg (3.41 mmoles, 69%) of a white crystalline solid, mp 168–170°. This compound was shown to be identical with authentic 3,4,5-trimethoxybenzoic acid by melting point, mixture melting point, and infrared spectrum. The chloroform extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness leaving 1.97 g of a tan amorphous solid. This material was then distributed between ether and 0.5 *M* phosphoric acid. The ether extracts were dried and evaporated leaving 410 mg of a yellow residue. This was the neutral fraction. Addition of ethyl acetate to this fraction caused it to crystallize. After filtration and recrystallization from methanol, 123 mg of white crystalline 16-methyl-19-methoxy-21-oxoyohimbane (X) was obtained, mp 245–247° dec, $[\alpha]^{25}_D + 142^\circ$ (*c* 0.8, chloroform). An infrared spectrum showed no absorption between 5.0 and 6.0 μ . The nmr spectrum showed one methoxyl absorption at δ 3.25 and a C-CH₃ doublet at δ 1.03. The mass spectrum exhibited a molecular ion peak at *m/e* 338.

Anal. Calcd for $C_{21}H_{25}N_2O_5$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.62; H, 7.84; N, 8.55.

The acidic aqueous layer containing the basic fraction was basified with aqueous sodium carbonate to pH 8 (Hydriol paper) and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness leaving 1.39 g of a tan amorphous solid. Addition of ethyl acetate to this material caused it to crystallize. Recrystallization from methanol gave 156 mg of white crystals, mp 224–226° dec, $[\alpha]^{25}_D - 123^\circ$ (*c* 0.3, chloroform). This compound had a rate of methiodide formation of $7.2 \times 10^{-4} \text{ sec}^{-1}$, characteristics of the epiallo configuration. Its melting point was the same as authentic deserpidine, and a mixture melting point was undepressed. Infrared spectra in chloroform and acetonitrile showed the compounds to be identical. The nmr spectra were superimposable. *R_f* values in a number of solvent systems also showed their identity: *R_f* 0.50, chloroform:ethanol:acetone (90:5:5); *R_f* 0.92, ether:methanol (80:20); *R_f* 0.63, ether:ethanol (95:5). Finally, both compounds had the same specific rotation, $[\alpha]^{25}_D - 123^\circ$ in chloroform.

From the mother liquor of the above crystallization, 1.20 g of amorphous material was obtained. A thin layer chromatogram with chloroform:acetone:methanol (80:16:4) as the solvent system showed that the material consisted of at least nine compounds. A preparative scale, thin layer chromatogram was used to purify this mixture, but only one fraction crystallized, mp 266–267° dec, and was shown to be identical with authentic α -yohimbine methyl ether (XII). The infrared spectra were identical. Thin layer chromatograms showed the two compounds to have the same *R_f* values in a number of different solvent systems: *R_f* 0.74, chloroform:acetone:methanol (90:8:2); *R_f* 0.81, benzene:acetone (80:20); *R_f* 0.67, benzene: ether (50:50); *R_f* 0.42, chloroform:acetone (94:6); *R_f* 0.41, benzene:acetone (90:10); *R_f* 0.33, benzene:ether (80:20); *R_f* 0.53, chloroform:ether (80:20).

Preparation of 16-Methyl-19-methoxyalloyohimbane (XI). A solution of 25 mg (0.074 mmole) of 16-methyl-19-methoxy-21-oxoalloyohimbane (X) in 50 ml of anhydrous ether was added dropwise to a stirred suspension of 150 mg of lithium aluminum hydride in 50 ml of refluxing ether. After addition was completed, the stirring and refluxing were continued for 12 hr. The excess lithium aluminum hydride was decomposed by the dropwise addition of water, and the inorganic salts were filtered. The ether was evaporated leaving 21 mg (0.065 mmole, 87%) of white 16-methyl-19-methoxyalloyohimbane (XI) that could be recrystallized from either acetonitrile or methanol, mp 217–220° dec. An infrared spectrum showed the disappearance of the band at 6.13 μ , and the pseudo-first-order rate of methiodide formation was $2.5 \times 10^{-4} \text{ sec}^{-1}$, indicative of an allo configuration. The mass spectrum exhibited a molecular ion peak at *m/e* 324 in accord with the molecular formulation $C_{21}H_{25}N_2O$.

Hydrogenation of Methyl Deserpideate (IV). Platinum oxide (34 mg) in 6 ml of 95% ethanol was reduced by stirring in the presence of hydrogen for 20 min. To this mixture, 66 mg (0.173 mmole) of methyl deserpideate in 11 ml of 95% ethanol was added, and the reaction was allowed to proceed with stirring for 4 days. The mixture was flushed with nitrogen, and the catalyst was filtered (Schleicher and Schuell Filter Paper No. 576). The solvent was removed under reduced pressure leaving 60 mg of an oil. This oil was shown to consist of at least 12 components by thin layer chromatography. An infrared spectrum showed an absorption at 6.12 μ . Partial separation of the mixture was accomplished by extraction with aqueous hydrochloric acid and chloroform. The chloroform layer (neutral material) was dried and solvent removed under reduced pressure. The residue was crystallized by the addi-

ethanol and yielded 12 mg of white crystalline 16-methyl-19-methoxy-21-oxaalloyohimbane, mp 287–289° dec. The infrared spectrum showed no absorption between 5.0 and 6.0 μ . The mass spectrum showed a strong amide band at 6.12 μ . The mass spectrum molecular ion peak at m/e 354.

Calcd for $C_{24}H_{34}N_2O_3$: C, 71.16; H, 7.39. Found: C, 71.16; H, 7.76.

The aqueous hydrochloric acid fraction was basified by adding sodium carbonate, and this was then extracted with chloroform. The chloroform extracts were dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure.

This gave 45 mg of a yellow solid which was subjected to preparative scale thin layer chromatography using chloroform:acetone (60:20:20) as the solvent system. The band value corresponded to authentic methyl deserpidate (R_f 0.46). The organic material was eluted from the plate by use of hot chloroform and hot methanol. This gave an oil which was once again subjected to preparative scale thin layer chromatography using the same solvent system, and again the band was removed. After elution, 10 mg of a white solid was collected. This compound gave an infrared spectrum identical with authentic methyl deserpidate in chloroform and in acetonitrile solution. The nmr spectrum was also identical with that of authentic methyl deserpidate and different from deserpidate. Thin layer R_f values further established the identity of the two compounds: R_f 0.49, chloroform:methanol (50:20:20); R_f 0.46, ether:methanol (50:50).

Aluminum Hydride Reduction of 11-Demethoxytetrahydro-11H-benzof[3,4-b]indolizine (VIII). 11-Demethoxytetrahydroalstoniline hydrochloride (300 mg, 0.135 mmole) was converted to the free base by treatment with aqueous sodium carbonate and ether. The ether solution (10 ml) was dried over anhydrous sodium sulfate, filtered, and added to a 50-ml addition tube. This solution was added to a stirred suspension of 300 mg of lithium aluminum hydride in 10 ml of ether. After addition was completed (1 hr), the mixture was stirred for 1 hr. Subsequently, 200 mg more of lithium aluminum hydride was added, and the mixture was stirred for 1 hr.

The excess lithium aluminum hydride was decomposed by the dropwise addition of water. Sodium sulfate (1 g) was added; the mixture was filtered, and the solvent was evaporated until about half its volume was removed. The hydrochloride salt was prepared by adding methanolic hydrogen bromide to a solution of the free base. The precipitate was filtered and dried to give 45 mg (0.112 mmole, 83%) of white crystalline 1-hydroxymethyl-11H-benzof[3,4-b]indolizine hydrochloride (trivial name: 11-demethoxytetrahydroalstoniline hydrochloride) that decomposed without sharp melting around 280°. The infrared spectrum as a KBr pellet was identical with that of authentic material.⁵ Paper chromatography R_f values in three solvent systems were the same for the two compounds: R_f 0.49, acetic acid:5% sodium acetate (v/v), saturated with ether; R_f 0.92, *n*-butyl alcohol saturated with water; R_f 0.49, *n*-butyl alcohol:ethanol, saturated with water.

Calcd for $C_{20}H_{22}BrN_2O$: C, 62.34; H, 5.49. Found: C, 62.34; H, 5.62.

Reduction of 3-Isodeserpideine (VII). A solution of 576 mg (0.955 mmole) of deserpidine in 10 ml of glacial acetic acid was heated on a steam bath. To this stirring solution, 56 ml of lead tetraacetate in glacial acetic acid was added dropwise over a course of 90 min. The temperature was maintained at 45–50° and the system was kept under a nitrogen atmosphere. The wine red solution was stirred at 45–50° for an additional 1 hr. The acetic acid was then removed *in vacuo*, leaving 1 oil. This oil was dissolved in 400 ml of chloroform; 20 ml of water was added and the mixture chilled. To this mixture, sodium hydroxide was added dropwise until the material turned blue on Hydrion paper (about 10 ml was needed). The chloroform layer was separated and washed once with 20 ml of water. The chloroform layer was dried over anhydrous sodium sulfate and filtered. It was then made acidic by adding dropwise ethanolic hydrochloric acid, a color change from dark red to orange being observed. The chloroform was removed under reduced pressure leaving 0.955 mmole, 95% of an orange solid that resisted recrystallization attempts. The infrared spectrum showed absorptions at 9.3, 5.8, 6.1, and 6.3 μ .

The orange solid was dissolved in 25 ml of methanol and cooled in an ice bath. Sodium borohydride (676 mg) was added in small portions over a course of 15 min. After 10 min, the dark brown solution

was refluxed for 5 min on a steam bath. Water (70 ml) was added, and the methanol was removed under reduced pressure. The solid was filtered and dried to constant weight (495 mg). This material was dissolved in a minimal amount of chloroform and passed through a 4-in. column of Florisil giving a yellow solution. The chloroform was evaporated leaving a yellow amorphous material that weighed 270 mg. A thin layer chromatogram of this showed it to consist of two compounds which were separated by preparative thin layer chromatography using chloroform:acetone:methanol (90:8:2) as the solvent system. The main component of the reaction was shown to be 3-isodeserpideine (230 mg, 40%). Its rate of methiodide formation was $31 \times 10^{-4} \text{ sec}^{-1}$ and its infrared spectrum showed the 3-iso bands at 3.4–3.6 μ .

A solution of 3-isodeserpideine was prepared by dissolving 80 mg (0.138 mmole) of pure 3-isodeserpideine (VII) in 0.5 ml of methanol. This solution was made slightly acidic by the dropwise addition of glacial acetic acid. Eight drops of a saturated ammonium nitrate in methanol solution was then added. A white precipitate formed immediately. This was filtered and recrystallized from methanol giving 73 mg (0.114 mmole, 83%) of white crystalline 3-isodeserpideine nitrate salt, mp 246–249° dec.

Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 60.24; H, 5.83. Found: C, 60.07; H, 5.77.

Exactly 32 mg (0.055 mmole) of 3-isodeserpideine was dissolved in 1.0 ml of ethyl acetate and cooled to 0°. Then, 0.5 ml of pure methyl iodide was added, and the solution was allowed to stand at 0° for 3 days. Crystallization commenced after 6 hr. The solvent was removed under reduced pressure, and the residue was crystallized from methanol. Filtration gave 23 mg (0.032 mmole, 58%) of white crystals of 3-isodeserpideine methiodide, mp 250–253° dec. An analytical sample was prepared by recrystallizing from methanol–water to give white clusters, mp 254–255° dec.

Anal. Calcd for $C_{22}H_{27}IN_3O_4$: C, 54.70; H, 5.43. Found: C, 55.02; H, 5.64.

Hydrogenation of 3-Isodeserpideine (VII). Exactly 32 mg of platinum oxide in 4 ml of 95% ethanol was reduced to platinum black in a microhydrogenation apparatus. To this mixture 100 mg (0.173 mmole) of 3-isodeserpideine in 7 ml of 95% ethanol was added, and the reduction was allowed to proceed for 15 hr. The catalyst was removed by filtration through very retentive filter paper (Schleicher and Schuell, No. 576), and the ethanol was removed under reduced pressure. A yellow amorphous solid weighing 92 mg remained which was extracted with 5% sodium carbonate and chloroform. The aqueous layer was acidified by adding cold concentrated hydrochloric acid, and a white precipitate formed. Filtration and drying gave 16 mg (64% yield) of a white crystalline compound that was shown to be 3,4,5-trimethoxybenzoic acid by its melting point (168–170°), mixture melting point (undepressed), and infrared spectrum. The chloroform layer was then extracted with dilute hydrochloric acid, and the chloroform layer was dried and evaporated. This left 10 mg of a neutral fraction that showed a amide peak in the infrared at 6.13 μ . The aqueous hydrochloric acid layer was basified and extracted with chloroform. The chloroform layer was dried and evaporated leaving 62 mg of a yellow solid. Addition of methanol caused crystallization to occur. Filtration and drying gave 12 mg (0.033 mmole, 20%) of a white crystalline material that was shown to be α -yohimbine methyl ether (XII) by melting point and mixture melting point (266–267° dec) and thin layer R_f values.⁶

Hydrogenation of Raujemidine (Ia). Exactly 39 mg of platinum oxide in 5 ml of 95% ethanol was reduced to platinum black in a microhydrogenation apparatus. To this mixture 200 mg (0.33 mmole) of raujemidine in 12 ml of 95% ethanol was added, and the hydrogenation was allowed to proceed for 72 hr. The catalyst was removed by filtering three times through very retentive filter paper (Schleicher and Schuell, No. 576). The solvent was removed under reduced pressure leaving 190 mg of a yellow amorphous solid. This solid was extracted with 5% sodium carbonate and chloroform. The aqueous phase was acidified with concentrated hydrochloric acid leaving a white precipitate. Filtration and drying of this precipitate gave 25 mg (0.118 mmole, 38%) of a white crystalline solid that was shown to be 3,4,5-trimethoxybenzoic acid by its melting point (168–170°), mixture melting point (undepressed), and infrared spectrum. The organic phase was evaporated and gave a yellow amorphous solid. This was subjected to preparative scale thin layer chromatography using chloroform:ethanol:acetone (90:6:4) as the solvent system and the band whose R_f values corresponded to reserpine (R_f 0.60) was removed. Elution of the compound from the silica gel and recrystallization of the eluted material gave 19 mg (9% yield) of pure reserpine (IIa) as

shown by infrared and nmr spectra, melting point, and mixture melting point.

Rate Studies. The rates of methiodide formation were determined by the method used previously,⁴ except for a few minor

changes. Instead of using 10 mg of sample, rates were determined on 3 mg of sample in the present study. The acetonitrile that was used was carefully distilled from CaH₂ and had an observed initial resistance of greater than 1,000,000 ohms.

Biosynthesis of Methylcyclopentane Monoterpenoids. I. *Skytanthus* Alkaloids^{1,2}

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Abstract: The biosynthesis of the steam-volatile *Skytanthus* alkaloids has been investigated by administering DL-mevalonate-2-¹⁴C and L-methionine-methyl-¹⁴C into the green stems of mature flowing *Skytanthus acutus* M. plants. Radioactivity from mevalonate-2-¹⁴C was incorporated into the alkaloid. Radioactivity from DL-lysine-2-¹⁴C was not incorporated, which indicates that lysine is not a precursor. Gas-liquid chromatographic analysis of the alkaloid fraction indicated that the natural oil contains a mixture of which about 90% is α -, β -, δ -, and dehydro-skytanthines. The amounts of these alkaloids vary with the parts of the plant, with roots containing most. Specific activities of the alkaloids derived from mevalonate-2-¹⁴C and methionine-methyl-¹⁴C also vary in different parts of the plant. At least four alkaloids of unknown structure which comprise about 10% of natural *Skytanthus* oil were detected. Chemical degradations on micro quantities of alkaloid to eliminate nitrogen and to determine the amount of radioactivity located in carbons 3, 4, 7, 9, and 10 were devised. It was found that L-methionine-methyl-¹⁴C was the precursor of the N-methyl group of β -skytanthine. The results of biosynthesis experiments using mevalonate-2-¹⁴C as a precursor provide evidence for the formation of skytanthine isomers *via*: (a) an isoprenoid pathway which involves randomization of the label between the terminal methyl carbon atoms of the monoterpene or monoterpene (i.e., geranyl pyrophosphate) intermediate in 1.3-year-old plants, and (b) an isoprenoid pathway which does not involve randomization of the label between the monoterpene terminal methyl carbon atoms in 3-year-old plants.

Natural oil of *Skytanthus acutus* M. contains a mixture of alkaloids of the rare monoterpene class. At least three skytanthine isomers (Figure 1: Ia, Ib, Id) and a dehydro-skytanthine (II) are produced by *Skytanthus acutus* M.^{4,5} *Skytanthus acutus* M. is native to the Atacama desert of Chile and owing to the characteristic shape of its seed pods is commonly referred to as "Goats-horn" by natives of the area. *Skytanthus* alkaloids have no known physiological activity, in contrast to most other methylcyclopentane monoterpene alkaloids, most of which possess biological activity. The biosynthesis of the *Skytanthus* alkaloids is of interest because they are terpenoid alkaloids⁴⁻⁹ and

because they may serve as a link to higher alkaloids.¹⁰⁻¹³

The structures of the *Skytanthus* alkaloids suggest that the piperidine nucleus of these molecules could arise from an isoprenoid precursor. The present evidence for the route of formation of the piperidine ring in plants is based largely on studies of the alkaloid biosynthesis of anabesine^{14,15} produced by tobacco, homostachydrine¹⁶ by alfalfa, and pipercolic acid¹⁷⁻²⁰ by various plants and microorganisms. These molecules are derived from lysine. In contrast, the piperidine ring of coniine and conhydrine, which are alkaloids of hemlock, appears to be formed from a poly- β -keto acid derived from four acetate units.^{21,22} Thus, if the piperidine ring of skytanthine is isoprenoid in origin, a third

(1) Supported in part by Research Grants GM-11144 and GM-08624 from the National Institutes of Health, U. S. Public Health Service, and GB-5607 from the National Science Foundation.

(2) A preliminary account of this work was presented at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 115C.

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ay for the formation of piperidine rings by plants
Leete²³ has recently reviewed the biosynthesis
piperidine ring.

results reported in this paper conclusively estab-
at the skytanthine isomers are of isoprenoid origin
that lysine is not involved in the biosynthesis.
onine was shown to be a precursor of the N-
l group.

Experimental Section

Isolation of Labeled Compounds. Mature, flowering
Skutanthus acutus M. plants 3 years old were used except for the
ment reported on 1.3-year-old plants. These plants were
in a greenhouse.

aqueous solution of the labeled compound was injected into
ns of a plant. After 4 days the plants were harvested and
into leaves, green stems, woody stems, and roots for analysis.
arts were stored in plastic bags at -15° until used.

Labeled Compounds Used. Chromatographically pure DL-
nic acid-2- 14 C (N,N'-dibenzylethylenediamine salt obtained
uclear Research Chemicals, Orlando, Fla., or New England
r Corp., Boston, Mass., was used.²⁴ Chromatography was
ned using Whatman No. 1 filter paper and 2-propanol-am-
n hydroxide-water (80:5:15) as the solvent. DL-Lysine-
with a specific activity of 0.6 mcurie/mole was purchased
Tracerlab-Keleket, Waltham, Mass., and L-methionine-
 14 C with a specific activity of 2.25 mcurie/mole was ob-
from Nuclear Research Chemicals, Orlando, Fla. The
acids were radiochemically pure as determined by paper
itography on Whatman No. 1 filter paper and development
enol saturated with water and 1-butanol-acetic acid-water
:15).

location of radioactivity was made with a Nuclear-Chicago
ph II paper strip scanner.

Isolation of Steam-Volatile Alkaloids. The frozen plant seg-
were cut into 0.5-in. pieces and ground with a mortar and
and the pH was adjusted to 10 with 4 N potassium carbonate.
mogenate was steam distilled until 300 ml of distillate was
ed. The distillate was acidified to pH 2 with concentrated
ad steam distilled. This latter steam-volatile fraction con-
the neutral material. The pH of the material in the steam
tion flask was adjusted to 10 with 4 N NaOH and the volatile
ds were steam distilled and collected. The neutral and basic
ns were saturated with sodium chloride and extracted with
ether. The ether layers were dried over anhydrous magnesium
, filtered, and concentrated by distillation. The concen-
which remained were each dissolved in a small amount of
laced in 1-ml volumetric flasks, and stored at -15° until used.

Chromatography. Analyses of the alkaloids by gas-liquid
atography were made on 0.125 in. \times 10 ft stainless steel col-
packed with 10% Carbowax 20M on 100-120 mesh base-
²⁵ Firebrick. The injector temperature was kept at 160°
e thermal conductivity detector cell at 230° . Peak areas
asured with a disc integrator²⁶ and the amounts represented
stimated by comparison with standard curves obtained with
r- and β -skytanthine and dehydroskytanthine. The pure
ds were obtained by preparative gas chromatography (0.375
10 ft column with the same packing as described above).

Isotope Analyses. Carbon-14 activity of the compounds ad-
red to the plants, the isolated alkaloids, and the products
d during chemical degradation of I β was determined using
di chromatography and/or liquid scintillation counting.^{27,28}
gas radiochromatography measurements were performed
Perkin-Elmer Model 801 gas-liquid chromatograph equipped
thermal conductivity detector and a Nuclear-Chicago Model
roportional gas flow counter. The total effluent from the
r was fed into the counting chamber through a heated inlet

E. Leete, *Science*, 147, 1000 (1965).

Preliminary experiments indicated that no difference in incorpo-
of carbon-14 was found when either the free acid or the salt was
s the precursor.

Washed three times with saturated methanolic KOH and once
H₂OH.

Disc Instruments, Inc., Santa Anna, Calif.

Tri-Carb, Model 314, Packard Instrument Co., La Grange, Ill.

K. S. Yang, R. K. Gholson, and G. R. Waller, *J. Am. Chem.*
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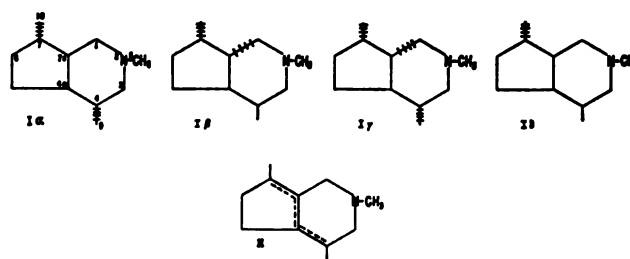


Figure 1. Structures of *Skutanthus* alkaloids. The Greek letters refer to isomers of skytanthine.^{4,6} II is dehydroskytanthine.

line. The inlet line and the gas counting chamber were held at
 250° . Peak areas were measured using a Nuclear-Chicago Model
8350 automatic integrator. The efficiency was 32% as calculated
from a reference standard of *n*-heptane-1- 14 C, specific activity
0.25 mcurie/ μ mole.

Chemical Degradation of β -Skytanthine (I β). Hofmann Deg-
radation of Skytanthine (I β) to the Amino Olefin IV. A 2.5-g
sample of β -skytanthine (I β), purified by preparative gas chroma-
tography on a 0.375 in. \times 10 ft column of alkali-treated Chromo-
sorb P coated with 15% Carbowax 20M, was dissolved in 15 ml
of absolute ethanol and 5 ml of methyl iodide was added. The
mixture was heated at reflux temperature for 6 hr. The reaction
mixture was cooled, ether was added to precipitate the methiodide,
and the precipitate was filtered out to give 3.5 g of β -skytanthine
methiodide, mp $293-295^{\circ}$ (lit.⁷ $296-298^{\circ}$). The methiodide, 3.5 g,
was dissolved in 200 ml of water and then stirred with freshly pre-
pared silver oxide.²⁹ The suspension was filtered, and the filtrate
was concentrated at $40-50^{\circ}$ under vacuum to give 3 g of oil. A
10- μ l sample of the N-methyl- β -skytanthine hydroxide (III) was
injected into the alkaline 20M Carbowax column. The injection
port, column, and detector temperatures were 200, 123, and 250° ,
respectively. Two peaks were observed, one corresponding to
recovered β -skytanthine (I β) and the other to the amino olefin IV.
The retention times were 16.5 and 12.5 min, respectively. The
amino olefin IV was purified by preparative gas chromatography
on the alkaline Carbowax 20M column with a yield of about 40%.
The infrared spectrum of IV showed bands at 3.26, 6.07, and 11.3 μ .

Amine Oxide Degradation of Amino Olefin IV. A 0.2-g sample
of IV was stirred with 1.5 g of 30% hydrogen peroxide for 16 hr
until a positive test for base using phenolphthalein was no longer
observed. The excess hydrogen peroxide was destroyed by stirring
with 24 mg of platinum oxide catalyst until lead sulfide treated
paper showed no reaction. The reaction mixture was filtered and
concentrated at $30-40^{\circ}$ under vacuum and then pyrolyzed. The
pyrolysis products were analyzed on the 0.375 in. \times 10 ft alkaline
Carbowax 20M column. Peaks were observed for N,N-dimethyl-
hydroxylamine VII (1.8 min), the diene VI (2.3 min), and un-
reacted IV and I β .

Ozonolysis of Amino Olefin IV. The amino olefin IV (0.6 g) in
ether was dissolved in 10 ml of acetic acid and treated at room
temperature for 15 min with oxygen containing ozone. The
ozone solution was transferred to a flask containing a solution
of 1 g of ferrous sulfate in 10 ml of water, and the reaction mixture
was stirred at room temperature for 30 min, heated for 30 min,
and immediately steam distilled into a solution of 0.4 g of dimedon
in 100 ml of water. The dimedon derivative was filtered out and
crystallized from hot aqueous methanol to give 0.022 g, mp $192-193^{\circ}$.
The purity of the dimedon derivative of formaldehyde was
tested by thin layer chromatography,³⁰ using benzene-ethanol-ac-
etate (1:1:4) as the solvent system for separation and 2,4-dinitro-
phenylhydrazine spray solution for detection.

The steam distillation pot residue was cooled, basified with
sodium hydroxide solution, and extracted several times with ether.
The ether extract was dried over anhydrous sodium sulfate and
filtered, and the ether was removed through a fractionating column
to give a concentrate containing the amino ketone VIII.

The amino ketone VIII (80 mg) was obtained by preparative gas
chromatography, using a 0.375 in. \times 10 ft aluminum column packed
with 15% Carbowax 20M loaded on base-washed 60-80 mesh

(29) The silver oxide was prepared from 7.0 g of silver nitrate in 70 ml
of water containing 1.7 g of sodium hydroxide by heating the resulting
suspension at 85° and washing free of alkali with hot water.

(30) Eastman Kodak Type K301 R Chromatogram sheet.

Chromosorb P. The temperatures of the column, injection port, and detector were 140, 200, and 250°, respectively. A gas pressure of 80 psi at a flow rate of 160 cc/min was used. The retention time of the amino ketone VIII was 31 min. VIII was further purified by thin layer chromatography, using silica gel G in 0.2 N sodium hydroxide solution for coating the glass plates and hexane-acetone-ethanol (4:1:1) as the solvent system with 1% iodine solution in methanol as a detecting spray. The infrared spectrum of VIII showed an absorption peak at 5.85 μ .

Peroxytrifluoroacetic Acid Oxidation of Amino Ketone VIII.¹⁷ Peroxytrifluoroacetic acid was prepared by adding 1.5 ml of trifluoroacetic anhydride to a stirred mixture of 0.4 ml of 90% H₂O₂ and 7.5 ml of methylene chloride and then stirring at room temperature for 30 min. This product was added dropwise over a period of 5 min to a well-stirred mixture containing 0.6 g of amino ketone VIII in 1 ml of ether and 0.4 g of sodium dihydrogen phosphate in 15 ml of methylene chloride. After addition of the peroxide, the reaction mixture was stirred at room temperature for 30 min and heated at reflux temperature for 1.5 hr. The reaction mixture was cooled and a concentrated solution of sodium sulfite added dropwise with stirring until no more gas was released. Water (10 ml) was then added and stirring continued for 30 min to ensure complete hydrolysis of any excess anhydride. The reaction mixture was basified with sodium hydroxide solution and extracted several times with methylene chloride. The methylene chloride extract was dried over anhydrous magnesium sulfate and filtered and the methylene chloride removed by fractionation to give 0.1 g of the amino acetate IX containing a trace of methylene chloride. The infrared spectrum of the amino acetate IX showed absorption peaks at 5.76 and 8.00 μ .

Saponification of the Amino Acetate IX. The amino ester IX (0.1 g) was added to 1 ml of 20% aqueous sodium hydroxide containing a few drops of methanol. The mixture was heated at reflux temperature for 30 min. The alkaline reaction mixture was cooled and extracted exhaustively with ether. This ether extract was dried over anhydrous sodium sulfate and then distilled to give 50 mg of the amino alcohol X which was purified by thin layer chromatography, using silica gel G in 2% sodium hydroxide solution for coating the glass plates, hexane-acetone-ethanol (2:1:1) as the solvent system, and 1% iodine solution in methanol as a detecting spray. The infrared spectrum of the amino alcohol X showed an absorption peak at 2.95 μ .

The alkaline residue remaining from the extraction of the amino alcohol X was acidified with 0.5 N sulfuric acid and steam distilled until 50 ml were collected. The steam distillate was neutralized using 0.07 N sodium hydroxide. The 10 mg of sodium acetate obtained on evaporation under reduced pressure was purified by chromatography on a Celite column.

Kuhn-Roth Oxidation of β -Skytanthine.²¹ β -Skytanthine (I β) (20 mg) was oxidized with Kuhn-Roth reagent by heating at reflux temperature for 90 min. The reaction mixture was steam distilled until 50 ml was collected, and the steam distillate was neutralized with 0.07 N sodium hydroxide. The 10 mg of sodium acetate obtained on evaporation under reduced pressure was purified by chromatography on a Celite column.

Preparation of Skytanthine-¹⁴C Used for Chemical Degradation. The alkaloids from the methionine-methyl-¹⁴C biosynthesis experiment were diluted 30-fold with pure β -skytanthine (I β) and degraded to give amino olefin IV, the diene VI, and dimethylhydroxylamine VII.

β -Skytanthine-¹⁴C formed from mevalonate-2-¹⁴C biosynthesis experiments was purified by preparative gas chromatography as previously described, diluted two- to fivefold with pure I β , and degraded as described above. A portion of diluted I β was degraded using the Kuhn-Roth oxidation procedure.

The specific activity of the diluted alkaloid was redetermined using gas radiochromatography and the liquid scintillation procedures described above.

Results²²

Distribution of Alkaloids. The distribution of α -, β -, and dehydro-skytanthine in mature *Skytanthus acutus* M. plants is shown in Table I. The roots contained about 5% of the total alkaloids. The β isomer pre-

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(32) Unless otherwise stated results and discussion are based on results obtained from 3-year-old plants.

dominated in all tissues. These three alkaloids constituted about 90% of the total alkaloids isolated. The remaining 10% of the alkaloid fraction was composed of at least four unknown alkaloids and δ -skytanthine; the structure of these unknown alkaloids is being investigated. It has been previously reported that natural skytanthine alkaloids are a mixture of three and possibly four diastereoisomers (α , β , γ , and δ).⁴ No γ isomer was found in this study; however, dehydro-skytanthine was found in all parts of the plant. Most of the δ isomer, which constitutes about 1% of the natural skytanthine alkaloids, was located in the roots.

Table I. Distribution of α -Skytanthine, β -Skytanthine, and Dehydro-skytanthine in Mature *Skytanthus acutus* M. Plants^{a, b}

Plant parts	α	—Skytanthus— alkaloids, %	
		β	Dehydro
Leaves	0.007	0.06	0.006
Green stems	0.007	0.03	0.009
Woody stems	0.006	0.03	0.02
Roots	0.018	0.13	0.07
Whole plant	0.033	0.25	0.105

^a Fresh-weight basis. ^b Three-year-old plants.

Alkaloid Biosynthesis. The results obtained using DL-lysine-2-¹⁴C, DL-mevalonate-2-¹⁴C, and L-methionine-methyl-¹⁴C are shown in Table II. The α -, β -, and dehydro-skytanthine alkaloids contained 0.56% of the administered carbon-14 from mevalonate-2-¹⁴C, none from lysine-2-¹⁴C, and 1.04% from methionine-methyl-¹⁴C. The incorporation of radioactivity from mevalonate-2-¹⁴C along with lack of incorporation from lysine-2-¹⁴C provides evidence that the carbon skeleton of skytanthine arises *via* an isoprenoid precursor rather than a pathway which involves lysine. These results confirm and extend the preliminary report of Casinovi and Marini-Bettolo²³ on the incorporation of radioactivity from mevalonate-2-¹⁴C into skytanthine produced by sterile excised roots of *Skytanthus acutus* M. A comparison of the specific activities of the skytanthine isomers produced in the various parts of the plant from mevalonate-2-¹⁴C and methionine-methyl-¹⁴C shows that the highest values were observed in the alkaloids isolated from the green stems. Most of the carbon-14 in the alkaloids is in the β isomer, which might be expected since it is present in the largest amount. The isotope dilution values, which are readily calculated from the specific activities, indicate that the least dilution occurs in the green stems for all three skytanthine isomers. The distribution of carbon-14 in α -, β -, and dehydro-skytanthine formed from mevalonate-2-¹⁴C was 13, 53, and 34%, respectively. Corresponding values from the methionine-methyl-¹⁴C experiment were 9.5, 74.0, and 12.1%. In the methionine-methyl-¹⁴C experiment 4.4% of radioactivity was found in an unknown alkaloid.²⁴

Chemical Degradation of β -Skytanthine (I β). A. Elimination of Nitrogen. The structure of the skytan-

(33) (a) C. G. Casinovi and G. B. Marini-Bettolo, Abstract Ab-3, IUPAC Meeting, London, 1963, p 285; (b) C. G. Casinovi, G. Giovannozzi-Sermanni, and G. B. Marini-Bettolo, *Gazz. Chim. Ital.*, **94**, 1356 (1964).

(34) Mass spectral data indicate that this unknown alkaloid has a molecular weight of 165, which corresponds to a dehydro-skytanthine

Table II. Incorporation of Carbon-14 from Labeled Compounds into α -, β -, and Dehydroskytanthine Alkaloids Produced by Mature *Skytanthus acutus* M. Plants^a

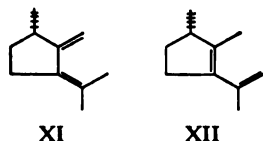
Compd admin (μ moles injected; sp act., μ curies/ μ mole)	Plant part	Skytanthus alkaloids					
		α isomer		β isomer		Dehydro	
		Yield, μ moles	Specific activity, μ curies/ μ mole	Yield, μ moles	Specific activity, μ curies/ μ mole	Yield, μ moles	Specific activity, μ curies/ μ mole
DL-Lysine-2- ¹⁴ C (85; 0.6)	Leaves	14	0	47	0	4	0
	Green stems	2	0	13	0	3	0
	Woody stems	8	0	117	0	20	0
	Roots	38	0	296	0	110	0
DL-Mevalonate-2- ¹⁴ C (21.4; 4.18)	Leaves	144	0.07	1250	0.04	123	0.07
	Green stems	128	0.17	562	0.23	179	0.29
	Woody stems	120	0.18	730	0.05	480	0.12
	Roots	358	0.04	2500	0.02	1410	0.04
L-Methionine-methyl- ¹⁴ C (60; 2.25)	Leaves	21	3.4	69	5.3	7	7.4
	Green stems	3	4.7	4	16.4	1	7.4
	Woody stems	9	0.9	41	5.7	14	1.0
	Roots	38	1.0	152	2.4	75	1.3

^a Three-year-old plants.

thine skeleton I was initially established by dehydrogenation to actinidine^{7,8} and by partial degradation to the amino olefin IV and the amino ketone VIII.⁷

The existence of three isomers of skytanthine ($I\alpha$, β , and δ) in *Skytanthus acutus* M., their structures, and their absolute configurations and stereochemistry were established by comparison with isomers of skytanthine obtained by partial synthesis from the nepetalinic acids of known absolute configuration and stereochemistry.^{4,5}

Despite these extensive studies, a nitrogen-free degradation product of skytanthine has not been reported. The reported degradation routes were extended to provide a series of molecules which would reveal location of carbon-14 incorporated into the skytanthine skeleton. The results show that when pure β -skytanthine ($I\beta$) is subjected to the Hofmann elimination reaction it is cleanly converted to the previously reported amino olefin IVa.^{7,25,26} The choice of the route to be used for complete removal of nitrogen from IVa was then between a second-stage Hofmann or an amine oxide elimination reaction. These methods were compared and both were found to give nitrogen-free diene. The amine oxide elimination from IVa via V was preferred because the resulting diene VI appeared to be a single product, whereas a conventional Hofmann elimination reaction of IVa proceeded to a mixture of dienes possibly having the structures XI and XII. This mix-



ture is to be expected in view of the well-known course of the Hofmann elimination of nitrogen from piper-

(35) Analysis of the methines produced in the reaction was made on the combination mass spectrometer-gas chromatograph (prototype of the LKB-9000) using a 0.25 in. \times 16 ft glass column packed with 20% Carbowax 20M on 100-120 mesh base-washed²⁸ Firebrick. The column conditions were 200° for injection port, 125° for the column, and a flow rate of 45 cc of He/min. The retention time of IVb was 21 min and that of IVa was 23 min. Quantitative estimation of the relative amounts of each methine was performed by planimetry. IVa comprised over 99% of the mixture.

(36) We are investigating the Hofmann elimination reaction as applied to δ -skytanthine ($I\delta$) to determine whether stereochemical alteration in the carbon skeleton of the skytanthine isomers affects the direction of elimination and whether more than one olefin is formed.

idine to give piperylene (1,3-pentadiene) rather than 1,4-pentadiene.

The paucity of starting material and lack of knowledge of the structure of skytanthine possibly prevented earlier workers from fully eliminating nitrogen from the skytanthine skeleton. In our hands, this was accomplished without difficulty and procedures (Figure 2) were developed so that complete nitrogen elimination could be carried out on a milligram scale.

The results presented in Table III show the distribution of label in the skytanthine alkaloids formed from L-methionine-methyl-¹⁴C. When the products of the degradation were analyzed by gas radiochromatography it was found that 47% of the radioactivity was in VI and 26 and 27% of the radioactivity was present as unreacted I and IV, respectively. The diene VI was completely devoid of radioactivity. These results provide conclusive evidence that the N-methyl group of the skytanthine alkaloids originated from the methyl group of methionine.

Table III. Distribution of Radioactivity in β -Skytanthine Biosynthetically Formed from L-Methionine-methyl-¹⁴C^a

Compd	Sp act., μ curie/ μ mole	%
β -Skytanthine ($I\beta$)	0.10	100
Methine (IV)	0.105	105
Diolefin (VI)	0	0
N,N-Dimethylhydroxylamine (VII)	...	100

^a Three-year-old plants.

B. Chemical Degradation of β -Skytanthine ($I\beta$) to Remove Carbons 3, 4, and 9. The previously reported degradation^{7,8} of the amino olefin IV to the amino ketone VIII and the amino alcohol X was utilized in obtaining techniques to provide suitable derivatives and degradation products for carbon-14 assay to locate the positions of radioactive labeling in $I\beta$.²⁶ The ozonolysis of amino olefin IV readily provided the amino ketone VIII and formaldehyde. The latter was isolated as the dimedon derivative, purified by recrystallization and thin layer chromatography to constant specific activity, and then counted to determine the carbon-14

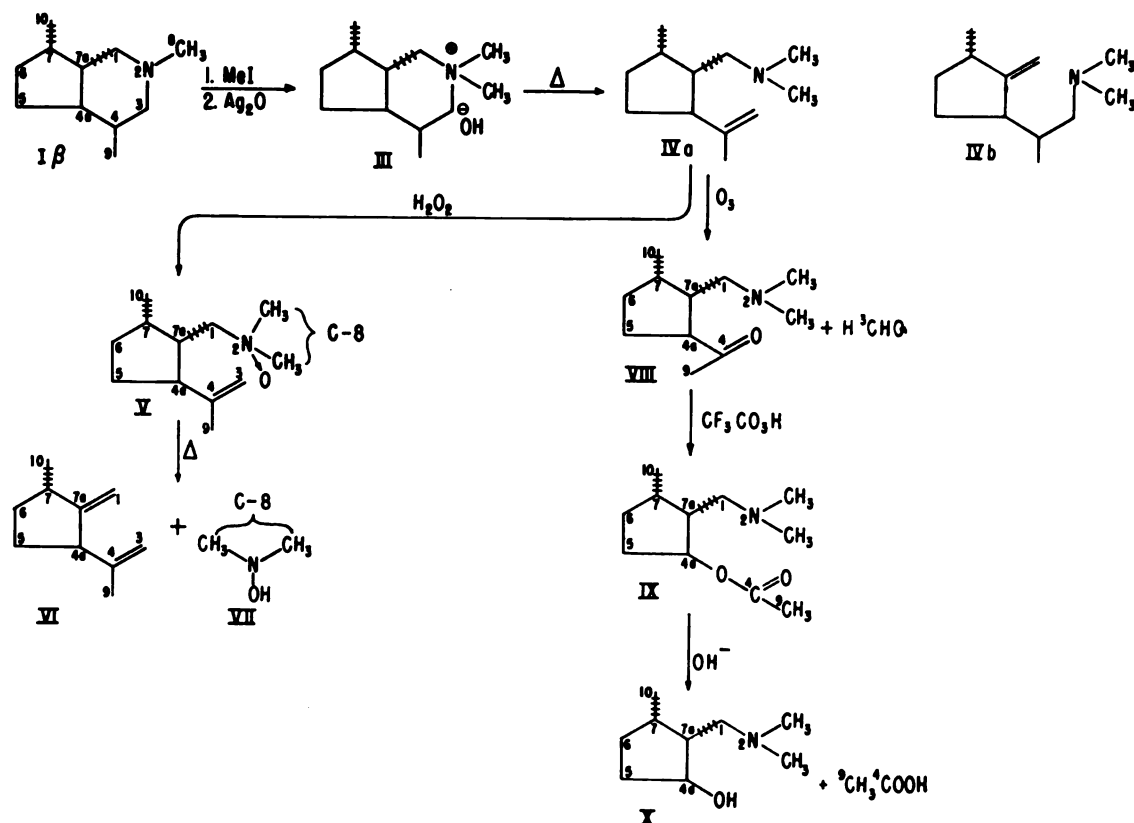


Figure 2. Chemical degradation of β -skytanthine to remove carbons 8, 3, 4, and 9.

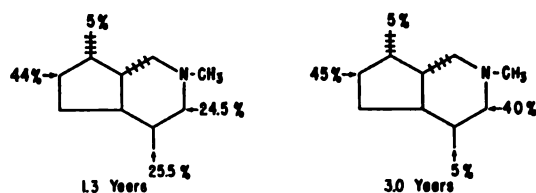


Figure 3. Labeling patterns of β -skytanthine biosynthesized by *Skytanthus acutus* plants from mevalonate-2- ^{14}C .

radioactivity at position 3 of $I\beta$. A conventional Baeyer-Villiger oxidation of the amino ketone VIII with peroxytrifluoroacetic acid³⁷ yielded the expected amino acetate IX which was hydrolyzed to the amino alcohol X and acetic acid. The acetic acid was isolated and used to determine the carbon-14 radioactivity of carbons 4 and 9 of $I\beta$.

The results presented in Table IV show the distribution of the label in β -skytanthine ($I\beta$) formed from mevalonate-2- ^{14}C using plants of two ages. The data reported in this table are the results of specific activity determinations made using the liquid scintillation method on weighed, purified samples of $I\beta$ and its derivatives. Gas radiochromatography experiments (3-year-old plants) on $I\beta$, IV, VIII, and X agree with the results obtained using liquid scintillation counting, but in general these were less reliable because of the low specific activities encountered. The dimedon derivative of formaldehyde and acetate were counted only by the liquid scintillation technique.

A Kuhn-Roth oxidation on the carbon-14-labeled amino alcohol X would provide information on the

(37) W. F. Sager and A. Duckworth, *J. Am. Chem. Soc.*, **77**, 188 (1955).

amount of radioactivity residing in carbons 7 and 10. Because insufficient carbon-14-labeled X was available, this degradation was applied directly to β -skytanthine- ^{14}C which yields acetate representing carbons 7 and 10 and 4 and 9.

Three-Year-Old Plants. Results from the chemical degradation indicated that carbon 3 contained 40% of the radioactivity present in the original β -skytanthine- ^{14}C ($I\beta$). The amino alcohol X and the sodium acetate formed from the amino ketone VIII had 49 and 5% of the radioactivity, respectively (Table IV). Results from the Kuhn-Roth oxidation on the original $I\beta$ are shown on the last line of Table IV and indicate that 5% of the carbon-14 resides in carbons 4 and 9 and 7 and 10. These data are interpreted to mean that about 10% of the original radioactivity present in β -skytanthine is present in carbons 4 and 9 and 7 and 10 (Figure 3).

Of the original activity present in β -skytanthine- ^{14}C , 94% (carbons 3, 4, 9, and the amino alcohol X) was recovered in these experiments (Table IV). These results combined with the results of the Kuhn-Roth oxidation of $I\beta$ provide convincing evidence for the nonrandomization of the carbon-14 label in β -skytanthine- ^{14}C formed from mevalonate-2- ^{14}C . In addition, a Kuhn-Roth oxidation was performed on α -skytanthine possessing a specific activity of 9.25 $\mu\text{curies/mmole}$. The sodium acetate obtained was found to possess a specific activity of 0.70 $\mu\text{curie/mmole}$, which indicates that 7.6% of the radioactivity was located in carbons 4 and 9 and 7 and 10.

16-Month-(1.3 years)-Old Plants. The degradation of β -skytanthine- ^{14}C from 1.3-year-old plants yielded entirely different results than were obtained with 3-year-

Distribution of Radioactivity in β -Skytanthine Biosynthetically Formed by *Skytanthus acutus* on Mevalonate-2- ^{14}C

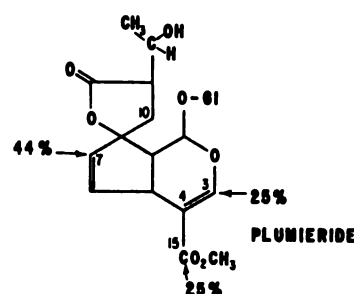
Compound	β -Skytanthine carbon atom	3 years old		1.3 years old	
		Sp act., $\mu\text{curies/mmole}$	%	Sp act., $\mu\text{curies/mmole}$	%
β -Skytanthine (I β)	All	8.87	100	5.63	100
Methine (IV)	All	8.7	98	5.70	101
Ketone (VIII)	All but 3	5.1	57	4.25	75.5
HCHO (dimedon deriv)	3	3.5	40	1.37	24.4
Amino alcohol (X)	All but 3, 4, and 9	4.3	49
Sodium acetate (from VIII)	4 and 9	0.41	5
Sodium acetate (from I β)	4 and 9, also 7 and 10	0.41	5	0.77	13.7

nts (Table IV). Owing to the limited quantity of β -skytanthine- ^{14}C , chemical degradation could be carried beyond the formation of the amino VIII and the dimedon derivative of formaldehyde (carbon 3). The results indicate that 24% of the radioactivity is located in carbon 3. Sodium acetate obtained from the Kuhn-Roth oxidation of the β -skytanthine contained about 14% of the radioactivity in the alkaloid. A theoretical value of 15% radioactivity would be expected to be found in sodium acetate if, in the original β -skytanthine- ^{14}C , the radioactivity was located in carbon 9 and carbon 10 (this is assuming that the acetate obtained from the Kuhn-Roth oxidation of I β is formed in amounts from carbons 4 and 9 and 7 and 10). On the other hand, if carbons 9 and 10 each contained the radioactivity, then the acetate obtained from Kuhn-Roth oxidation would be expected to contain 15% of the radioactivity. If these carbons contained the radioactivity present originally, then the acetate obtained would be expected to contain 5% of the radioactivity also. The fact that the acetate contained 14% of the radioactivity provides evidence that one of carbons 9 and 10 contained about 25% and the other contained about 5% of the original radioactivity present in β -skytanthine- ^{14}C . To further support this view, a Kuhn-Roth oxidation of dehydroskytanthine- ^{14}C (obtained from the same biosynthesis experiment) possessed a specific activity of 41.0 $\mu\text{curies/mmole}$ was obtained and sodium acetate possessing a specific activity of 6.10 $\mu\text{curies/mmole}$ corresponding to 15% of the radioactivity originally found in II, was obtained. These data and the data shown in Table IV support the conclusion that about 25% of the radioactivity originally present in β -skytanthine- ^{14}C (I β) is located in carbon 9 and that 5% is located in carbon 10. It would then appear that in the young, growing *Skytanthus acutus* M. plants, randomization of the methyl label from mevalonate-2- ^{14}C at the monoterpene level occurs when the two terminal methyl groups were labeled (i.e., geraniol, geranyl pyrophosphate, or methylcyclopentane monoterpene intermediate). A comparison of the different labeling patterns in β -skytanthine- ^{14}C (I β) biosynthesized from mevalonate-2- ^{14}C using 1.3-year-old and 3-year-old *Skytanthus acutus* M. plants is shown in Figure 3.

Discussion

It is of interest to compare these results with those obtained by Yeowell and Schmid.³⁸ Results from A. Yeowell and H. Schmid, *Experientia*, 20, 250 (1964).

chemical degradation of plumieride formed biosynthetically from mevalonate-2- ^{14}C showed that randomization occurred between carbon atoms 3 and 15 (25% of the radioactivity residing in each), and that carbon 7 contained 44%. It can be assumed that



carbon atom 10 would contain about 6% of the radioactivity, which is in agreement with our finding on β -skytanthine. Yeowell and Schmid³⁸ suggested that randomization might occur after ring closure of the cyclopentanoid ring and that carbon atoms 3 and 15 might be equivalent aldehyde groups. Randomization of the terminal methyl label in the isoprenoid portion of certain indole alkaloids has also been reported,³⁹⁻⁴¹ and the proposed mechanisms are similar to that suggested for plumieride. These data are also supported by labeling experiments using geranyl pyrophosphate-2- ^{14}C ^{42,40-43} and geraniol-2- ^{14}C .⁴²⁻⁴⁴ For a review on methylcyclopentane monoterpene intermediates in the biosynthesis of indole alkaloids see Taylor.¹² It seems logical that randomization might occur at the monoterpene level in these compounds since carbon 15 of plumieride is further oxidized to a carboxylic acid group and this biological oxidation might be expected to proceed in a stepwise direction involving alcohol, aldehyde, and finally acid. In skytanthine carbon atom 9 (equivalent to carbon 15 of plumieride) remains as a methyl carbon, and the chance for randomization of label via a similar type of intermediate involving methyl groups as carbon atoms 3 and 9 exists at the geraniol or geranyl pyrophosphate state in β -skytanthine biosynthesis. In contrast to the experiments showing the occurrence of randomization, the

(39) F. McCapra, T. Money, A. I. Scott, and I. G. Wright, *Chem. Commun.*, 1, 537 (1965).

(40) H. Goeggel and D. Arigoni, *ibid.*, 1, 538 (1965).

(41) A. R. Battersby, R. T. Brown, R. S. Kapil, A. O. Plunkett, and J. B. Taylor, *ibid.*, 2, 47 (1966).

(42) A. R. Battersby, R. T. Brown, J. A. Knight, J. A. Martin, and A. O. Plunkett, *ibid.*, 2, 346 (1966).

(43) P. Loew, H. Goeggel, and D. Arigoni, *ibid.*, 2, 347 (1966).

(44) E. S. Hall, F. McCapra, T. Money, K. Fukumoto, J. R. Hanson, B. S. Mootoo, G. T. Phillips, and A. I. Scott, *ibid.*, 2, 348 (1966).

results obtained by Birch, *et al.*,⁴⁵ from the incorporation of mevalonate-2-¹⁴C into the terpenoid side chain of mycelianamide indicated that 80% of the radioactivity was not randomized, and it was suggested that the degree of randomization observed was more likely a result of the chemical degradative procedure than of a lack of specificity during biosynthesis. It is possible that the extent of randomization which can occur on the appropriate intermediate (*i.e.*, geranyl pyrophosphate) is subject to control at the enzyme level and by the pool size of the substrate. Insufficient knowledge exists on both of these points to permit a definite conclusion.

There may be several possible types of enzymatic control. For example, different enzyme inhibitors or different levels of enzyme may be present in the old and young plants. Also, it may be possible that the particular enzyme responsible for randomization of the monoterpenoid intermediate does not exist in the old plant. An analogous situation is known to occur in the rapid appearance and disappearance of diamine oxidase in pea seedlings.⁴⁶ Control by the substrate pool size can best be visualized by considering that the young plant has a rather large pool of monoterpenoid intermediate and that the two terminal methyls become equivalent. In the old plant perhaps only a small pool of monoterpenoid intermediate exists, and this substrate is immediately utilized in the biosynthesis and does not remain long for randomization of the methyl carbons to occur.

An alternative explanation, although remote, to the finding of randomization of label in the 1.3-year-old plant is the possibility of incorporation of mevalonate-

U-¹⁴C which has been formed by degradation of the administered mevalonate-2-¹⁴C to ¹⁴CO₂, which, in turn, is reincorporated *via* CO₂ fixation. The results recently reported by Battu and Youngken⁴⁷ suggest that degradation of mevalonate to CO₂ and reincorporation of the latter into monoterpenes of *Mentha piperita* can occur.

Our data also support the mechanism of isomerization of isopentenyl pyrophosphate proposed first by Agranoff, *et al.*,⁴⁸ and later established by Shah, *et al.*⁴⁹ In this mechanism, the methylene carbon atom of isopentenyl pyrophosphate is protonated, the proton from carbon atom 2 is discharged into the medium, and dimethylallyl pyrophosphate is formed. In the reverse reaction, a proton is added stereospecifically at carbon atom 2 of dimethylallyl pyrophosphate. Hence this isomerization does not result in a randomization of label originally present in the methylene group of isopentenyl pyrophosphate.

The metabolic relationship of mevalonate-2-¹⁴C and β -skytanthine-¹⁴C (1 β) in 1.3-year-old plants and 3.0-year-old plants has been examined and this compound has been implicated in the biosynthesis of skytanthine by *Skytanthus acutus* M. The pathway for the biosynthesis of skytanthine isomers is not well understood. The contrast in our finding of randomization of label in β -skytanthine formed from mevalonate-2-¹⁴C in 1.3-year-old plants with that of nonrandomization of label in 3.0-year-old plants requires additional study before its significance can be determined. Variation in an enzymatic reaction mechanism due to age appears to be a new phenomenon.

(47) R. G. Battu and H. W. Youngken, *Lloydia*, **29**, 360 (1966).

(48) B. W. Agranoff, H. Eggerer, U. Henning, and F. Lynen, *J. Biol. Chem.*, **235**, 326 (1960).

(49) D. H. Shah, W. W. Cleland, and J. W. Porter, *ibid.*, **240**, 1946 (1965).

(45) A. J. Birch, M. Kocor, N. Sheppard, and J. Winter, *J. Chem. Soc.*, 1502 (1962).

(46) R. H. Kenton and P. J. G. Mann, *Biochem. J.*, **50**, 360 (1952).

Communications to the Editor

Reactions of Vapor-Produced *t*-Butyl Carbonium Ion Injected into Liquid Isobutylene

Sir:

The reactions of specific, highly reactive hydrocarbon ions in the liquid phase are difficult to study directly. Ions may be produced in the liquid by direct liquid radiolysis, but the situation is complicated because many other reactive species such as electrons, radicals, and excited molecules are produced simultaneously. This complex situation may be simplified by producing specific ions in the vapor phase and injecting them by means of an electric field into a liquid or solid matrix. Under such conditions the positive ion is separated from its concomitant electron and is accelerated into the liquid or solid alone. To achieve this we describe a successful experimental method which is based on previous experiments by Schlag and Sparapany.^{1,2}

(1) E. W. Schlag and J. J. Sparapany, *J. Am. Chem. Soc.*, **86**, 1875 (1964).

(2) J. J. Sparapany, *ibid.*, **88**, 1357 (1966).

By this method we have studied the liquid phase reaction of *t*-butyl carbonium ion with isobutylene to form C₈ carbonium ions and their subsequent neutralization reactions.

The apparatus has been described.³ A krypton resonance lamp^{4,5} with intensity of greater than 10¹⁵ quanta/sec ionizes research grade isobutylene in the vapor phase. An electric field at right angles to the photon beam drives the positive ions into a detachable arm containing liquid isobutylene. The liquid arm of the cell extends into a dewar and is thermostated with a cold nitrogen gas stream; the temperature may be varied by changing the flow rate. A voltage of 400 v was applied to the external electrodes during photolysis. At -128° the per cent conversion of isobutylene was linear beyond 120 min of photolysis time; the conversion rate was 0.01%/min. Gas chromatography showed

(3) L. Kevan, J. Zimbrick, and N. S. Viswanathan, Annual Summary Report AFRPL-TR-66-359, Nov 1966, p. 76.

(4) H. Okabe, *J. Opt. Soc. Am.*, **54**, 478 (1964).

(5) L. J. Stief and R. J. Mataloni, *Appl. Opt.*, **4**, 1674 (1965).

that C_8 and C_{12} compounds comprised all detectable products; no products between C_8 and C_{12} were observed. Material balance calculations showed that the C_8 and C_{12} compounds detected constituted over 95% of the reacted isobutylene. In several experiments the polarity of the electric field was reversed. With reversed polarity no products were observed; also, direct photolysis of isobutylene vapor at 5 torr produced no detectable C_8 or C_{12} products. These results support our contention that the positive ions are reacting in the liquid phase.

The C_8 products were analyzed on a $AgNO_3$ -benzyl cyanide gas chromatographic column, which discriminates between alkenes and alkanes, and on an SE-30 column, which discriminates according to boiling point. The compounds were identified by retention-time comparison on both columns with C_8 standards from Chemical Samples Co., and identification was confirmed in part by mass spectrometry. Table I summarizes the products found at -128° ; it will be seen that the individual C_8 isomers reveal the probable structure of the C_8 carbonium ions and how they are neutralized.

Table I. Relative Yields of C_8 and C_{12} Products from $t-C_4H_9^+$ Reaction with Liquid Isobutylene^a

Product	Yield, %
Relative Total Products	
C_8 products	73 ± 6
C_{12} products	27 ± 4
Relative C_8 Products	
2,2,4-Trimethylpentane	4.5 ± 1.0
2,4,4-Trimethylpentene-2	48.4 ± 4.8
2,2,3-Trimethylpentane	19.8 ± 1.1
3,4,4-Trimethylpentene-2	27.3 ± 3.8

^a 120-min photolysis, -128° .

The krypton resonance lamp emits photons at 1236 Å (10.0 eV) and 1165 Å (10.6 eV) with relative intensities of 1.00 and 0.28, respectively.⁶ The ionization potential of isobutylene is 9.4 eV, and the lowest appearance potential for a fragment ion from isobutylene is 11.3 eV ($C_4H_9^+$).⁷ Therefore the only ion produced is the parent $C_4H_9^+$. Under our experimental pressure (0.05 torr) and nominal electric field (70 v/cm), we calculate that the $C_4H_9^+$ ion will make one or two collisions with isobutylene to form mainly $t-C_4H_9^+$ as shown by mass spectrometry⁸⁻¹⁰ before reaching the liquid. The electron released may gain sufficient energy in the electric field to cause ionization and fragmentation. However, variation of the nominal electric field produces no change in product distribution, so such electron fragmentation does not seem to be significant. We conclude that most of the ions striking the liquid are $t-C_4H_9^+$ with some unreacted $C_4H_9^+$ also present.

$t-C_4H_9^+$ can react with the two double-bonded carbons in isobutylene. Reaction with the terminal carbon in isobutylene gives a 2,2,4-trimethylpentyl carbonium ion. This yields the correct carbon skeleton for the major product. There are two basic neutral-

ization reactions for the C_8 carbonium ions: one is hydride transfer to the carbonium ion to yield an alkane plus $C_4H_9^+$, and the other is proton transfer from the carbonium ion to give an alkene plus $C_4H_9^+$. Both the 2,2,4 alkene and alkane are observed, but their relative abundances show that proton transfer predominates by 10:1. This selectivity is probably associated with the stability of the product $C_4H_9^+$; it also demonstrates that we can obtain relative rates of ion-molecule reactions in certain liquids.

The other two C_8 products indicate somewhat surprisingly that $t-C_4H_9^+$ also reacts at the tertiary carbon in isobutylene. This yields a 2,2,3,3-tetramethylbutyl primary carbonium ion which is expected to rearrange rapidly to give the tertiary 2,2,3-trimethylpentyl structure. Proton transfer from and hydride transfer to this carbonium ion lead to the observed 3,4,4 alkene and 2,2,3 alkane, respectively. For this carbonium ion the results show that proton transfer again predominates, but only by 2:1.

It is interesting to point out that the total reactivity of $t-C_4H_9^+$ at both the primary and tertiary carbons in isobutylene is about 50%. Since $t-C_4H_9^+$ shows so little selectivity in this situation, it may well be excited. We are presently studying the effects of electric field and temperature to gain more insight into this possibility. We are also investigating other liquid-phase ion-molecule reactions by this new technique.

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Evidence for Trapped Dielectrons in Ice

Sir:

Electrons produced by γ radiation are trapped in hydroxide ices at 77°K. The trapped electron, e_t^- , is characterized by an epr singlet at $g = 2.001$,¹ a broad absorption band with a maximum at 5850 Å,² and a hydroxide anion vacancy trapping site.³ We have found that at high radiation doses e_t^- reacts to form a diamagnetic species which we believe to be best described as a dielectron, e_2^{2-} , or two electrons trapped in the same hydroxide anion vacancy.

Frozen solutions of 10.0 and 6.0 M NaOH were γ irradiated at 77°K with Co^{60} . The yields of e_t^- and O^- were measured by epr under conditions where power saturation was absent. The results as a function of radiation dose are shown in Figure 1.

The e_t^- yield saturates at about 2 Mrads in both 6 and 10 M NaOH, and the saturation yield in 6 M NaOH is proportionately less than in 10 M NaOH. The striking result is the decrease in the e_t^- yield above 8 Mrads; the optical absorption band shows a similar decrease. Since the O^- yield continues to increase over the entire dose range, and since no new para-

(1) B. G. Ershov, A. K. Pikaev, P. Ya. Glazunov, and V. I. Spitsyn, *Dokl. Akad. Nauk SSSR*, **149**, 363 (1963).

(2) D. Schulte-Frohlinde and K. Eiben, *Z. Naturforsch.*, **17a**, 445 (1962); **18a**, 199 (1963).

(3) L. Kevan, *J. Am. Chem. Soc.*, **87**, 1481 (1965).

(6) J. R. McNesby and H. Okabe, *Advan. Photochem.*, **3**, 157 (1964).

(7) F. H. Field and J. L. Franklin, "Electron Impact Phenomena," Academic Press Inc., New York, N. Y., 1957, Table 45.

(8) V. L. Talroze and A. K. Lyubimova, *Dokl. Akad. Nauk. SSSR*, **86**, 909 (1952).

(9) R. Fuchs, *Z. Naturforsch.*, **16a**, 1026 (1961).

(10) I. Koyano, *J. Chem. Phys.*, **45**, 706 (1966).

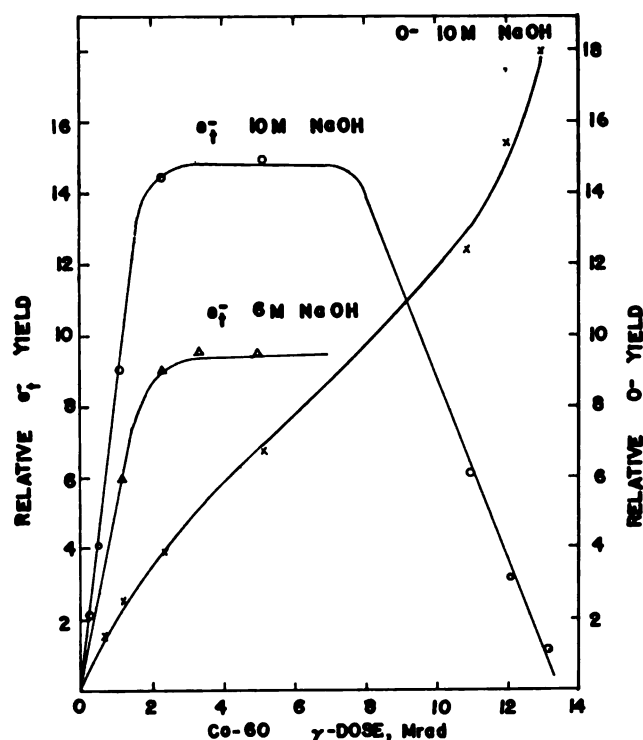
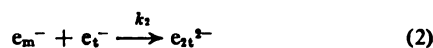


Figure 1. Relative e_t^- and O^- yields as a function of γ radiation dose in alkaline ices at 77°K.

magnetic species are observed, the e_t^- must react above 8 Mrads with a species other than O^- to form a diamagnetic species.

A plausible explanation for the dose saturation behavior is suggested by considering reactions which can compete with the trapping reaction for radiation-produced mobile electrons, e_m^- . The trapping reaction is shown by (1) where T denotes an available trap for e_m^- , and possible competing reactions for e_m^- are given by (2) and (3).



From the dose saturation data for 6 and 10 M NaOH, it is seen that the number of traps available in the system is proportional to $[OH^-]$. Reaction 3 involving the radiation-produced hole, $(H_2O)^+$, predicts that the dose saturation yield should be independent of $[OH^-]$ and that the dose at which saturation occurs should depend on $[OH^-]$. Neither prediction is observed experimentally, so reaction 3 does not explain the results.

The formation of e_{2t}^{2-} by reaction 2 is consistent with our results. The onset of dose saturation occurs when a specific fraction of the available traps are filled; hence it is independent of $[OH^-]$. At low doses, $k_1[T] \gg k_2[e_t^-]$; saturation occurs when $k_1[T] = k_2[e_t^-]$; and for $k_2 > k_1$, $[e_t^-]$ decreases at high doses.

In an e_{2t}^{2-} center we expect that the second electron would be bound more weakly than the first electron. In this case thermal dissociation could lead to $e_{2t}^{2-} \rightarrow e_t^-$. We searched for this reaction by warming colorless spheres of 10 M NaOH that had been irradiated to 15 Mrads at 77°K and showed no epr spectrum due to

e_t^- . Above 120°K a blue color was observed to appear; this was trapped by suddenly recooling to 77°K. Both the epr line and optical band of e_t^- were then observed for the warmed samples. We believe this experiment conclusively demonstrates the existence of e_{2t}^{2-} .

The direct analogy of e_{2t}^{2-} in hydroxide ices is the F' center in irradiated alkali halides.⁴ The F' center consists of two electrons trapped in the same halide ion vacancy; it is diamagnetic, has broad optical absorption in the near-infrared, can be thermally dissociated to yield the F center which is analogous to e_t^- , and can be produced by optical bleaching of the F center. Symons and co-workers⁵ have studied optical bleaching of e_t^- and indeed find a new, broad absorption in the near-infrared, although no maximum could be observed. This observation is additional evidence for e_{2t}^{2-} .

The binding of two electrons in the same anion vacancy can be understood qualitatively as follows. The wave function of e_t^- extends over a greater volume than that of the OH^- which it replaces; consequently, there will be a small potential well in the e_t^- volume which can bind a second electron. This argument implies that the second electron is bound more weakly than the first. Vinetskii and Gitterman⁶ have calculated the interaction of two electron centers in a dielectric medium. They find a minimum in the potential curve at an ~ 4 -Å separation between the two electrons. The radius of the e_t^- charge distribution has been previously estimated as 3–4 Å from experimental data.³ Hence the existence of e_{2t}^{2-} seems compatible with the approximate theoretical calculations.

Acknowledgment. This research was generously supported by the Air Force Rocket Propulsion Laboratory and the U. S. Atomic Energy Commission. This is AEC Document No. COO-1528-11. J. Z. is grateful to the U. S. Atomic Energy Commission for an Advanced Health Physics Fellowship and to Professor F. E. Hoecker for his cooperation. We thank Professor R. N. Adams for making available the epr equipment and Professor R. Friauf and D. Renneke for helpful discussions.

(4) J. H. Schulman and W. D. Compton, "Color Centers in Solids," The Macmillan Co., New York, N. Y., 1962, pp 107–112.

(5) M. J. Blandamer, L. Shields, and M. C. R. Symons, *J. Chem. Soc.*, 4352 (1964).

(6) V. L. Vinetskii and M. Sh. Gitterman, *Soviet Phys. JETP*, **6**, 560 (1958); see also J. Jortner, S. A. Rice, and E. G. Wilson in "Metal Ammonia Solutions," W. A. Benjamin, Inc., New York, N. Y., 1964, p 245.

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Molecular Orbital Symmetry Conservation in Transition Metal Catalyzed Transformations

Sir:

Woodward and Hoffmann have published a series of communications extending simple molecular orbital theory into the area of reaction chemistry.¹ This

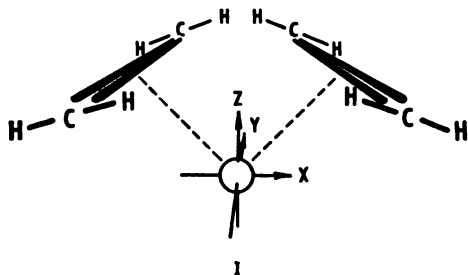
(1) (a) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395, 2511, 4389 (1965); (b) *ibid.*, **87**, 2046 (1965); (c) *ibid.*, **87**, 4388 (1965); (d) see also H. C. Longuet-Higgins and E. W. Abrahamson, *ibid.*, **87**, 2045 (1965); and K. Fukui, *Tetrahedron Letters*, 2009 (1965).

fresh approach to understanding reacting systems underlines a fundamental concept which correlates, with respect to symmetry, the molecular orbitals of reactants with those of products. The Woodward-Hoffmann postulate, dividing molecular transformations into "allowed" and "forbidden" categories, has proven a powerful tool for understanding a large body of complex chemistry. This communication extends the concept of symmetry conservation into transition metal catalysis.

Bicyclo[2.2.1]hepta-2,5-diene undergoes smooth dimerization to cyclobutane derivatives in the presence of zerovalent Fe,² Ni,^{3a-c} and Co⁴ catalysts, and tetracyclo[2.2.1.0^{2,6}.0^{3,5}]heptane (quadricyclene) has recently been reported to undergo a facile valence isomerization to bicyclo[2.2.1]hepta-2,5-diene catalyzed by various noble metal complexes.⁵ Since, in the metal-free system, a mechanism involving a concerted molecular transformation in these reactions is strictly forbidden by the Woodward-Hoffmann rules,^{1b} the role of the transition metal catalysts invites examination.

The concerted fusion of two olefins to a ground-state cyclobutane ring requires the introduction of two electrons into the olefin AS orbital and the removal of two electrons from the olefin SA orbital (A = anti-symmetric; S = symmetric).^{1b} A transition metal system containing d orbitals of sufficient energy and possessing the appropriate number of d electrons can, conceivably, carry out these operations. We propose a mechanism for metal-catalyzed cycloaddition in which the metal orbitals combine with the olefin orbitals, giving a set of occupied molecular orbitals of the symmetry required for an allowed reaction path.

Consider the metal-diolefin complex I. For the



concerted cyclobutanation, the elements of symmetry are the ZX and YZ planes. The symmetry classifications of the π -orbital combinations of I (C_{2v}) are the same as those reported for the uncatalyzed reaction.^{1b} These orbitals interact with combinations of metal atomic orbitals as follows: SS (a_1) with metal s, p_z , d_{z^2} , and $d_{x^2-y^2}$; SA (b_1) with metal p_x and d_{xz} ; AS (b_2) with metal p_y and d_{yz} ; AA (a_2) with metal d_{xy} . Metal orbitals of the appropriate energy could combine with the olefin orbitals yielding a set of new molecular orbitals of the same symmetry classification; bonding between the metal and the olefin, then, could result with electronic population of the bonding molecular orbitals.

(2) C. W. Bird, D. L. Colinese, R. C. Cookson, J. Hudec, and R. O. Williams, *Tetrahedron Letters*, 373 (1961); P. W. Jolly, F. G. A. Stone, and K. Mackenzie, *J. Chem. Soc.*, 6416 (1965).

(3) (a) C. W. Bird, R. G. Cookson, and J. Hudec, *Chem. Ind. (London)*, 20 (1960); (b) G. N. Schrauzer and S. Eichler, *Chem. Ber.*, 95, 2764 (1962); (c) L. G. Cannell, U. S. Patent 3,258,502 (1966).

(4) D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Am. Chem. Soc.*, 87, 2596 (1965).

(5) H. Hogeveen and H. C. Volger, *ibid.*, 89, 2486 (1967).

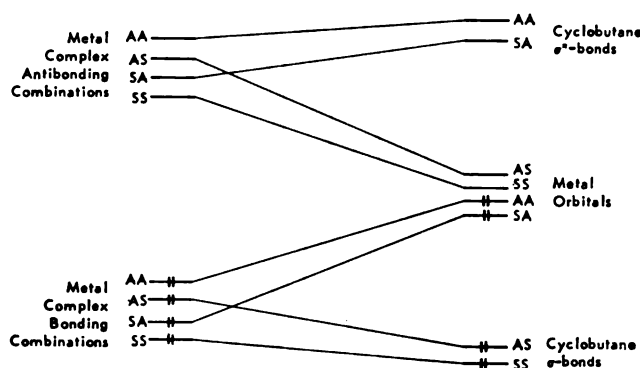


Figure 1.

A correlation diagram for the cyclobutanation of the ligand-bound olefins is illustrated in Figure 1, which describes an orbital pathway for the placement of electron pairs into the cyclobutane σ bonds and for the removal of the appropriate olefin π electrons. In this process, the electron density in the AS and SA orbitals of the complex is redistributed; in the AS orbital, electron density shifts into the incipient cyclobutane σ bond while in the SA orbital, electron density is localized in the metal d_{xz} orbital. This can be envisaged as a change in ligand-to-metal bonding as the system moves across the reaction coordinate. Ring closure draws the olefin SA combination sharply upward in energy, thereby diminishing the ligand-to-metal orbital mixing and increasing the electron density in the d_{xz} orbital. The olefin AS orbital, rehybridizing to a σ bond, undergoes an increase in electron density with diminished metal d_{yz} orbital mixing. An electronically excited product can conceivably result depending on the nature and geometry of the metal system, but, given the general ordering of orbitals pictured in Figure 1, a reaction path to a ground-state cyclobutane ligand exists. This simple description is supported by extended Hückel molecular orbital calculations⁶ carried out on the cyclobutanation of two olefin ligands attached to nickel dicarbonyl, a system reported to cyclobutanize bicyclo[2.2.1]hepta-2,5-diene.^{3a} The calculations yielded correlation diagrams describing the allowed transformation.⁷

Other transition metal catalyzed reactions suggest metal participation of this sort. The nickel-catalyzed conversion of acetylene to cyclooctatetraene, the Reppe synthesis,⁸ is an example. In a close examination of this reaction, Schrauzer has favored a concerted mechanism in which the four σ bonds of the cyclooctatetraene are formed essentially simultaneously.⁹ Since the isolated transformation is thermally forbidden,^{1b} such a mechanism suggests the electronic participation by the metal. The molecular orbital symmetry aspects of this reaction were examined using as a model the structure II proposed by Schrauzer.⁹

The four π orbitals of the acetylene ligands in II can be treated as two sets, each containing a pair of

(6) R. Hoffmann, *J. Chem. Phys.*, 39, 1397 (1963).

(7) Orbital functions were taken from E. Clementi and D. L. Raimondi, *ibid.*, 38, 2686 (1963); J. W. Richardson, W. C. Nieuwpoort, R. R. Powell, and W. R. Edgell, *ibid.*, 36, 1057 (1962); J. W. Richardson, R. R. Powell, and W. C. Nieuwpoort, *ibid.*, 38, 796 (1963); H. Basch, A. Viste, and H. B. Gray, *ibid.*, 44, 10 (1966).

(8) W. Reppe, O. Schlichting, K. Klager, and T. Towpel, *Ann. Chem.*, 560, 1 (1948).

(9) G. N. Schrauzer, *Angew. Chem. Intern. Ed. Engl.*, 3, 185 (1964).

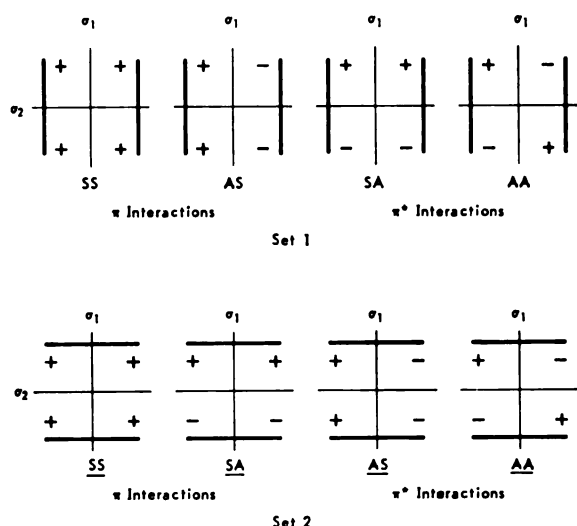
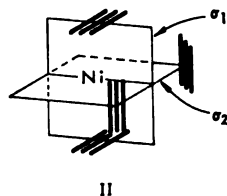


Figure 2.

π orbitals (Figure 2). The ligands seated at the corners of σ_2 comprise set 1 and the ligands positioned on the edges of σ_1 constitute set 2. The members of each set



interact yielding the following combinations. Orbitals in set 1 will interact with orbitals in set 2 of the same symmetry yielding a new set, half the members of which are bonding in the region of space between the sets and the other half antibonding. The SS and SS orbitals, for example, combine giving two orbitals, both of SS symmetry, one bonding in the region of the incipient cyclooctatetraene σ bonds and the other antibonding in that region. The four bonding members of the final set correspond in symmetry to the incipient σ bonds of cyclooctatetraene. If the interaction between the orbitals of the metal system and the olefin combinations results in the electronic population of these four molecular orbitals, then an orbital pathway to the concerted cycloaddition exists.

The application of symmetry conservation concepts to the selected reactions¹⁰ introduces a novel mechanism involving a role for the transition metal unique in catalysis. The results suggest that certain metal systems containing orbital configurations of the prerequisite energy are capable of rendering otherwise forbidden cycloaddition reactions allowed by providing a template of atomic orbitals through which electron pairs of transforming hydrocarbon ligands and metal systems can interchange and flow into the required regions of space.

Acknowledgment. We are grateful to Drs. J. Merritt, F. S. Mortimer, Isaac Dvoretzky, and J. H.

(10) Electronic involvement by a transition metal is suggested in other systems. The cobalt-catalyzed isomerization of allylbenzene to β -methylstyrene is an example.¹¹ Back donation of d electrons converts the suprafacial [1,3] sigmatropic change of order¹⁰ to an allowed process.

(11) L. Roos and M. Orchin, *J. Am. Chem. Soc.*, **87**, 5502 (1965).

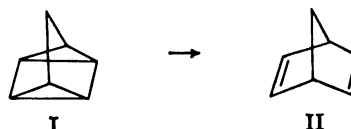
Raley for stimulating discussions and helpful comments.

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Valence Isomerization of Quadricyclene^{1a} to Norbornadiene^{1b} Catalyzed by Transition Metal Complexes

Sir:

The thermal isomerization of quadricyclene (I) to norbornadiene (II) is known to proceed slowly ($t_{1/2} > 14$ hr at 140°).² It has now been found that the rate of this reaction is dramatically increased by transition metal-olefin complexes. For instance, $t_{1/2}$ at -26° was found to be 45 min for a 0.7 M solution of I in CDCl_3 in the presence of 2 mole % of di- μ -chloro-bis(bicyclo[2.2.1]hepta-2,5-diene)dirhodium(I).



Complexes such as di- μ -chloro-tetrakis(ethylene)dirhodium(I), dichloro(1,5-cyclooctadiene)palladium(II), di- μ -chloro-bis(π -methallyl)dipalladium(II), and dichloro(bicyclo[2.2.1]hepta-2,5-diene)platinum(II) behave similarly. For all complexes a quantitative conversion of I into II was observed. The isomerization catalyzed by di- μ -chloro-bis(bicyclo[2.2.1]hepta-2,5-diene)dirhodium(I) was followed kinetically by integration of the olefinic triplet (δ 6.82 ppm) in the nmr spectrum of the norbornadiene formed. The samples were prepared at about -60° in CDCl_3 , warmed up rapidly to the desired temperature, and then transferred to the cavity of the nmr spectrometer (being at the same temperature).

The reaction proved to be first-order in quadricyclene and, as shown in Table I, about first order in catalyst.

Table I. Pseudo-First-Order Rate Constants of the Reaction^a Quadricyclene \rightarrow Norbornadiene

$[\text{Rh}_2(\text{norbornadiene})_2\text{Cl}_2]$, M	$10^3 k$, sec ⁻¹
0.02	0.025
0.06	0.068

^a At -26° ; [quadricyclene] = 0.7 M (CDCl_3).

The apparent values of the activation parameters (inaccurate because of experimental difficulties, such as temperature control and instability of the catalyst solution) are $\Delta H^\ddagger = 21 \pm 5$ kcal mole⁻¹, $\Delta S^\ddagger = 45 \pm 18$ eu (catalyst concentration 0.036 M).

The mechanism of the reaction is thought to involve a coordination of quadricyclene to the transition metal either *via* an exchange with the originally coordinated olefin or by extension of the coordination around the metal. For the rhodium-olefin complexes and for the

(1) (a) IUPAC designation tetracyclo[3.2.0.0^{2,7}.0^{4,5}]heptane; (b) IUPAC designation bicyclo[2.2.1]hepta-2,5-diene.

(2) G. S. Hammond, N. J. Turro, and A. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961).

π -allyl-palladium complex coordination is possible with either the binuclear or the mononuclear species. This coordination of quadricyclene (I) may well be due to the π character of the cyclopropane bonds common to the three- and four-membered rings.³

The valence isomerization I \rightarrow II described is, by the Woodward-Hoffmann rule for cycloadditions,⁴ thermally forbidden. The catalysis observed might well be caused by the presence in the complex of occupied molecular orbitals with symmetries that make the isomerization an allowed process.⁵

(3) A. D. Walsh, *Nature*, **159**, 165, 712 (1947); C. A. Coulson and W. E. Moffitt, *J. Chem. Phys.*, **15**, 151 (1947).

(4) R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 2046 (1965).

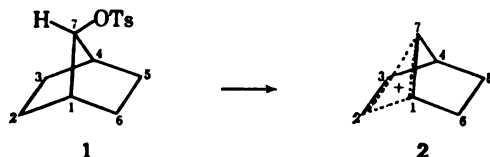
(5) F. D. Mango and J. H. Schachtschneider, *ibid.*, **89**, 2484 (1967).

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The 7-Norbornyl Cation

Sir:

The nature of the cation formed in the solvolysis of 7-tosyloxybicyclo[2.2.1]heptane (1) has not been clearly established. Winstein and co-workers have described the ionization of 1 as an "example of carbon participation in solvolysis" in which the delocalized ion, 2, is formed.¹ In contrast, Foote² and Schleyer³



have used the solvolysis of 1 as an example of a system which solvolyzes without anchimeric assistance.⁴

We have found that solvolysis of *exo,exo*-2,3-dideuterio-*anti*-tosyloxybicyclo[2.2.1]heptane (3), in acetic acid buffered with sodium acetate, gave the mixture of products previously reported in the literature.¹ Isolation of the 7-acetoxycyclo[2.2.1]heptane, which constituted greater than 90% of the reaction product, provided a mixture of deuterium labeled compounds. Infrared analysis *vs.* standard mixtures showed that the solvolysis product consisted of $90 \pm 3\%$ of 4 and $10 \pm 3\%$ of 5.

Both the tosylate, 3, and the acetate, 4, were prepared from 6. The synthesis of 6 involved dideuteriodiimide^{5,6} reduction of *anti*-7-hydroxybicyclo[2.2.1]heptene.⁷ The acetate, 5, was synthesized from 7, which

(1) S. Winstein, F. Gadiant, E. T. Stafford, and P. E. Klinedinst, Jr., *J. Am. Chem. Soc.*, **80**, 5895 (1958).

(2) C. S. Foote, *ibid.*, **86**, 1853 (1964).

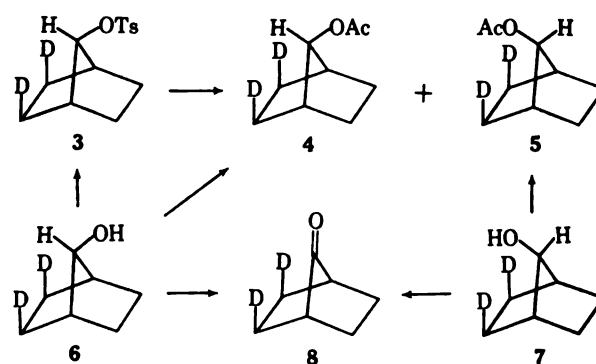
(3) P. Schleyer, *ibid.*, **86**, 1854, 1856 (1964).

(4) It is assumed in this paper that anchimeric assistance and participation of neighboring groups are interrelated phenomena. For discussion of this relationship see P. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965, and J. Berson, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 3.

(5) We wish to thank Professor J. Berson for providing us with experimental details for dideuteriodiimide reductions.

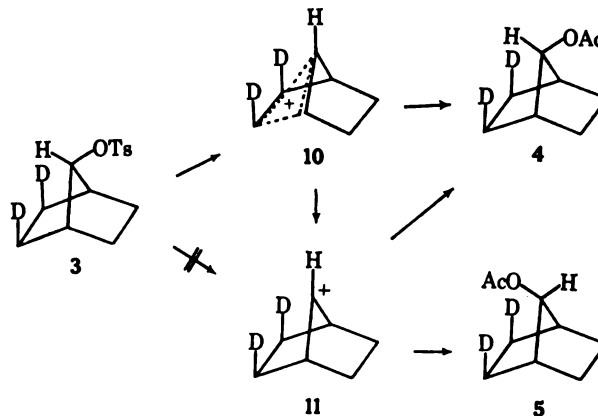
(6) The acetate prepared from 6 was shown to contain 90% of the theoretical amount of deuterium. All deuterium analyses were performed by J. Nemeth, Urbana, Ill.

(7) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955); S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).



had been prepared *via* diimide reduction of the known⁸ *exo,exo*-2,3-dideuterio-*syn*-7-hydroxybicyclo[2.2.1]hept-5-ene.⁹ In order to ascertain that the dideuteriodiimide reduction occurred from the *exo* side, both 6 and 7 were oxidized to the same ketone, 8. Whereas the ketones obtained from 6 and 7 were identical in all respects, the infrared and nmr spectra of each member of the epimeric pairs, 6 and 7, 4 and 5, and 3 and 9, were different.

We propose that the large degree of retention of configuration observed in the solvolysis of 3 is most consistent with concerted participation of the 1,2 σ electrons to form the delocalized ion, 10. Unlike certain explanations of the formation of the 2-nor-



bornyl cation,¹⁰ the formation of 10 may not be postulated to proceed *via* an initially formed classical ion such as 11 since, if 11 were an intermediate, approximately equal amounts of 4 and 5 should be formed.¹¹ Thus, it appears likely¹² that concerted ionization and carbon participation occur in the acetolysis of 3.

(8) B. Franzus and E. I. Snyder, *ibid.*, **87**, 3423 (1965).

(9) A tosylate, 9, prepared from 7, was shown to contain 95% of the theoretical amount of deuterium.

(10) It has been suggested that the initial step in the solvolysis of 2-tosyloxybicyclo[2.2.1]heptane is formation of a classical carbonium ion at C-2 of the bicyclo[2.2.1]heptyl system. For a discussion of this point of view see H. C. Brown, "The Transition State," Special Publication No. 16, The Chemical Society, London, 1962.

(11) It is assumed that the steric requirements of deuterium *vs.* hydrogen would not be sufficiently different to cause the observed product distribution.

(12) An alternate rationalization of the observed results would invoke a front-side displacement on the ion pair by solvent. Indeed, Brown has suggested¹³ the possibility "that even static classical ions, where the structure inhibits approach from the back side, may well undergo substitution with retention." Obviously, special classes of molecules, such as bridgehead tosylates where back-side approach is impossible, can only solvolyze with retention.¹⁴ However, we doubt whether the tosylate, 3, can be justifiably classified as one in which solvent approach from the back side is hindered to the extent that the mechanism of acetolysis becomes one of "front-side displacement." In the absence of such steric hindrance to back-side approach of solvent we see no obvious reason for suggesting front-side displacement of solvent on any ion pair derived from 3.

The occurrence of *ca.* 10% of the inverted product 5 merits comment. Two reasonable possibilities exist for the formation of 5. A direct displacement of tosylate ion by acetic acid with inversion of configuration at C-7 could account for the presence of 5. Alternately, 10 could be "leaking" to the classical ion 11 which would then be partitioned between 4 and 5. Precedent for this latter type of interconversion has been noted in the bicyclo[2.2.2]octyl system.¹⁵ Experiments aimed at distinguishing between these two possibilities are in progress.

Acknowledgment. This investigation was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society.

(13) H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Scheppele, *J. Am. Chem. Soc.*, **89**, 370 (1967).

(14) It should be noted that an unusual case of partial retention has recently been found in the solvolysis of a tertiary *p*-nitrobenzoate [H. L. Goering and S. Chang, *Tetrahedron Letters*, No. 40, 3607 (1965)].

(15) J. A. Berson and D. Willner, *J. Am. Chem. Soc.*, **86**, 609 (1964).

(16) National Science Foundation Trainee, 1965-1967.

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Retention of Configuration in the Solvolysis of 2,3-Dideuterio-7-norbornyl *p*-Bromobenzenesulfonate

Sir:

Acetolysis and formolysis of *anti*-2,3-dideuterio-7-norbornyl *p*-bromobenzenesulfonate (Ia)¹ proceed with predominant retention of configuration. Therefore,

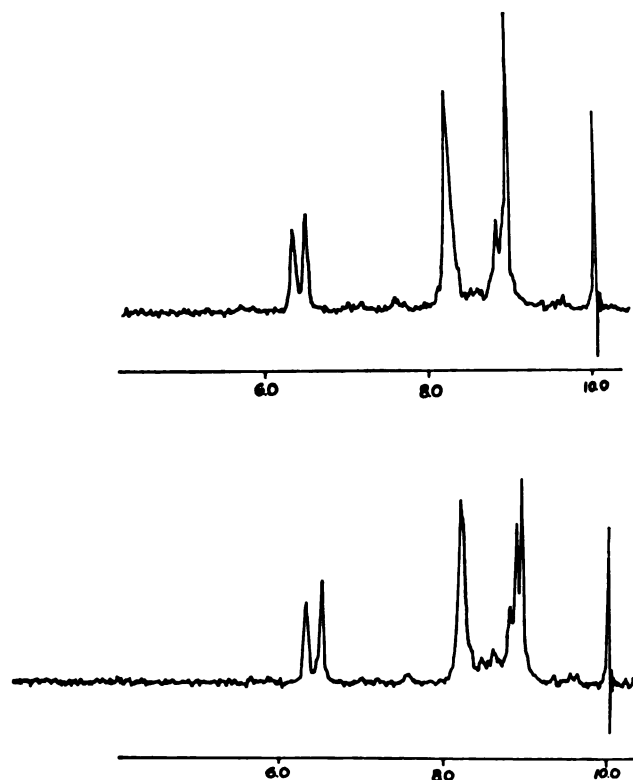


Figure 1. Nmr spectra of *anti*-2,3-dideuterionorbornan-7-ol (Ib) (top) and an equimolar mixture of *syn* and *anti* deuterated alcohols (bottom) in carbon tetrachloride containing tetramethylsilane.

(1) The terms *syn* and *anti* will be used to refer to the position of the deuterium atoms with respect to the oxygen function.

solvolysis cannot proceed through the free classical 7-norbornyl cation.

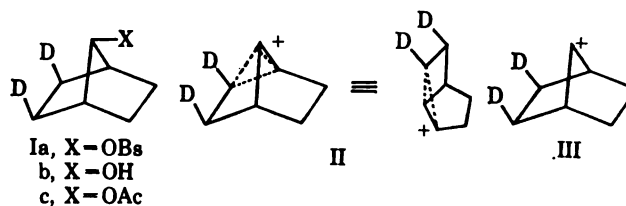
Deuterated *p*-bromobenzenesulfonate (Ia) was prepared from the corresponding alcohol (Ib) by treatment with *p*-bromobenzenesulfonyl chloride in pyridine. The alcohol was prepared by addition of deuterium gas to *anti*-7-norbornenol.² The *syn* isomer of alcohol Ib was prepared as an equimolar mixture with the *anti* alcohol by oxidation of *anti* alcohol with chromium trioxide in pyridine followed by lithium aluminum hydride reduction of the resulting ketone. Nuclear magnetic resonance (nmr) spectra are given in Figure 1 for *anti*-2,3-dideuterionorbornan-7-ol (Ib) and for an equimolar mixture of *syn* and *anti* deuterated alcohols.

Deuterated *p*-bromobenzenesulfonate Ia was solvolyzed for 90 min (*ca.* two half-lives) in acetic acid at 205°. The product, 7-norbornyl acetate, was isolated and purified by gas chromatography. Examination of the nmr spectrum of this acetate revealed that it consisted of 90 ± 5% *anti* acetate (Ic) (retention of configuration) and 10 ± 5% *syn* acetate (inversion of configuration).³ The relative amounts of inversion and retention were unaffected by the presence of added sodium acetate.

Solvolysis of deuterated *p*-bromobenzenesulfonate Ia for 16 hr (*ca.* one half-life) in refluxing formic acid containing sodium formate gave (after saponification of the product formates) deuterated 7-norbornanol with 85 ± 5% retention of configuration.³

The predominant retention of configuration in the solvolysis of deuterated *p*-bromobenzenesulfonate Ia may be explained in terms of nonclassical ion II or in terms of classical ion III.

For the case of classical ion III, one assumes that



solvolysis proceeds through front-side collapse of an ion pair. Brown and co-workers have mentioned the possibility of front-side ion-pair collapse.^{4,5} Examples of this have been provided by Goering and Chang in the case of 2-phenyl-2-butyl *p*-nitrobenzoate⁶ and Shoppee and Johnston in the case of 4,4-dimethyl-cholestan-3-yl systems.⁷

The classical ion hypothesis is further supported by the fact that on the basis of the acetolysis rate correlations of Foote⁸ and Schleyer⁹ (a correction has been applied to Foote's correlation¹⁰) there is no evidence

(2) Alcohol Ib and *p*-bromobenzenesulfonate Ia both contained 88% of the theoretical amount of deuterium. Deuterium analysis was by J. Nemeth, Urbana, Ill.

(3) The analysis was carried out by comparison with the nmr spectra of mixtures of *syn* and *anti* alcohols or acetates of known proportion. Acetates were prepared by acetylation of the alcohols with acetic anhydride in pyridine.

(4) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *J. Am. Chem. Soc.*, **87**, 2137 (1965).

(5) H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Scheppele, *ibid.*, **89**, 370 (1967).

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chimeric acceleration in the acetolysis of 7-norbornyl *p*-toluenesulfonate. Dominant retention of configuration in the solvolysis of deuterated *p*-bromobenzenesulfonate is fully explained by the postulate that nonclassical ion is an intermediate. The corresponding unattained nonclassical ion was proposed in 1958 by Winstein, *et al.*, in their work on the acetolysis of 7-norbornyl *p*-bromobenzenesulfonate in order to explain the fact that the rearranged acetate formed in this solvolysis, 2-bicyclo[3.2.0]heptyl acetate, is exclusively *trans* isomer.¹² The presence of some *syn*-7-norbornyl product in the present work may be explained by concurrent SN2 reaction (unlikely since sodium acetate does not change the proportion of *anti* acetate in the acetolysis product) or by "leakage" to classical ion III. "Leakage" to a classical ion seems reasonable since there appears to be no any rate enhancement in acetolysis.⁸⁻¹⁰ There is some rate enhancement, though. (Acceleration by a factor of up to ten or so would not be distinguishable from the scatter in the Foote and Schleyer correlations.)

As hoped that the results of the formolysis might give a means of choosing between the classical and nonclassical ion interpretations. If nonclassical ion involved, formolysis at a lower temperature (100°) would be expected to give relatively more inversion than does acetolysis at a higher temperature (205°) on the basis of the fact that in solvolysis *threo*- and *threo*-3-phenyl-2-butyl *p*-toluenesulfonates the amount of retention of configuration increases from 95% to over 99% in going from acetic acid at 75° to formic acid at 25°.¹³ On the other hand, if retention is to be explained on the basis of ion pair collapse of ion pairs, formolysis at 100° would be expected to give much more inversion than acetolysis at 205°, on the basis of the fact that Winstein found that acetolysis of *p*-methoxyethyl *p*-toluenesulfonate at 75° needed to be explained in terms of ion pairs and dissociated ions while formolysis at 25° was explained in terms of dissociated ions only.¹⁴ Also, Winstein, *et al.*, report the same finding for 2,4-dimethoxyphenylethyl arenesulfonates.¹⁵ The experimental observations of 10 ± 5% inversion in acetic acid at 205° and 15 ± 5% inversion in formic acid at 100° if anything fit the ion pair explanation slightly better than they do the classical ion explanation, but are clearly about halfway between the extremes cited above. It is

therefore not possible to make a clear-cut choice between the classical and nonclassical ion interpretations at this point.

Further work on the solvolysis of 7-norbornyl *p*-bromobenzenesulfonate is in progress.

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The Structure of Cyclooctatetraeneiron Tricarbonyl in Solution¹

Sir:

We recently reported that cyclooctatetraeneiron tricarbonyl (COTFe(CO)₃) *in solution* has a 1,3-diene-bonded structure (I) and that the nmr spectrum of the compound at -145° is that of the "frozen" structure I.² Two other groups of workers, Cotton, Davison, and Faller (CDF)³ and Keller, Shoulders, and Pettit (KSP),⁴ subsequently reached conclusions different from ours. We now show that our original interpretation is correct, and that the deductions of CDF and KSP are invalid.

That COTFe(CO)₃ has structure I in the crystalline state is well established⁵ and is not in dispute. CDF³ present two arguments against COTFe(CO)₃ having structure I *in solution*, and they suggest a 1,5-diene-bonded (tub) structure under these conditions.

CDF's first argument is that the infrared C-H stretching bands of COTFe(CO)₃ *in solution* are different from those found in the solid, but are similar to those of 1,5-diene-bonded (tub) COT complexes. However, the great similarity of the fingerprint region of COTFe(CO)₃ in the solid and in solution^{5,6} was ignored by CDF. These spectra are presented in Figure 1, together with the spectra of COTMo(CO)₃⁷ and COTW(CO)₃,⁸ two compounds which have 1,5-diene-bonded (tub) structures and which display the expected⁹ two sharp lines in their nmr spectra (τ 4.46, 5.80 and 3.66, 5.25, respectively).

In the structurally significant fingerprint region (1600-750 cm⁻¹), only very small differences (0.1-0.3%) in the frequencies of COTFe(CO)₃ are observed between the solid and solution spectra. The general

¹ Two of the twenty compounds used by Foote in his correlation are shown to have structures different from those accepted at the time the correlation was published.¹¹ Also, 7-norbornyl *p*-toluenesulfonate is itself used in establishing the correlation. Consequently, the squares line of the Foote correlation was recalculated omitting compounds whose structures were incorrect (case A) and omitting two compounds and also omitting 7-norbornyl *p*-toluenesulfonate (case B). The results are: case A: $\log k_{rel} = -0.132$ (720), correlation coefficient -0.98; case B: $\log k_{rel} = -0.133$ (720), correlation coefficient -0.95. The observed rate for 7-norbornyl *p*-toluenesulfonate is $\log k_{rel} = -7.00$. The calculated $\log k_{rel} = -7.00$ (case A) and -7.04 (Case B).
² von R. Schleyer, W. E. Watts, and C. Cupas, *J. Am. Chem. Soc.*, **86**, 2722 (1964).
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(1) (a) Research supported in part by the National Science Foundation; (b) research sponsored in part by the U. S. Army Research Office (Durham).

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(8) This complex has recently been prepared in these laboratories by procedures similar to those used in the preparation of the molybdenum analog (A. Maasbol, unpublished work).

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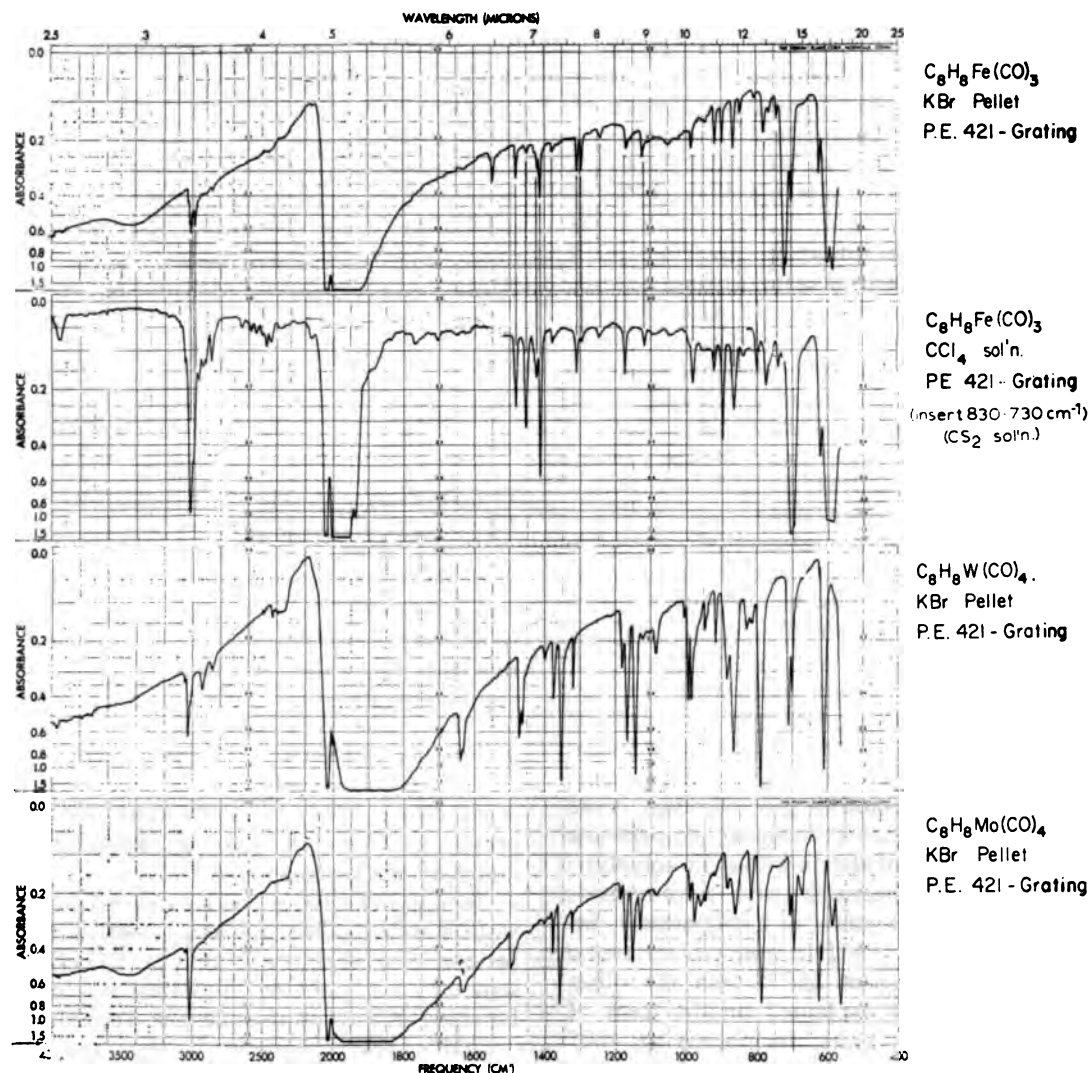
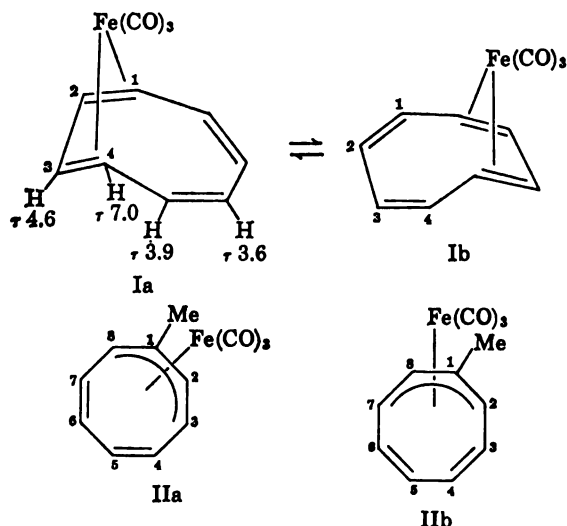


Figure 1.

similarity of the fingerprint region of the spectra of the molybdenum and tungsten (tub) complexes is to be contrasted with the great differences between these spectra on the one hand and the spectra of the iron



complex on the other. Therefore, despite the slight variation in the precise shape of the C-H stretching band¹⁰ of COTFe(CO)_3 in the solid and liquid phases,

the infrared evidence is overwhelmingly in favor of a single structure (1,3-diene bonded) in the two phases.

CDF's second argument is that the chemical shifts found for COTFe(CO)_3 at -145° are not those expected for structure Ia, especially for the protons on C₁ and C₄.¹¹ However, their suggested alternative tub structure certainly does not have the expected chemical shifts,¹² nor does it explain the widths² of the bands of the nmr spectrum of COTFe(CO)_3 at -145° .

KSP⁴ accept the 1,3-diene-bonded structure I for COTFe(CO)_3 in solution, but they present the same objections as did CDF² to our assignments of chemical

(10) The change in the C-H band of COTFe(CO)_3 on going from solid to solution appears to be due to a broadening of the low-frequency band of the C-H doublet and is not necessarily indicative of a structural change.

(11) On the basis of our published spectrum,² we estimate that the highest chemical shift occurring in COTFe(CO)_3 at -145° is *ca.* τ 5.7. Because of the peculiar structure of I, known 1,3-diene-iron tricarbonyl complexes may not be good model compounds. Furthermore, an examination of the literature^{4,9} indicates that H₁ and H₄ in 1,3-diene complexes have rather variable chemical shifts.

(12) Bonding of metals to olefins results in a high-field shift of the olefinic protons. These shifts⁹ are very similar (1.7 and 1.5 ppm, respectively) for norbornadiene and COT upon bonding to Mo(CO)_6 . This should also be true for the corresponding Fe(CO)_5 complexes. For norbornadiene this shift⁹ is 3.5 ppm. Therefore the high-field protons in a tub COTFe(CO)_3 complex should be at τ 4.3 + 3.5 = 7.8, whereas the observed shift is $\tau \leq 5.7$ ppm.

shifts at -145° . They agree that the spectrum at -145° is that of I, but propose that the valency tautomerism $Ia \rightleftharpoons Ib$ is still very rapid at -145° . By using plausible chemical shifts (see Ia), they predict that the low-temperature spectrum should consist of two bands at τ 4.1 and 5.5, roughly as observed.¹³

KSP⁴ claim support for their theory from the fact that the nmr spectrum of methylcyclooctatetraeneiron tricarbonyl ($MeCOTFe(CO)_3$) consists of three bands (τ 4.33, 4.92, and 5.50; intensity ratios of 3:2.3:1.8) at room temperature and of two bands (τ 4.05 and 5.62, reported as of "approximately equal areas") at -120° . They argue that the room-temperature band at τ 5.50 must be the average between two bands, one of which is of the normal olefinic type and at low field; therefore, the other band must be at much higher field than τ 5.5 for the average to be at τ 5.5. It is quite clear that this argument is fallacious as is shown below. Thus the nmr spectrum of $MeCOTFe(CO)_3$ does not support the ideas of KSP.¹⁴

We now show that the data of KSP on $MeCOTFe(CO)_3$ are actually in excellent agreement with our interpretation.² The evidence indicates that the $Fe(CO)_3$ group prefers to be attached to certain carbon atoms of the ring of MeCOT, a possibility ignored by KSP. These carbons are 8123 and 7812 in IIa and IIb, respectively. In our view, the spectrum at low temperatures is that of frozen IIa and IIb, whereas at room temperature the chemical shifts are the average of those in IIa and IIb. On this basis, and using¹⁵ the value τ 4.1 for any of the protons of noncomplexed olefinic groups and τ 5.4 for any of the iron-bonded olefinic protons, the chemical shifts shown in Table I

Table I. Predicted Chemical Shifts for IIa and IIb

Positions	Chemical shifts at -145° , τ		Av of IIa and IIb (intensity) at room temp
	IIa	IIb	
2 and 8	5.4, 5.4	5.4, 5.4	5.4 (2)
3 and 7	5.4, 4.1	4.1, 5.4	4.75 (2)
4 and 6	4.1, 4.1	4.1, 4.1	4.1 (3)
5	4.1	4.1	4.1

are predicted for $MeCOTFe(CO)_3$ at -145° and at room temperature. The predicted low-temperature spectrum (τ 4.1 and 5.4, relative intensities 4:3) and the high-temperature spectrum (τ 4.1, 4.75, and 5.4, relative intensities 3:2:2) are in substantial agreement with those reported by KSP.⁴ Valency tautomers with the $Fe(CO)_3$ at positions different from those in IIa or IIb give calculated spectra in gross disagreement with the experimental data and thus cannot be present in significant amounts.

(13) The high-field band² of $COTFe(CO)_3$ is actually much too broad and complex to be due to four protons all having the same chemical shift, as is required by KSP's theory.

(14) These authors do not attempt to explain the spectra of $MeCOTFe(CO)_3$. We find that it is impossible to explain both the room- and low-temperature spectra of $MeCOTFe(CO)_3$ with KSP's theory.

(15) For this calculation we have used rounded values of the chemical shifts given by KSP.⁴

The spectra of a deuterated derivative of $MeCOTFe(CO)_3$, described in the accompanying communication,¹⁶ confirm our conclusions.

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Valency Tautomerism in Methylcyclooctatetraeneiron Tricarbonyl¹

Sir:

We have shown² that the nmr data of Keller, Shoulders, and Pettit on methylcyclooctatetraeneiron tricarbonyl (I) can best be explained on the basis that the $Fe(CO)_3$ group exhibits a preference for bonding with carbon atoms 1, 2, 7, and 8 (Ia) or 1, 2, 3, and 8 (Ib) of the ligand, and that valency tautomerism, $Ia \rightleftharpoons Ib$, is fast (on the nmr time scale) at room temperature, but slow at -145° . An examination of the nmr spectrum of methyl-*d*-cyclooctatetraene-2,3,4,5,6,7-*d*₆-iron tricarbonyl (II), presented in this communication, confirms our deductions and clearly shows that the terminal and internal protons in the iron-bonded diene moiety of II have only slightly different chemical shifts.

Lithium aluminum hydride reduction of cyclooctatetraenyl-2,3,4,5,6,7-*d*₆-methyl-*d* bromide³ in diethyl ether gave methyl-*d*-cyclooctatetraene-2,3,4,5,6,7-*d*₆ (III)⁴ as a yellow oil, isolated by glpc. Reaction of III with an equimolecular amount of $Fe_2(CO)_9$ in boiling hexane for a few minutes gave, after removal of the solvent, the dark red complex⁵ II, which was purified by evaporative distillation *in vacuo*.

The nmr spectrum of II in deuterated chloroform showed only two bands: the CH_2D protons at τ 8.15 and the ring proton at τ 5.44. The high-field chemical shift of the ring proton is only consistent with IIa and IIb being the dominant species at room temperature.⁶

In $CHCl_2F$ solution, the ring proton in II changed from a sharp line at room temperature to two sharp lines at -145° (Figure 1). No change was observed in the CH_2D band, apart from some broadening at very low temperatures.⁷ At the coalescence temper-

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(4) The rate of bond shift in III has been determined from the temperature dependence of the nmr spectrum, which also confirms the structure and isotopic labeling of the compound (to be published).

(5) The same procedure applied to cyclooctatetraene was found to give a good yield of pure iron tricarbonyl complex. Mass spectra of II showed a ratio of 1-*d*:1-*d*₂:1-*d*₃ of 30:5:1 and a cracking pattern consistent with its structure.

(6) Other tautomers would have the ring proton at least half of the time in the unbonded diene portion of the molecule and would therefore exhibit a low chemical shift ($\tau < 5$). The presence of appreciable amounts of these tautomers would lower the average chemical shift of the ring proton of II, as compared with the high-field band (ca. τ 5.5) in the spectrum of $COTFe(CO)_3$ at -145° .

(7) The greater broadening of the CH_2D protons relative to the ring proton is consistent with the closeness of the two protons in the CH_2D

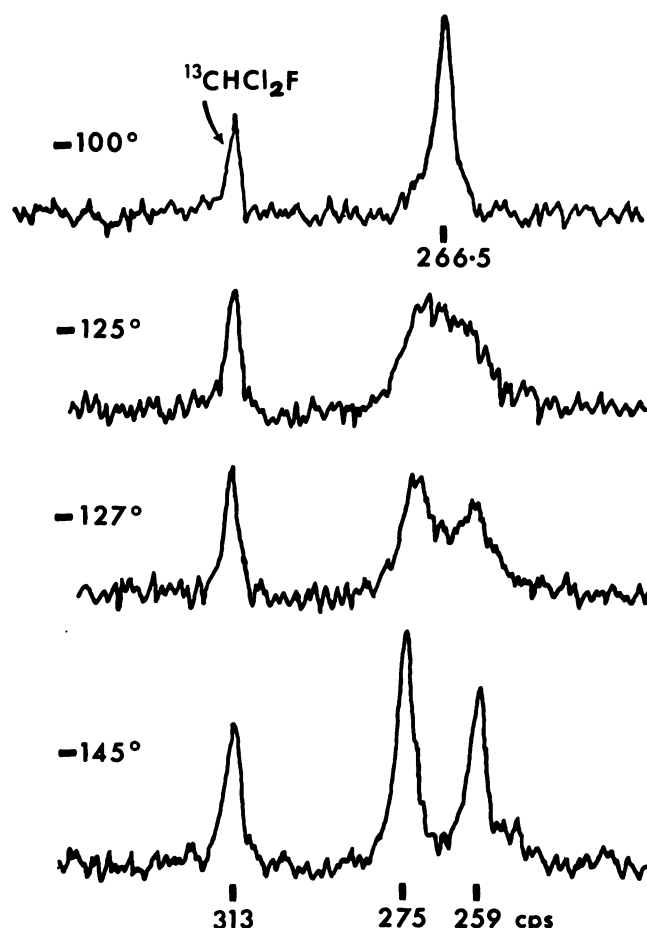
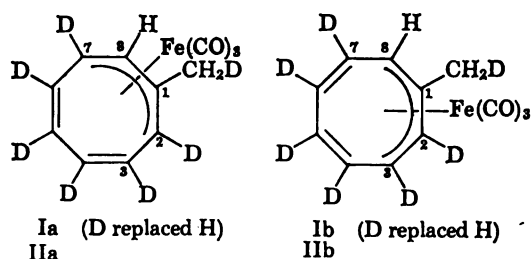


Figure 1. Proton spectrum (60 Mc/sec, deuterons decoupled) of II in CHCl_2F at various temperatures. Only the olefinic region is shown. The scale is cps downfield from internal tetramethylsilane.

ature (-125°) for the ring-proton bands, the rate constant for the valency tautomerism, $\text{IIa} \rightleftharpoons \text{IIb}$, is 35 sec^{-1} , and the free energy of activation (ΔF^\ddagger) is 7.5 kcal/mole, a value close to the 7.2 kcal/mole observed⁸ for the parent compound.



The average of the chemical shifts of the two ring-proton bands at -150° is very close to the chemical shift of the coalesced bands (e.g., at -100° or higher). This is in agreement with the conclusion based on the chemical shift of the ring proton that tautomers other than IIa or IIb must be present in very small amounts.

Tautomers other than IIa or IIb should show a ring-proton band at low field (ca. τ 4) at -145° , but unfortunately this region is partly obscured by a ^{13}C satellite of the solvent as well as being very close to an

group and relaxation by the direct spin-spin interactions modulated by molecular rotation.

(8) C. G. Kreiter, A. Maasbol, F. A. L. Anet, H. D. Kaesz, and S. Winstein, *J. Am. Chem. Soc.*, **88**, 3444 (1966).

intense solvent peak. We plan to examine the spectrum further in a deuterated solvent, which should allow the detection of small peaks in this region. On the basis of the present evidence, it appears that more than 90% of II is in the form of IIa and IIb.

The present work does not allow an unambiguous assignment to be made to the ring-proton bands in the low-temperature spectrum of II. Since the ring proton in IIb would be expected to be upfield from that in IIa,⁹ the bands at τ 5.42 and 5.68 can be assigned tentatively to IIa and IIb, respectively.

The origin of the low energy of IIa and IIb is of interest. In IIa or IIb the methyl group is attached to a ring carbon atom which in cyclooctatetraene tricarbonyl¹⁰ has an internal angle of 124.6° . In other tautomers of II the methyl group would be attached to carbon atoms having internal angles greater than 130° . From previous work^{3,11} on the rates of ring inversion and bond shift in derivatives of cyclooctatetraene (COT), it is known that large groups, and even methyl groups,¹² destabilize the planar form of COT (bond angles of 135°) relative to the tub form (bond angles of about 125°). This effect was ascribed to the greater steric repulsions existing between a substituent and adjacent hydrogen atoms in the planar form relative to the tub form. Although II is nonplanar, these steric effects should operate to make IIa and IIb more stable than other tautomers. Steric repulsions between the $\text{Fe}(\text{CO})_3$ and the methyl group would destabilize IIa and IIb and therefore do not appear to be important. Inductive and hyperconjugative effects of the methyl group may be significant in stabilizing IIa and IIb; experimental investigations of this possibility are planned.

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(12) The rate constant for bond shift⁴ in III at -10° is not more than one-tenth of that¹¹ in cyclooctatetraene.

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Mass Spectrometric Evidence for the Gaseous Si_2N Molecule

Sir:

Optical spectroscopic studies¹ and ionic-model calculations² have indicated that the binding energies of gaseous nitrides should be of the order of 100 kcal mole⁻¹, and thus one expects that gaseous nitrides should be relatively stable. Most of the refractory nitrides have been reported, however, to dissociate when heated under vacuum.³⁻⁷ Only gaseous gallium

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Partial Pressures of Gaseous Species over the Si-BN System and Heat of the Reaction $\text{Si}_2\text{N}(\text{g}) = 2\text{Si}(\text{g}) + 0.5\text{N}_2(\text{g})$

np, °C	Pressure, atm			$-4.576 \log K,$ cal deg ⁻¹ mole ⁻¹	$-\Delta \left(\frac{F^\circ_T - H^\circ_{298}}{T} \right)$ cal deg ⁻¹ mole ⁻¹	$\Delta H^\circ_{298},$ kcal mole ⁻¹
	Si	N ₂	Si ₂ N			
46	8.03×10^{-8}	2.82×10^{-4}	2.17×10^{-7}	24.3	(43)	124
56	4.34×10^{-8}	1.91×10^{-4}	1.08×10^{-7}	25.7	(43)	124
55	2.30×10^{-8}	1.19×10^{-4}	4.20×10^{-8}	26.8	(43)	123
42	1.66×10^{-8}	1.05×10^{-4}	2.83×10^{-8}	27.4	(43)	123

$$\Delta H^\circ_{298} = 123.5 \pm 1.0$$

has been observed mass spectrometrically,⁸ an attempt was made to establish its stability. Optical spectra have been cited as evidence for gaseous Si₂N and TiN.¹⁰

The course of a mass spectrometric study of the atomization of silicon from a boron nitride Knudsen cell Si₂N molecule has been identified in the gas phase.

This species is isoelectronic with the well-established gaseous species C₂N for which both the CCN and NC isomers are known from optical spectra.¹¹

Experiments were performed on a 12-in. radius, electron mass spectrometer, similar to that described by Rupka and Inghram.¹² The Knudsen cell was made from a high-purity boron nitride rod and was heated in a heavy tantalum crucible. The cell was heated by electron bombardment, and the temperature was measured with an optical pyrometer looking into the blackbody hole in the bottom of a tantalum crucible.

When the cell heated above 1500°K, the main peaks in the mass spectrum were N₂⁺ and Si⁺, both increasing with temperature. At temperatures above 1700°K, the Si₂⁺, Si₃⁺, and Si₄⁺, as well as peaks at *m/e* 70, 71, and 72, were observed. From the isotopic abundance ratios the peaks at masses 70, 71, and 72 were identified with the Si₂N⁺ ion. The appearance potential, determined by the vanishing-current method, the ionization potential of Si as standard was 0.3 eV. This value suggests that the Si₂N⁺ ion is formed by direct ionization of the Si₂N molecule and fragmentation.

It was impossible in these experiments to decide unambiguously whether the molecules Si₂N₂ or Si₂N₄ were present in the vapors, because of interference of Si₃⁺ and Si₄⁺ ions at the same mass.

The ion intensities of Si⁺, N₂⁺, and Si₂N⁺ were measured at several temperatures in the range 1742–1800°K and were used to calculate the equilibrium constant for the reaction



using the JANAF¹³ free-energy functions for Si(g) and N₂(g), values for Si₂N(g), estimated by analogy with

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Al₂O(g), and equilibrium constants derived from the ion-current data with the aid of a silver calibration, one can derive the heat of reaction 1 by the third-law method. The results are given in Table I.

From the heat of reaction 1 and the heat of sublimation of silicon, $\Delta H^\circ_{298} = 108.4 \pm 3.0$ kcal mole⁻¹,¹⁴ one calculates $\Delta H^\circ_f[\text{Si}_2\text{N}(\text{g})] = 93 \pm 5$ kcal mole⁻¹. The heat of atomization of Si₂N(g), as calculated from the heat of reaction 1 and the dissociation energy of N₂, $D_0^\circ = 225.0 \pm 2$ kcal mole⁻¹,¹⁵ is $\Delta H_a[\text{Si}_2\text{N}(\text{g})] = 236 \pm 10$ kcal mole⁻¹, close to the atomization energy for Al₂O of 248 kcal mole⁻¹.¹⁵

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(16) On leave from the Boris Kidrich Institute of Nuclear Sciences, Belgrade, Yugoslavia.

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Sulfur Dioxide Insertion. IV. A New Allylic Rearrangement¹

Sir:

The unusual paucity of data on insertion reactions of σ-bonded allylic complexes of the transition elements² prompted us to examine the behavior of several such organometallics toward sulfur dioxide. Reported now are some preliminary results on a new type of rearrangement which accompanies insertion of SO₂ into metal-carbon bonds.

The qualitative observation of one of us (F. A. H.) that allylmanganese pentacarbonyl inserts sulfur dioxide at a rate much faster than do the methyl and benzyl analogs³ suggested a possibility of mechanistic differences between these reactions. Particularly inviting was a path involving an allylic rearrangement resulting from cleavage of the Mn-C(1) bond and formation of the Mn-S and S-C(3) bonds (eq 1). In order to test for this possibility we have examined the reaction of

(1) For part III of this series, see J. P. Bibler and A. Wojcicki, *J. Am. Chem. Soc.*, **88**, 4862 (1966).

(2) The only example of such reactions known to the authors is the reversible carbonylation of allylmanganese pentacarbonyl: T. H. Coffield, J. Kozikowski, and R. D. Closson, Lecture to International Conference on Coordination Chemistry, London, England, April 1959; quoted by G. E. Coates, "Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1960, p 280.

(3) F. A. Hartman and A. Wojcicki, *J. Am. Chem. Soc.*, **88**, 844 (1966).

Table I. Infrared Carbonyl and Sulfur–Oxygen Stretching Frequencies (cm^{-1}) of the Complexes^a

Complex ^b	Carbonyl stretches ^c	SO stretches ^d
$\text{Mn}(\text{CO})_5\text{SO}_2\text{C}_3\text{H}_5$	2137 (mw), 2088 (w), 2057 (s), 2042 (s), 2025 (m)	1190 (s), 1043 (s)
$\text{Mn}(\text{CO})_5\text{SO}_2\text{C}_4\text{H}_7$	2136 (mw), 2089 (w), 2057 (s), 2040 (s), 2024 (m)	1189 (s), 1048 (s)
$\text{Mn}(\text{CO})_5\text{SO}_2\text{C}_5\text{H}_9$	2135 (mw), 2088 (w), 2058 (s), 2039 (s), 2020 (m)	1190 (s), 1041 (s)

^a Recorded on a Beckman Model IR-9 spectrophotometer. Abbreviations: s, strong; m, medium; mw, medium weak; w, weak.^b Satisfactory carbon, hydrogen, and sulfur analyses and molecular weights were obtained for all complexes reported. ^c CCl_4 solution.^d Nujol mull.**Table II.** Supplementary Information

	Analytical data						Molecular weight	
	Calcd, %			Found, %				
	C	H	S	C	H	S	Calcd	Found
Mn(CO) ₅ SO ₂ C ₃ H ₅	32.01	1.68	10.68	32.27	1.82	10.68	300	294
Mn(CO) ₅ SO ₂ C ₄ H ₇	34.41	2.25		34.38	2.28		314	314
Mn(CO) ₅ SO ₂ C ₅ H ₉	36.59	2.76	9.77	36.74	3.00	9.49	328	326

sulfur dioxide with 2-butenylmanganese pentacarbonyl and with 3-methyl-2-butenylmanganese pentacarbonyl, since structures of the sulfinato products of these reactions should resolve readily the question of occurrence of the postulated rearrangement.

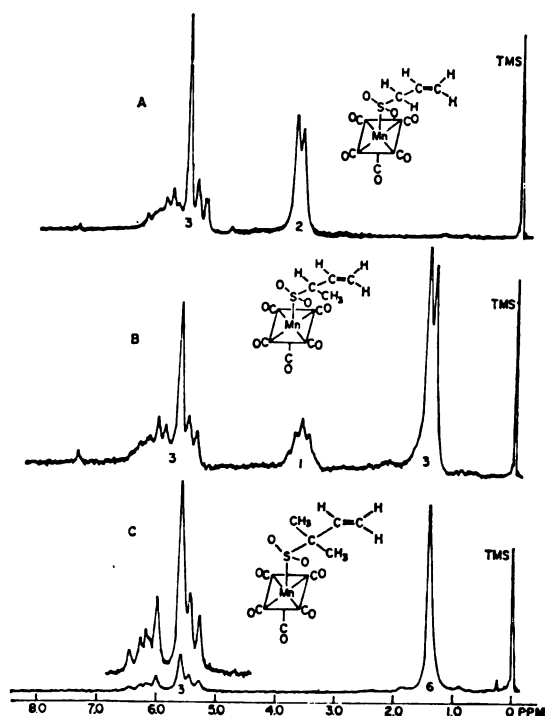


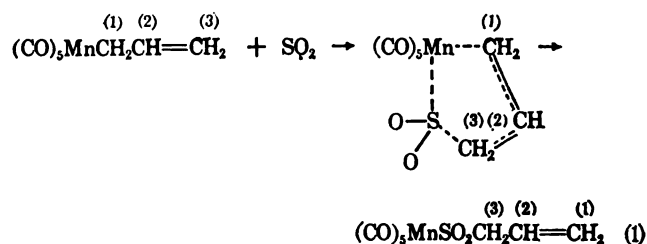
Figure 1. Proton magnetic resonance spectra of sulfinatopentacarbonylmanganese(I) complexes obtained from the reaction of sulfur dioxide with (A) 2-propenylpentacarbonylmanganese, (B) 2-butenylpentacarbonylmanganese, (C) 3-methyl-2-butenylpentacarbonylmanganese (recorded on a Varian Associates A-60 spectrometer in CDCl_3 solution).

In a typical reaction, an allylmanganese pentacarbonyl complex⁴ (ca. 3 g) was allowed to interact with about 15 ml of anhydrous liquid sulfur dioxide at ca. -40° for approximately 2 hr.⁵ The SO_2 was then re-

(4) Prepared from sodium pentacarbonylmanganate(-1) and the organic halide; see W. R. McClellan, H. H. Hoehn, H. N. Cripps, E. L. Muetterties, and B. W. Howk, *J. Am. Chem. Soc.*, **83**, 1601 (1961). The compound was characterized by nmr spectroscopy.

(5) Actually, these reactions reach completion in much shorter times.

moved, the orange residue was extracted with 20 ml of absolute ethanol, and 10 ml of ether was added to the extracts. Cooling the resulting solution to -40° for 1 hr caused separation of pale yellow crystals. The product was washed with 20 ml of ether and then recrystallized from chloroform-hexane. The yield ranged from 70 to 80%.



The infrared carbonyl and sulfur–oxygen stretching frequencies of the products, listed in Table I, are very similar to those reported for the analogous methyl,³ ethyl,⁶ and benzyl³ derivatives and attest to the S-sulfinatopentacarbonyl formulation of the complexes. Supplementary data are given in Table II.

The question concerning the position of attachment of the allyl moieties to sulfur in $(\text{CO})_5\text{MnSO}_2\text{C}_4\text{H}_7$ and $(\text{CO})_5\text{MnSO}_2\text{C}_5\text{H}_9$ is resolved upon examination of the proton magnetic resonance spectra of these derivatives in conjunction with the spectrum of the 2-propenylpentacarbonyl sulfinato, all shown in Figure 1. The nmr spectrum of $(\text{CO})_5\text{MnSO}_2\text{C}_3\text{H}_5$ consists of a doublet centered at τ 6.25 and of a complex multi-line absorption farther downfield (relative intensities 2:3). The former signal is assigned to the two protons of the methylene group bonded to SO_2 , and the latter to the three vinyl hydrogens. The salient features in the spectrum of $(\text{CO})_5\text{MnSO}_2\text{C}_4\text{H}_7$ are presence of a multiplet at τ 6.10–6.38 and of a complex absorption pattern at τ 3.59–4.66 (relative intensities 1:3). No signal is detectable in the τ 5–7 range of the spectrum of $(\text{CO})_5\text{MnSO}_2\text{C}_5\text{H}_9$; the resonances at τ 3.91–4.83 and the sharp line at τ 8.59 (due to the six methyl protons) occur with the intensity ratio of 3:6.

These data are in complete agreement with the structures containing rearranged allylic moieties of the last two derivatives (see Figure 1). Had there been no rearrangement, each spectrum would be expected to ex-

(6) F. A. Hartman, Ph.D. Thesis, The Ohio State University, 1966.

a doublet at τ 5–7 with the relative intensity corresponding to two methylene protons. Furthermore downfield signals would occur with the relative intensities and multiplicities reflecting the presence of one and one vinyl protons in the C_4H_7 and C_5H_9 sulfates, respectively.⁷

The generality of the above-described allylic rearrangement is supported by the behavior of the 2-butenyl derivatives of cyclopentadienyliron dicarbonyl, cyclooctadienylmolybdenum tricarbonyl, and cyclopentadienyltungsten tricarbonyl toward sulfur dioxide. The spectra of all of the resulting sulfates are consistent with the rearranged structure of the hydrocarbon moiety.⁹

We are currently examining insertion reactions between allyl metal complexes and substrates other than sulfur dioxide with a view to elucidating the scope of the rearrangement described herein.

Acknowledgment. The support of the National Science Foundation and of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

This argument receives support from the recent isolation of $(CO)_5FeSO_3CH_2CH=C(CH_3)_2$ via the reaction of $Na[C_5H_5Fe(CO)_5]$ with sulfur dioxide with 1-chloro-3-methyl-2-butene. The proton magnetic resonance spectrum of the sulfinate exhibits doublets at τ 4.68 (CH_2) and 6.17 (CH) with the relative intensity ratio of 6:2, a singlet at τ 4.68 (C_4H_7), and a complex signal at τ 4.30–4.95 (C), in complete accord with the proposed allylic attachment.⁸

R. L. Downs and A. Wojcicki, to be published. Although we cannot rule out the possibility that the "rearranged" sulfinate complexes result from the initial formation of the corresponding "normal" allyl sulfates, which then rapidly undergo isomerization, there is evidence against such a sequence of events. The five $C_5H_5Fe(CO)_5SO_3CH_2CH=C(CH_3)_2$ retains its identity after refluxing in liquid SO_2 ; a 3:1 mixture of the geometric isomers $(CO)_5FeSO_3CH_2CH=C(CH_3)_2$ and $C_5H_5Fe(CO)_5SO_3C(CH_3)_2CH=CH_2$ comes ca. 8:1 and 14:1 upon refluxing for 4 and 8 hr, respectively, with sulfur dioxide. Thus, at least in this case, isomerization of the sulfates does occur, albeit of the sterically more hindered $C_5H_5Fe(CO)_5C(CH_3)_2CH=CH_2$ to the less crowded $C_5H_5Fe(CO)_5SO_3CH_2CH=C(CH_3)_2$.

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c Polyethers and Their Complexes Metal Salts

Forty-three cyclic polyethers, derived from aromatic diols and containing from 9 to 60 atoms including 3–20 oxygen atoms in the ring, have been synthesized. Some of these have been prepared in good yield without the use of a high-dilution technique. Some of the compounds have been catalytically hydrogenated to the corresponding saturated cyclic polyethers.

Many of these cyclic polyethers have the unusual ability of forming relatively stable complexes with alkali and alkaline earth metal ions. The more effective ligands are those containing 5–10 oxygen atoms, separated from the next by 2 carbon atoms. This communication deals primarily with two examples of α -oxygen compounds which are the most effective versatile complexing agents: an aromatic compound derived from catechol, 2,3,11,12-dibenzo-1,1,13,16-hexaoxacyclooctadeca-2,11-diene (I); and

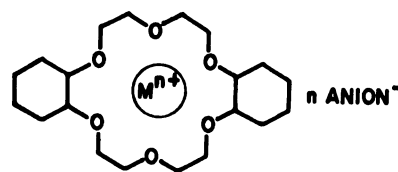


Figure 1. α -Benzo or 1,2-cyclohexyl polyethers.

its hydrogenation product, a mixture of *cis-trans* isomers, 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,14}]-hexacosane (II).

The two cyclic polyethers form stable complexes with ionic compounds of Li, Na, NH_4 , RNH_2 , K, Rb, Cs, Ag(I), Ca, Sr, Ba, Cd, Hg(I), Hg(II), La(III), Tl(I), Ce(III), and Pb(II). The complexes are thought to be field valency compounds formed by ion-dipole interaction between the cation and the negative dipoles of the oxygen atoms of the polyether ring, as shown in Figure 1; the formation of stable ammonium complexes supports this interpretation. The "hole" in I and II, estimated to be 4 Å in diameter, is large enough to accommodate any unsolvated or uncoordinated inorganic cation. The stoichiometry of the complexes is one molecule of polyether per single cation regardless of the valence.

Compound I is prepared by treating 1 mole of catechol, 2 moles of sodium hydroxide, and 1 mole of bis(2-chloroethyl) ether in 1-butanol at reflux temperature (115°) for about 24 hr. The yield is 44–48%, and 1 mole (360 g) of product can be synthesized in a volume of 5 l. White fibrous crystals are obtained by crystallization from benzene; mp 164°; bp ca. 380–384° (769 mm). *Anal.* Calcd for $C_{20}H_{24}O_6$: C, 66.6; H, 6.7; mol wt, 360. Found: C, 66.3; H, 6.8; mol wt, 371. Compound I is readily soluble in methylene chloride and chloroform, and very little soluble in methanol and water. Its ultraviolet spectrum in methanol has a peak at 274 m μ (ϵ 5200). Its infrared spectrum shows no OH band but two strong, broad ether bands near 8.1 and 8.5 μ . Its nmr spectrum is consistent with the proposed structure: a multiplet 4.11 ppm downfield from TMS, area ratio 2.2, and a singlet, 6.92 ppm, area ratio 1.00. The good yield of I obtained without resorting to a high-dilution technique is unusual for an 18-membered ring. Possibly the sodium ions promote ring formation by properly orienting the reactants and the intermediate products through ion-dipole interaction.

Compound II is prepared by hydrogenating I in a stainless steel autoclave at 100° and 1600 psig using *p*-dioxane as solvent and ruthenium dioxide as catalyst. The product, free of alcoholic by-products, is obtained by chromatography with acid-washed alumina and *n*-heptane in 67% yield. *Anal.* Calcd for $C_{20}H_{36}O_6$: C, 64.5; H, 9.7; mol wt, 372. Found: C, 64.5; H, 9.6; mol wt, 378. The product is a mixture of isomers, melts between 30 and 56°, and boils at about 344° (769 mm). It is soluble in organic solvents including petroleum ether. Its solubility in water at 26° is 0.036 mole/l. and decreases with rising temperature. Its ultraviolet spectrum shows no significant absorption above 200 μ , and its infrared spectrum shows no OH band but a strong, broad ether band near 9 μ . Its nmr spectrum is consistent with the proposed structure: a multiplet 1.50 ppm downfield from TMS,

area ratio 1.17, and a singlet, 3.67 ppm, area ratio 1.00.

Crystalline 1:1 complexes of I have been prepared with, for example, LiI , NaNO_2 , KI , KCNS , NH_4CNS , $\text{CN}_2\text{NH}_2\text{CNS}$, RbCNS , CsCNS , CaCl_2 , Ba(OH)_2 , CdCl_2 , HgCl_2 , and Pb(OAc)_2 . The potassium thiocyanate complex can be obtained as long, glistening crystals melting at $248\text{--}249^\circ$, considerably higher than the melting points of the components (172° for potassium thiocyanate). The ammonium thiocyanate complex melts at $187\text{--}189^\circ$ (149° for ammonium thiocyanate). The analytical data on the complexes are satisfactory.¹

The solubility of I in polar solvents is increased by the addition of soluble complexable salts. For example, the solubility of I in methanol at 30° (1.1 mmol/l.) is increased to the following values by the presence of the salts at 25 mM: NaCNS , 23.6 mmol/l., KF , 24.7; RbCNS , 25.6; AgNO_3 , 22.2; SrCl_2 , 17.9; and BaCl_2 , 26.6. The complexes tend to be more soluble in organic solvents of high dielectric constant, but most are decomposed by water. All soluble, ionic compounds of the complexable elements form complexes in solvents, such as methanol, regardless of the anion.

Compound II, being a mixture of isomers, forms solid complexes with not so well-defined melting points, but always higher than the melting point of II itself. Some of its complexes, such as that of potassium triiodide, are stable to water. II has the useful property of solubilizing ionic compounds in aprotic solvents including aromatic hydrocarbons. The following are a few examples. Crystals of potassium permanganate are insoluble in benzene, but they begin to dissolve immediately after the addition of II and continue to dissolve until the concentration of permanganate exceeds 0.02 M. Crystals of palladium chloride are insoluble in *o*-dichlorobenzene, but when crystals of potassium chloride and II are added, they go into solution as the complex of II with K_2PdCl_4 . The salts of many other alkali, alkaline earth, and transition metals have been solubilized by these two methods. A most interesting and useful complex is that of II with potassium hydroxide, which is soluble in toluene to over 0.3 mole/l. This solution saponifies the hindered esters of 2,4,6-trimethylbenzoic acid by the normal acyl-oxygen fission.

Not all complexable salts, however, can be solubilized even in the better aprotic solvents. Salts of high crystal lattice energy, such as potassium fluoride, sulfate, nitrate, phosphate, and carbonate, do not form complexes in aprotic solvents, and neither can these complexes be isolated as solids from protic solvents, such as methanol.

A detailed paper on the cyclic polyethers and their complexes with metal salts is being prepared for publication.

(1) Crystalline etherates of the alkali metal salts have not been common heretofore. Two $[(\text{Na}(\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2)_n)(\text{Ta}(\text{CO})_5)]$ and $[(\text{K}(\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2)_n)(\text{Mo}(\text{CO})_6)]$ are mentioned by F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1962, p 318.

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Received March 23, 1967

Observation of Helix-Coil Transition Using Nuclear Magnetic Resonance Halogen Ion Probe Technique

Sir:

Recent work has shown that nuclear magnetic resonance of halide ions may be a valuable tool for investigating the gross physical characteristics and specific chemical reactivities of large biological molecules in solution.¹ This note reports an observation of the well-substantiated helix-coil transition in synthetic poly-L-glutamate using ^{35}Cl resonance, and thus illustrates a direct application of wide-line nmr to the study of macromolecular structure. The ^{35}Cl line width is usually determined by quadrupole relaxation so that in the extreme narrowing limit the line width for a nucleus of spin $3/2$ is given by eq 1, where $\Delta\nu$ is the

$$\Delta\nu = \frac{2\pi}{5}(e^2qQ)^2\tau_c \quad (1)$$

full line width in cycles per second at half-height, q is the electric field gradient at the nucleus with quadrupole moment Q , τ_c is the correlation time for molecular rotation, and the asymmetry parameter has been neglected.² In aqueous sodium chloride solutions the chloride ion is symmetrically solvated producing a field gradient at the nucleus close to zero and a line width of about 16 cps. If, however, the quadrupolar chlorine nucleus can be found at environmentally different sites in solution, the line width will depend on the relative concentration of each site, the values of $(e^2qQ)^2$ and τ_c associated with each site, as well as the frequency with which the ^{35}Cl nucleus samples the various sites. In the case where exchange of the chloride is fast with respect to $1/\pi\Delta\nu$, a single composite line is observed with the line width given by

$$\Delta\nu = (\Delta\nu_a)P_a + (\Delta\nu_b)P_b \quad (2)$$

where $\Delta\nu_a$ and $\Delta\nu_b$ are the contributions to the line width associated with sites a and b, while P_a and P_b are the probabilities that the chlorine is at site a and b, respectively.³

When a 2 M sodium chloride solution is made 10^{-3} M in mercuric chloride, the $^{35}\text{Cl}^-$ resonance is broadened to 34 cps. The effect is explained by the rapid exchange of chloride ions in solution with the covalent chlorine associated with the HgCl_2^{2-} complex; thus, eq 2 correctly describes the line width. Since a similar effect is observed with species of the type RSHgCl in sodium chloride solutions, where R is almost any organic molecule, the mercury atom provides a convenient label for investigating changes in the correlation time of the molecule to which it is attached.¹

In aqueous solutions of low pH, poly-L-glutamate acquires a helical structure while at higher pH the randomly coiled form predominates. The transition from the helical to the randomly coiled structure has been investigated as a function of pH using measurements of optical rotation, viscosity, per cent ionization, optical rotatory dispersion, and the infrared spectrum.^{4,5} In solutions of low salt concentration the

(1) T. R. Stengle and J. D. Baldeschwieler, *Proc. Natl. Acad. Sci. U. S. A.*, **55**, 1020 (1966).

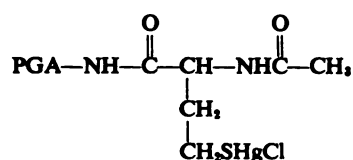
(2) A. Abragam, "The Principles of Nuclear Magnetism," The Clarendon Press, Oxford, 1961, p 314.

(3) T. J. Swift and R. E. Connick, *J. Chem. Phys.*, **37**, 307 (1962).

sition is quite sharp at about pH 5.8, but in 0.2 M sodium chloride the transition is shifted to approximately pH 5.2.

poly-L-glutamic acid (DP 530) as the sodium salt was purchased from Pilot Chemical Co. Sodium chloride, mercuric chloride, sodium hydroxide, and potassium hydrogen phthalate were purchased as analyzed reagents from the Baker Chemical Co. The N-acetyl-L-homocysteine thiolactone was obtained from Professor L. Stryer of Stanford University. The ^{35}Cl width measurements were made on a Varian Model V-4300 nmr spectrometer at 4.3 Mc using 500-Hz modulation and lock-in-detection to stabilize the line.

poly-L-glutamate was labeled at the terminal amide function by reaction with N-acetyl-DL-homocysteine thiolactone using the method reported by Benesch and Schach.⁶ The solutions measured were made using a 0.1 M hydroxide-potassium hydrogen phthalate buffer at a pH range from 4 to 8. All solutions were 1.00 M sodium chloride, 1.0×10^{-4} M in mercuric chloride, and 0.18% poly-L-glutamate by weight. On the ^{35}Cl labeled poly-L-glutamate with the mercury solution the mercury adds to the -SH group so that the molecule observed may be represented as



though the mercury(II) is in approximately a tenfold excess, the line broadening caused by 10^{-4} M mercury in 1.0 M sodium chloride is less than 2 cps.⁷ Under these conditions the probabilities of the chloride being at each site are a constant from one solution to the next so that any change in line width reflects only changes in the correlation time of the mercury site caused by the variations of pH. The experimental results are summarized in Figure 1.

The detailed features of the experimental curve are in excellent agreement with those reported by Idelson and Doty for optical rotation as a function of pH for a 0.2% solution of poly-L-glutamate in 0.2 M sodium chloride.⁴ In that plot, however, there was a maximum at about pH 4.6 and the authors suggested that the decrease in the maximum rotation associated with the helical transition could be caused by a contraction of the helix resulting from protonation of the carboxyl groups. In such a maximum is consistent with the data in Figure 1, the data are also consistent with a straight line of zero slope. This indicates that a change in the correlation time for the helix associated with such a transition is on the order of the experimental error of this technique. These results demonstrate that the ^{35}Cl ion probe is a sensitive technique for the investigation of structural properties and gross behavior of large molecules in solution.

M. Idelson and E. R. Blout, *J. Am. Chem. Soc.*, **80**, 4631 (1958).
P. Doty, A. Wada, J. T. Yang, and E. R. Blout, *J. Polymer Sci.*, **1** (1957).
R. Benesch and R. E. Benesch, *Biochim. Biophys. Acta*, **63**, 166 (1972).

At high pH the OH^- ion interferes with the chloride exchange mercury site; however, below pH 9 the exchange is unaffected: Bryant, unpublished results.

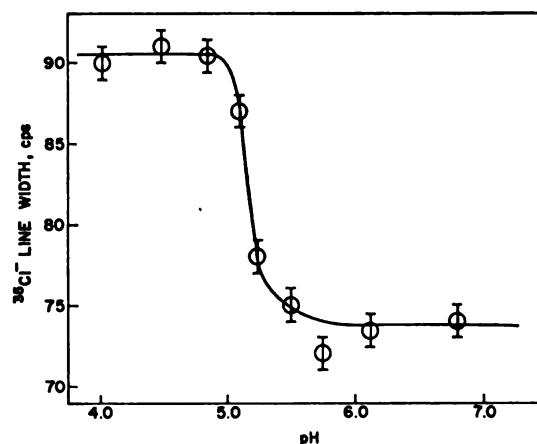


Figure 1. ^{35}Cl line width as a function of pH for 0.18% poly-L-glutamic acid in 1.0 M sodium chloride showing the poly-L-glutamic acid helix-coil transition at pH 5.2.

Acknowledgment. Helpful discussions with Professor John D. Baldeschwieler are gratefully acknowledged. This work was supported by the National Science Foundation under Grant GP 4924, The National Institutes of Health under Grant GM 13545-01, and the Center for Materials Research, Stanford University.

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Oxidation of Radon in Aqueous Solutions

Sir:

We have observed an apparent oxidation of radon in aqueous oxidizing solutions under certain conditions. Previously, Fields, Stein, and Zirin reported that a radon fluoride of low volatility was formed when radon and fluorine were heated to 400° ,¹ but research on the chemistry of radon has been limited because of the short half-life and high specific activity of radon, a radioactive daughter of radium.

In our experiments, 10^{-7} M RaBr_2 solutions were allowed to remain in contact with various aqueous, oxidizing solutions for a period of 23 days or longer (six half-lives of radon). These solutions were then extracted with equal amounts of hexane. The relative amounts of radon in the two phases were determined by counting the 0.35-Mev α activity of a subsequent daughter, ^{214}Pb . The samples were counted after a 2-hr aging period which was sufficient time to essentially establish a state of secular equilibrium between the ^{222}Rn and the ^{214}Pb . The ratios of the ^{214}Pb counting rates in the two phases are given in Table I as the distribution ratio of radon between hexane and the various aqueous solutions. The error given is the standard deviation of the 6-12 trials run on each particular aqueous phase. A change from a nonpolar species in water to a polar or ionic species in oxidizing solutions is apparent. This behavior is not due to merely the influence of electrolyte in the aqueous phase. Tatsuya

(1) P. R. Fields, L. Stein, and M. H. Zirin, "Noble Gas Compounds," H. H. Hyman, Ed., The University of Chicago Press, Chicago, Ill., 1963, pp 113-119; *J. Am. Chem. Soc.*, **84**, 4164 (1962).

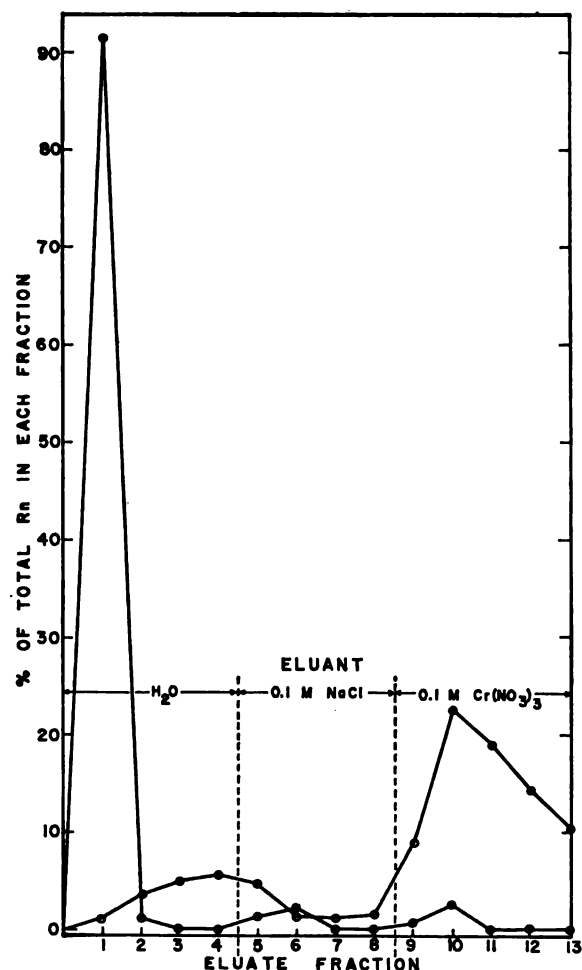


Figure 1. Anion exchange of nonoxidized Rn (●) in H_2O and oxidized Rn (○) in $0.1 \text{ M K}_2\text{S}_2\text{O}_8$, made strongly alkaline with NH_4OH .

and Yamasaki² have shown that addition of strong electrolyte to water lowers the solubility of radon in that phase, whereas in our experiments, the opposite effect was observed in that the distribution ratio for extraction was diminished when oxidizing electrolytes were present in the aqueous phase.

Table I. Distribution Ratios for Extraction of Radon into Hexane from Aqueous Solution

Aqueous phase (all contained RaBr_2)	Distribution ratios (hexane/aqueous)
H_2O	33.2 ± 6.3
5% H_2O_2	10.4 ± 1.5
5% H_2O_2 -1 N HNO_3	7.0 ± 0.9
25% H_2O_2	4.3 ± 1.8
25% H_2O_2 -1 N HNO_3	3.4 ± 1.5
0.5 M $\text{K}_2\text{Cr}_2\text{O}_7$	7.3 ± 0.8
0.2 M KMnO_4	2.6 ± 0.8
0.1 M $\text{K}_2\text{S}_2\text{O}_8$	0.2 ± 0.1

This apparent oxidation of radon is substantiated by the results of flushing the aqueous solutions with air or argon. Five times the amount of radon was removed from a nonoxidizing solution as was removed

(2) S. Tatsuya and A. Yamasaki, *Bull. Chem. Soc. Japan*, **38**, 1110 (1965).

from an oxidizing solution after 1 hr of bubbling air through the solutions. Further argon flushing of the nonoxidizing solution removed an additional small amount of radon, while further flushing of the oxidizing solution produced no additional loss.

Ion-exchange experiments were conducted with the radon from the $0.1 \text{ M K}_2\text{S}_2\text{O}_8$ and the 25% H_2O_2 solutions. They have shown the oxidized radon species to be nonionic in a neutral or acidic solution and to be negatively charged in a strongly alkaline solution. The resins used were 100–200 mesh Dowex 1-X8 anion exchanger (Cl^- form) and Dowex 50-X8 cation-exchange resin (H^+ form). The anion-exchange resin bed was washed exhaustively with sodium hydroxide to convert the resin to the hydroxide form. The various radon solutions were allowed to flow through the particular resin at a rate of 1 ml/min. The elution process then consisted simply of passing the desired eluent through the column at the same rate and collecting the eluate in 5-ml fractions. The amount of radon in each fraction was then determined in the previously described manner. The eluents consisted of water, 0.1 M NaCl , and $0.1 \text{ M Cr}(\text{NO}_3)_3$, consecutively. Oxidized radon in solutions that had been made strongly alkaline with ammonium hydroxide (trials at pH 11.4, 11.8, and 12.5) was retained on the anion-exchange column. Elution was not accomplished with water or chloride ions, but the radon was removed by elution with nitrate ions (see Figure 1). Oxidized radon in a neutral or acidic solution, when passed through the anion-exchange column, could be eluted with water. The same was found for oxidized radon, regardless of acidic or basic conditions, when passed through the cation-exchange resin. Nonoxidized radon produced from radium decay in water was not retained on either the cation- or anion-exchange resin regardless of the pH of the radon solution. Figure 1 gives an example of nonoxidized radon passed through an anion-exchange resin.

Oxidized radon in neutral or acidic solutions behaved as a polar but nonionic species. It was non-extractable into hexane, and, when it was passed through either an anion- or cation-exchange column, a larger volume of water (ca. 25 ml) was required for elution than was required for the elution of the nonoxidized form (ca. 5 ml).

If an analogy is drawn between radon and xenon,^{3,4} the oxidized radon species could be RnO_2 below a pH of 11 and HRnO_4^- above a pH of 11. However, further work is required to reveal the extent to which any such analogy can be made.

The oxidation of radon has been accomplished only in solutions in which ^{222}Rn has been allowed to come to secular equilibrium with ^{226}Ra . Attempts at oxidizing elemental radon, which had previously been separated from its parent radium, have been unsuccessful.⁵

(3) E. H. Appelman and J. G. Malm, *J. Am. Chem. Soc.*, **86**, 2141 (1964).

(4) H. H. Claassen and G. Knapp, *ibid.*, **86**, 2341 (1964).

(5) This work was supported by the Atomic Energy Commission, Contract AT(11-1)-584.

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Formation of Small Peptides. I. Secondary Structure in a Tetrapeptide

Previous work in this laboratory has shown that a folded hexapeptide is hydrogen-bonded intramolecularly between the two tripeptide moieties.¹ Goodman earlier reported that the onset of secondary structure occurred at the pentapeptide level in small peptides.² It appears from our data that the tetrapeptide *tert*-butoxycarbonyl-L-valyl-L-valyl-L-alanylglycine ethyl ester (I) has a secondary structure in chloroform, in methanol, and even in hexafluoroacetone sesquihydrate (HFA). Only in 0.5 M KF in HFA does I seem to have no secondary structure.

The amino acid structure of I corresponds to the sequence 133-136 of the β chain of human hemoglobin. This occurs at approximately the center of helix 3 of the β chain, a long helical segment which extends to the carboxyl terminus of the native polypeptide.³ Tetrapeptide I was synthesized in a stepwise manner by the dicyclohexylcarbodiimide⁴ method. Carboxy-L-alanine and glycine ethyl ester hydrochloride were coupled to give carbobenzoxy-L-alanylglycine ethyl ester, mp 103°, which was treated with hydrogen bromide in acetic acid and coupled with carbobenzoxy-L-valine to give carbobenzoxy-L-valyl-L-alanylglycine ethyl ester, mp 192-192.5°, $[\alpha]_D^{25} +5^\circ$ (c 2.0, dimethylamide). This tripeptide was similarly treated to the crystalline tripeptide L-valyl-L-alanylglycine ethyl ester hydrobromide, mp 181.5-182°, $[\alpha]_D^{25} +33^\circ$ (c 0.5, water), which was coupled with *t*-butoxycarbonyl-L-valine to give I, mp 212-213°, $[\alpha]_D^{25} +77^\circ$ (c 0.5, methanol). *Anal.* Calcd for $C_{22}H_{40}N_4O_7$: C, 55.94; H, 8.53; N, 11.86. Found: C, 55.94; H, 8.53; N, 11.75.

Solutions of I in deuteriochloroform were examined in the infrared at concentrations from 1.45×10^{-2} M to 1.45×10^{-5} M. The absorption band at 3330 cm^{-1} due to hydrogen-bonded N-H showed a marked decrease on the first tenfold dilution, so that its intensity at 1.45×10^{-3} M was roughly half that at 1.45×10^{-2} M. However, the two subsequent dilutions produced no significant changes in the relative intensities of the 3330- and 3430- cm^{-1} bands compared to the 1.45×10^{-2} M sample. This concentration-independent absorption indicates the presence of intramolecularly hydrogen bonded N-H.

The optical rotatory dispersion of I in the far-ultraviolet was found to show two troughs and a positive peak in both methanol and HFA (see Table I). In methanol, the troughs occurred at 235 and 205 $m\mu$ with a weak peak lying below 200 $m\mu$. A similar curve was obtained in HFA: troughs at 227 and 205 $m\mu$ and the weak peak again below 200 $m\mu$. On examination of the dispersion in 0.5 M KF in HFA, the trough at ca. 230 $m\mu$ was no longer present. The trough at 205 $m\mu$ and a peak at 189 $m\mu$ were the only distinguishable features. With molecular models, one can build three structures

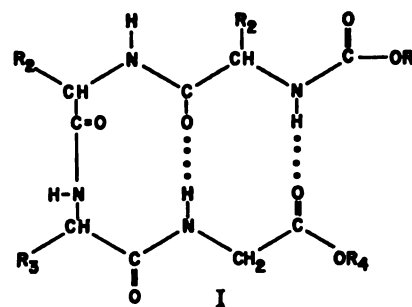


Figure 1. The folded β form.

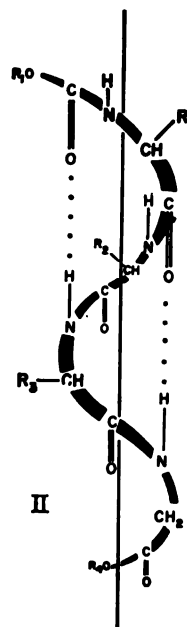


Figure 2. The 3_{10} helix.⁷

Table I. Mean Residue Rotations of ORD Troughs

Solvent	$[m]_{205}^{\text{deg}}$	$[m]_{235}^{\text{deg}}$
Methanol	-2800	-4100
HFA	-4200	-4800 ^a
0.5 M KF in HFA	-7000	... ^b

^a Minimum shifted to 227 $m\mu$. ^b Minimum absent.

for I with internal hydrogen bonds. One of these represents the beginning of an α helix and allows formation of a single intramolecular bond. The differences between the other two appear to be slight, and both allow formation of two hydrogen bonds. Structure I (Figure 1) corresponds to the folded, antiparallel β -sheet conformation proposed by Schwyzer⁶ for cyclization of hexapeptides. The other, structure II (Figure 2), is the 3_{10} helix of Bragg, Kendrew, and Perutz⁷ after Huggins.⁸ Our models appear to allow either a left-

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M. Goodman, E. E. Schmitt, and D. A. Yphantis, *J. Am. Chem. Soc.*, 84, 1288 (1962); M. Goodman, M. Langsam, and I. G. Rosen, *J. Am. Chem. Soc.*, 88, 305 (1966).

W. A. Schroeder, *Ann. Rev. Biochem.*, 32, 301 (1963).

J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, 77, 1067 (1955); H. G. Khorana, *Chem. Ind. (London)*, 1087 (1955).

M. Bergmann, L. Zervas, J. S. Fruton, F. Schneider, and H. G. Khorana, *J. Biol. Chem.*, 109, 325 (1936); lit. mp 98-99°.

(6) R. Schwyzer, *Ciba Found. Symp. Amino Acids Peptides Anti-metabol. Activity*, 1958, 171 (1958).

(7) L. Bragg, J. C. Kendrew, and M. F. Perutz, *Proc. Roy. Soc. (London)*, A203, 321 (1950).

(8) M. L. Huggins, *Chem. Rev.*, 32, 195 (1943).

handed or a right-handed screw sense in the 3_{10} structure.

The trough at 235 $m\mu$ observed for I in methanol suggests the 233- $m\mu$ minimum found for α -helical polypeptides,⁹ while the 227- $m\mu$ trough in HFA suggests the minimum found for certain proteins thought to have the β -sheet structure.¹⁰ The 205- $m\mu$ trough found in all our systems is probably the same as that found for the random-coil⁹ structure of polypeptides.

The mean residue rotations observed for small peptides at the extrema of the optical rotatory dispersion curves have been found to be much smaller than in the cases for high molecular weight polyamino acids. This is to be expected, since the amide groups involved in intramolecular hydrogen bonding in these peptides are so engaged on only one of their sides,² leaving the other free to interact with solvent. Our data on dipeptides and tripeptides are similar in nature but do not indicate the presence of such secondary structure as has been found for tetra- and higher peptides.²

Acknowledgment. This work was supported in part by Grant GM-11182 from the National Institute for General Medical Sciences, National Institutes of Health, U. S. Public Health Service, and by a grant from the American Chemical Society, Petroleum Research Fund.

(9) J. A. Schellman and C. Schellman, *Proteins*, **2**, 1 (1964).

(10) P.-Y. Cheng, *Proc. Natl. Acad. Sci. U. S.*, **55**, 1535 (1966).

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Metalated Carboxylic Acids. I. Alkylation

Sir:

Aliphatic carboxylic acids and their salts have not been reported to metalate by a simple, generalized process on treatment with Grignard reagents,¹ organolithium reagents,^{2,3} or alkali metal amides.⁴ Except for salts of acetic acid^{4a} and methacrylic acid,^{4b} homologous metalated carboxylic acid salts apparently decompose under conditions used for their formation.^{4a} Arylacetic acids, as well as their salts and simple carboxyl derivatives, are exceptional in that they produce "Ivanov" reagents on treatment with Grignard reagents or "Ivanov-like" reagents on treatment with other organometallic agents.⁵ Phenylacetic acid has been metalated also with sodium (potassium) amide in ammonia.⁶ This communication reports the metalation of aliphatic carboxylic acids to be a general

(1) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p 948 ff.

(2) The reaction of carboxylic acids with 2 equiv of an organolithium has preparative value for the synthesis of ketones, particularly methyl ketones.³

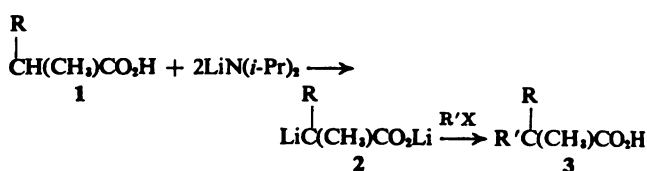
(3) E. A. Braude, *Progr. Org. Chem.*, **3**, 188 (1955).

(4) (a) D. O. DePree and R. D. Closson, *J. Am. Chem. Soc.*, **80**, 2311 (1958); (b) D. O. DePree, *ibid.*, **82**, 721 (1960); (c) R. D. Closson, U. S. Patent 2,850,528 (1958); D. O. DePree and W. R. Ellis, U. S. Patent 2,852,559 (1958); R. D. Closson and D. O. DePree, U. S. Patent 2,918,494 (1959).

(5) The terms "Ivanov" and "Ivanov-like" reagents apparently originated with F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952). For a recent review see P. E. Wright, Ph.D. Dissertation, University of Michigan, 1959; *Dissertation Abstr.*, **21**, 3642 (1960).

(6) C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956); W. J. Chambers, W. R. Brasen, and C. R. Hauser, *ibid.*, **79**, 879 (1957).

phenomenon which is illustrated by the metalation of isobutyric acid⁷ (1, R = CH₃) on treatment with lithium diisopropylamide.



The addition of isobutyric acid, 1 (R = CH₃), to lithium diisopropylamide, prepared from *n*-butyllithium and diisopropylamine, in tetrahydrofuran-heptane (hexane) at 0° produced 2 (R = CH₃) in homogeneous solution. Metalated isobutyric acid, 2 (R = CH₃), is apparently quite stable in the indicated solvent system at least up to 40°. The success of the metalation can be attributed in large measure to the use of lithium as metal, which, among other factors, confers favorable solubility on the metalated species.⁸ Homogeneous solutions of 2 (R = CH₃) of at least 1 *M* in tetrahydrofuran-heptane (hexane) (1:5, v/v) have been prepared. The existence of 2 (R = CH₃) could be demonstrated by alkylation with *n*-butyl bromide (iodide) to produce 2,2-dimethylhexanoic acid in preparatively useful yields (Table I).

The alkylation of 2 (R = CH₃) has synthetic utility for the preparation of highly hindered trialkylacetic acids. Several examples are illustrated in Table I. Useful yields were obtained for those alkyl halides that were not especially susceptible to elimination or related side reactions. The alkylation of dilithium derivative 2 (R = CH₃) appears to be superior, even for such a sterically hindered example, to the alkylation of sodium sodioacetate⁹ and more direct than most syntheses of trialkylacetic acids.¹⁰ The yields of product are comparable to those obtained for the alkylation of lithioisobutyronitrile.¹¹ When 2 (R = CH₃) was similarly treated with aliphatic dihalides, the tetramethyldicarboxylic acids listed in Table II were obtained.¹²

Table I. Synthesis of Alkyldimethylacetic Acids from Metalated Isobutyric Acid

$$\text{LiC}(\text{CH}_3)_2\text{CO}_2\text{Li} + \text{RX} \longrightarrow \text{RC}(\text{CH}_3)_2\text{CO}_2\text{H}$$

Alkylating agent	Alkyldimethylacetic acid, %
<i>n</i> -Butyl bromide	80
<i>n</i> -Butyl iodide	89
Allyl chloride	61
Benzyl chloride	46
β -Bromophenetole	41
2-Bromoethyl ethyl ether	66
Cyclohexyl bromide	6

* Satisfactory combustion analyses and consistent spectral data have been obtained for all products, as well as satisfactory comparison of physical properties with reported values. Yields are based on purified product.

(7) The metalation of other aliphatic, olefinic, araliphatic, and toluic acids will be subjects of future reports.

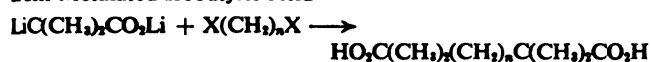
(8) Contrast with the poor solubility of sodium sodioacetate.^{4a,8}

(9) H. Hopff and H. Diethelm, *Ann.*, **691**, 61 (1966).

(10) C. Hennart, *Ind. Chim. Belge*, **30**, 820 (1965), reviews the various syntheses.

(11) K. Ziegler and H. Ohlinger, *Ann.*, **495**, 84 (1932).

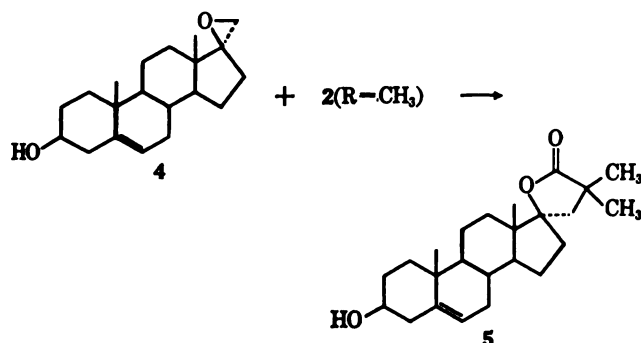
(12) A. M. Durr, Jr., H. H. Eby, and M. S. Newman, U. S. Patent 3,210,404 (1965); *Chem. Abstr.*, **64**, 1968d (1966) (for comparison with the preparation of $\alpha,\alpha,\omega,\omega$ -tetraalkyldicarboxylic acids by alkylation of esters).

Table II. Synthesis of Tetramethyldicarboxylic Acids from Metalated Isobutyric Acid

Alkylating agent	Tetramethyldicarboxylic acid, %
Ethylene dichloride	0
1,3-Dibromopropane	65
1,4-Dibromobutane	75 (97) ^a

^a Crude yield.

The utility of metalated carboxylic acids (2) for synthetic purposes can be partially illustrated with the following examples. Addition of 2-methylbutyric acid, 1 ($\text{R} = \text{C}_2\text{H}_5$), to lithium diisopropylamide as above produced 2 ($\text{R} = \text{C}_2\text{H}_5$) in homogeneous solution. Subsequent addition of *n*-butyl bromide gave 2-ethyl-2-methylhexanoic acid (76%) on acidification and distillation.¹³ Alkylation of 2 ($\text{R} = \text{CH}_3$) with 2,3-dichloropropene yielded 4-chloro-2,2-dimethyl-4-pentenoic acid (70%) which on hydrolysis in sulfuric acid¹⁴ conveniently produced 2,2-dimethyllevulinic acid (98%). Finally, to illustrate the reaction of metalated carboxylic acids with epoxides, treatment of 17 β ,20-epoxy-17 α -methyl-5-androsten-3 β -ol (4)¹⁵ with excess 2 ($\text{R} = \text{CH}_3$) at 40° produced spiro lactone 5 (81%).



(13) R. E. Pincock and J. H. Rolston, *J. Org. Chem.*, **29**, 2990 (1964), obtained 38% of the ethyl ester by alkylation with *n*-butyl bromide.

(14) J. A. Marshall and D. J. Schaeffer, *ibid.*, **30**, 3642 (1965).

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Acid-Catalyzed Ester Hydrolysis

Sir:

The mechanism of acid-catalyzed hydrolyses of ordinary esters is most frequently represented as occurring *via* water attack on preprotonated esters. Because the concentration of protonated ester is minute in aqueous

solutions of dilute acids, general acid catalyzed attack of water possibly *via* a cyclic transition state has been proposed as an attractive alternative pathway.¹ An attempt is made in this article to assess whether the activation produced by protonation of a small fraction of ester molecules is sufficient to account for observed hydrolysis rates in weakly acid solutions. A comparison is made between the specific rate constant for water attack on protonated esters and that calculated from hydrolysis rates of esters chelated to transition metal ions.

Observed second-order rate constants for acid hydrolysis of ordinary esters such as ethyl acetate² at 25° are about $10^{-4} \text{ M}^{-1} \text{ sec}^{-1}$. When these constants are multiplied by the acid ionization constants of about 10^{-5} M for carboxylic acids and esters,³ a first-order rate constant of about 10^{-9} sec^{-1} is calculated for the rate of water attack upon protonated esters in aqueous solutions. Protonation of esters is known to occur at the carbonyl oxygen.⁴ If the species with a protonated ether oxygen is advanced as the kinetically active one, its greater acid ionization constant decreases the concentration of kinetically significant protonated species which must be compensated by a correspondingly greater reactivity.⁵ In this research, 10^{-9} sec^{-1} is taken as the rate of water attack on the kinetically significant carbonyl oxygen protonated ester. The remainder of this paper attempts to determine whether this rate constant is reasonable.

An estimate may be made of the hydrolysis rate to be expected from placement of a positive charge on the carbonyl oxygen atom from two studies of transition metal ion catalyzed glycine ethyl ester hydrolysis. At 25° the first-order rate constant for water attack upon the dipositive cupric ion complex of glycine ethyl ester⁶ is $4.3 \times 10^{-5} \text{ sec}^{-1}$. The corresponding value for water attack upon N-protonated glycine ethyl ester⁶ is $5 \times 10^{-9} \text{ sec}^{-1}$. Since the rate for the cupric complex exceeds the last figure by almost 10^4 , while the effect predicted for an increase of unit positive charge at the nitrogen atom is less than 10^2 , hydrolysis in the cupric ion case proceeds *via* a chelated ligand with the transition metal ion positive charge located at the carbonyl oxygen. A similar argument for chelation has been presented for hydroxide ion attack at protonated and cupric ion complexes of glycine ethyl ester.⁶ Though hydrolysis proceeds *via* a chelated cupric ion complex, it is not known to what extent the carbonyl oxygen is chelated to the cupric ion, the primary binding site of which is at the amino nitrogen.⁶ Complete chelation might serve to increase the rate constant if it represents a value for a condition where the complexes are not chelated most of the time. It has been established that glycine ethyl ester is virtually completely chelated in the cobaltic complex $[\text{Co}(\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2)(\text{NH}_2\text{CH}_2\text{COOC}_2\text{H}_5)]^{3+}$. At 25° the first-order rate constant for ester hydrolysis due to water attack

(1) Ya. K. Syrkin and I. I. Moiseev, *Usp. Khim.*, **27**, 717 (1958); M. L. Bender, *Chem. Rev.*, **60**, 68 (1960).

(2) R. P. Bell, A. L. Dowling, and J. A. Noble, *J. Chem. Soc.*, 3106 (1955).

(3) E. M. Arnett, *Frogr. Phys. Org. Chem.*, **1**, 223 (1963).

(4) G. Frankel, *J. Chem. Phys.*, **34**, 1466 (1961).

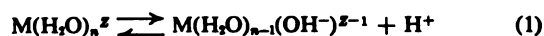
(5) G. Aksnes and J. E. Prue, *J. Chem. Soc.*, 103 (1959).

(6) H. L. Conley, Jr., and R. B. Martin, *J. Phys. Chem.*, **69**, 2914 (1965).

upon this tripositive complex⁷ is $7.2 \times 10^{-3} \text{ sec}^{-1}$, about 170 times faster than for the dipositive cupric complex. That this factor is about twice as large as might be predicted from the difference of one unit of positive charge in the two transition metal ion complexes may be due to only about half the cupric complexes being chelated at any one time or to a greater polarizing power for cobaltic ion at the carbonyl oxygen.

The rate constant from the second paragraph of $10^{2.5} \text{ sec}^{-1}$ for water attack at carbonyl oxygen protonated ester of unit positive charge exceeds by $10^{0.9}$ and $10^{4.6}$ the respective rate constants for water attack of $10^{-4.4} \text{ sec}^{-1}$ at the dipositive cupric chelate and $10^{-2.1} \text{ sec}^{-1}$ at the tripositive cobaltic chelate of glycine ethyl ester. On the basis of the argument so far presented, the large rate advantages for the protonated ester over the transition metal ion chelates suggest that acid-catalyzed ester hydrolysis proceeds much too rapidly to be accounted for by water attack on the small concentrations of preprotonated ester existing in weakly acid solutions. The argument presented is an electrostatic one based on considerations of specific rate constants of species of known charge distribution. It is generally recognized, however, that the polarizing power of the proton even when hydrated is greater than that of metal ions in similar solvents. It is necessary, therefore, to attempt an estimate of the relative charge densities at the carbonyl carbon, where water attack takes place, due to the different polarizing powers of the hydrated proton and cupric or cobaltic ions located at the carbonyl oxygen atom.

The relative σ -bond polarizing powers due to the hydrated proton and cations at an atom attached to oxygen may be estimated from the acid ionization constants for loss of a proton from their respective hydration spheres according to eq 1, where H^+ is an abbrevi-



ation for the hydrated proton. For M as H^+ , Cu^{2+} , and Co^{2+} , the respective $\text{p}K_a$ values⁸ for eq 1 are -1.7, 7.3, and 1.7, indicating that the polarizing power of the proton is about $10^{9.0}$ and $10^{3.4}$ times greater than for the aquo metal cations. However, when cobaltic ion is combined with five nitrogen donors, its polarizing power appears much decreased since for eq 2 $\text{p}K_a$ is 6.2. A steady increase in $\text{p}K_a$ for ionization from water



occurs as nitrogen is substituted for oxygen donors about the cobaltic ion.⁸ The hydrated proton appears to be $10^{7.9}$ times more polarizing than cobaltic ion with five nitrogen donors. No corresponding information seems to be available for cupric ion where the $\text{p}K_a$ for coordinated water ionization from a complex with one nitrogen donor is desired. Allowing one log unit per nitrogen donor, we may estimate the hydrated proton to be 10^{10} times more polarizing than cupric ion with one nitrogen donor.

(7) M. D. Alexander and D. H. Busch, *J. Am. Chem. Soc.*, **88**, 1130 (1966).

(8) "Stability Constants," Special Publication, No. 17, The Chemical Society, London, 1964.

Rate constants for water attack at carbonyl oxygen protonated esters may now be calculated by multiplying the rate constant for water attack at each metal ion chelate of glycine ethyl ester by the relative polarizing powers of hydrated proton and cation. We obtain for the cobaltic chelate, $10^{-2.1} \times 10^{7.9} = 10^{5.8} \text{ sec}^{-1}$ and for the cupric chelate, $10^{-4.4} \times 10^{10} = 10^{5.6} \text{ sec}^{-1}$. These values are about $10^{3.2}$ times greater than the experimental value of $10^{2.5} \text{ sec}^{-1}$ so that this last rate constant appears to be an attainable one. We conclude that acid-catalyzed hydrolysis of ordinary esters may well proceed by water attack on preprotonated ester.

Because of the symmetrical nature of ester hydrolysis and formation reactions⁹ and the similar values of carboxylic acid and ester ionization constants³ as suggested by their comparable dipole moments,¹⁰ the conclusion advanced here is applicable to the formation as well as the hydrolysis reaction. Partitioning of the tetrahedral carbon addition intermediate to yield ester or acid is comparable in both acid¹¹ and metal ion¹² catalyzed reactions so that the conclusions are not affected by a change in the rate-limiting step.

(9) R. B. Martin, *J. Am. Chem. Soc.*, **84**, 4130 (1962); **86**, 5709 (1964).

(10) C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p 304.

(11) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951); M. L. Bender, R. D. Ginger, and J. P. Unik, *ibid.*, **80**, 1044 (1958).

(12) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1889 (1957).

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N-Sulfonylamines

Sir:

We wish to report the generation of a new class of electrophilic amine derivatives designated as N-sulfonylamines ($\text{RN}=\text{SO}_2$). Unlike the related N-sulfinylamines¹ ($\text{RN}=\text{S}=\text{O}$), the N-sulfonylamines studied so far appear to be stable only at low temperature in solution. Ethylsulfamoyl chloride² (II) reacts rapidly with 1 equiv of triethylamine in toluene solution at -78° to afford a nearly quantitative yield of precipitated triethylamine hydrochloride. Filtration at this temperature provides solutions of I, which undergoes mildly exothermic polymerization upon warming. Successful interception of the N-sulfonylethylamine was accomplished by the addition to this solution of a nucleophile such as aniline which results in a 21% yield of N-phenyl-N'-ethylsulfamide (III).^{3,4}

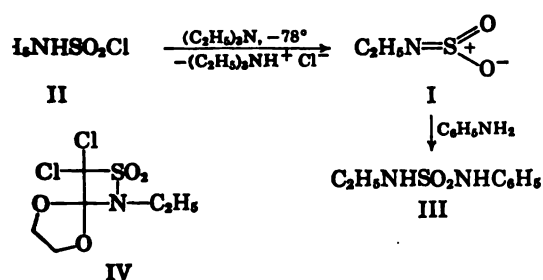
(1) G. Kresze, *et al.*, *Angew. Chem. Intern. Ed. Engl.*, **1**, 89 (1962).

(2) Prepared by the interaction of ethylamine hydrochloride and sulfonyl chloride in diethyl ether solution: N. C. Hansen, *Acta Chem. Scand.*, **17**, 2141 (1963); G. Schulze and G. Weiss, Belgian Patent 667,311 (1966).

(3) Identified by mixture melting point (where appropriate) and infrared spectral comparison with an authentic sample.

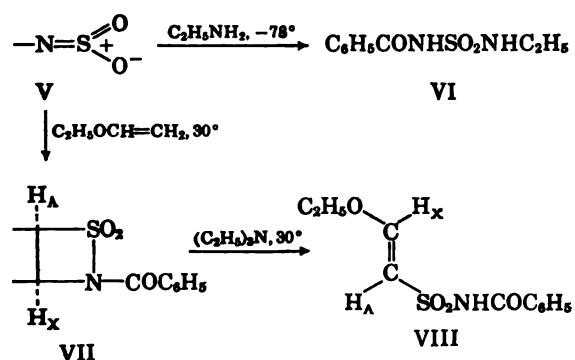
(4) A. Dorlars in Houben-Weyl's "Methoden der Organischen Chemie," Vol. 8, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, Germany, 1952, pp 720-721.

generation of I at room temperature in the presence of 2-(dichloromethylene)-1,3-dioxalane⁵ affords a quantitative yield of a cycloadduct, mp 74–75°, and the 1,2-thiazetidine 1,1-dioxide structure IV.⁶



Mass spectrum of IV displayed a molecular ion⁷ at m/e 262 and prominent ions at m/e 107 ($C_2H_5^+$) and 154 ($C_4H_4O_2Cl_2^+$) resulting from 1,4 and 1,5 cleavage only; therefore our proposed orientation of this cycloadduct rests upon the mechanistic consideration that the transition state polarization of $I + S + O_3$.

Electrophilic⁸ N-sulfonyl amines such as N-benzamide (V) were prepared in toluene solution at -78° in an analogous manner from benzoyl chloride.⁹ The existence of V was likewise confirmed by the formation of N-benzoyl-N'-ethylamide³ in 66% yield upon quenching with ethylamine at -78° .¹⁰



formation of V in the presence of excess ethyl ether at 30° in benzene solution affords a 71% of a cycloadduct, mp 87–88°, for which structure proposed based on the following evidence. The spectrum (CDCl₃, 60 Mc) displayed quartets for β_{B} and H_{X} centered at τ 6.53, 6.20, and 4.07,

M. McElvain and M. J. Curry, *J. Am. Chem. Soc.*, **70**, 3781

Satisfactory elemental analyses were obtained for all new compounds reported herein.

the appearance of a $M + 2$ and $M + 4$ ion resulting from the isotopic combinations substantiated the dichloro assignment

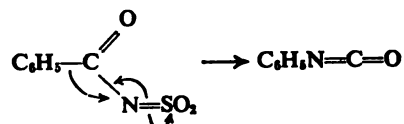
•Sulfonyl ethylamine fails to react at room temperature with low nucleophilicity such as ethyl vinyl ether.

prepared by the interaction of chlorosulfonyl isocyanate and acid in benzene solution. See ref 4, p 700.

Currently under investigation is the possibility that the reactive species is the triethylamine adduct, $C_6H_5CON^+SO_2^-(C_2H_5)_3$. As adducts of certain sulfenes have been reported recently by and D. Bucher, *Tetrahedron Letters*, 43, 5263 (1966).

respectively, with $J_{AB} = 14$ cps, $J_{AX} = 9$ cps, and $J_{BX} = 3$ cps, and the molecular ion appeared at m/e 255 in the mass spectrum. Treatment of VII with a benzene solution of triethylamine at 30° provided in nearly quantitative yield an isomer, mp $135\text{--}136^\circ$, assigned structure VIII.¹¹ The nmr spectrum (CDCl_3 , 60 Mc) of VIII indicated a doublet for H_X centered at τ 4.08 coupled ($J = 12$ cps) with H_A , whose absorption was superimposed on the aromatic and imide proton signals at τ 2.1–2.7. This evidence supports the structural assignment and establishes the orientation of the cycloaddition reaction leading to VII.

If a toluene solution of V at -78° is allowed to warm to room temperature in the absence of a trapping agent exclusive rearrangement to phenyl isocyanate⁷ occurs. It is interesting to speculate that this reaction may represent an α elimination of sulfur dioxide, *i.e.*



Studies are in progress on the synthetic usefulness of N-sulfonylamines in elaborating small-ring heterocycles.

Acknowledgment. We wish to thank the National Institutes of Health for a predoctoral fellowship to G. M. A. and Dr. C. C. Sweeley of the University of Pittsburgh (Graduate School of Public Health) for the mass spectra.

(11) This imide was isolated as the triethylamine salt which was converted to VIII upon silica gel chromatography. This salt also results from the reaction of ethyl vinyl ether with VI in the presence of excess triethylamine.

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Photoreduction of Acetone by Tributylstannane

Sir:

The intermediacy of the triplet states of ketones in their photoreductions is so well established¹⁻³ that there has been some doubt whether the corresponding excited singlet states have any chemical reactivity in bimolecular reactions in solutions. When it became clear that aliphatic ketones undergo type-II photoelimination from both singlet and triplet excited states,⁴ we suggested⁵ that the n, π^* excited singlet states of carbonyl compounds may in general be just as reactive

- (1) (a) G. Porter and F. Wilkinson, *Trans. Faraday Soc.*, **57**, 1686 (1961); (b) W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Am. Chem. Soc.*, **83**, 2789 (1961); (c) W. M. Moore and M. Ketchum, *ibid.*, **84**, 1368 (1962); (d) J. A. Bell and H. Linschitz, *ibid.*, **85**, 528 (1963).
(2) G. S. Hammond and P. A. Leermakers, *ibid.*, **84**, 207 (1962).
(3) P. J. Wagner, *ibid.*, **88**, 5672 (1966).
(4) (a) P. J. Wagner and G. S. Hammond, *ibid.*, **87**, 4009 (1965); (b) T. J. Dougherty, *ibid.*, **87**, 4011 (1965).
(5) P. J. Wagner and G. S. Hammond, *ibid.*, **88**, 1245 (1966).

as the corresponding triplet states but not undergo bimolecular reactions simply because the competing intersystem-crossing process is too rapid. If a bimolecular singlet-state photoreaction is to be observed, it seems obvious that both a very reactive substrate and a ketone with a low rate of intersystem crossing are necessary. Consequently, the photoreduction of acetone by tri-*n*-butylstannane has been studied.

Degassed hexane solutions containing 0.75 *M* acetone, 0.005 *M* fluorobenzene as internal standard, 0.38 *M* freshly prepared tri-*n*-butylstannane, and various concentrations of 2,5-dimethyl-2,4-hexadiene (0–0.10 *M*) or 1,3-pentadiene (5 *M*) were subjected to equal intensities of 3130-Å radiation. Quantum yields of 2-propanol formation were then determined by glpc analysis. Quite unexpectedly, it developed that a slow dark reaction produces isopropyl alcohol, or at least a compound with the same retention time on a FFAP glpc column, even in the presence of diene. It was at first assumed incorrectly that this unquenchable alcohol formation indicated some singlet photoreduction. However, in experiments in which analysis was performed immediately after irradiation, only traces of alcohol could be detected in samples containing 5 *M* diene and as much as 1.5 *M* stannane. Photochemical conversion of acetone to 2-propanol proceeded with unit quantum yield in samples containing no quencher. The 2-hydroxy-2-propyl radical initially formed apparently abstracts a hydrogen atom from a second stannane molecule with very high efficiency. In solutions containing 5 *M* diene, the quantum yield of 2-propanol formation was <0.01 for both 0.38 and 1.5 *M* stannane. Moreover, the quantum yield of acetone disappearance was negligible at high perylene concentrations, indicating that the dienes quench by triplet energy transfer rather than by trapping of intermediate radicals. The possibility of singlet quenching is eliminated by our observation⁴ that singlet type-II reactions are not quenched by dienes and by Rebbert and Ausloos' report that dienes do not quench the fluorescence of acetone.⁶ Stern–Volmer plots of relative quantum yields yielded a straight line, with a slope equal to $k_q/0.38k_{ah}$, where k_q is the bimolecular rate constant for quenching and k_{ah} is the bimolecular rate constant for hydrogen abstraction from the stannane by triplet acetone. The values of the slope were 32.5 and 29.1 M^{-1} in two separate runs.

That acetone should be photoreduced only from its triplet state by moderately high concentrations of tri-*n*-butylstannane becomes quite striking when the magnitudes of the relevant rate constants are considered. A 10% hexane solution of the stannane is only slightly more viscous than hexane itself, so that k_q can be estimated to equal $1 \times 10^{10} M^{-1} \text{sec}^{-1}$.⁵ The value of k_{ah} thus indicated by the Stern–Volmer slopes is $8 \times 10^8 M^{-1} \text{sec}^{-1}$. This very large number is not too surprising in view of the ability of the stannane to photoreduce acynaphthalenes² and greatly exceeds the measured rate of decay of triplet acetone in hexane alone,^{3,7,8} $1 \times 10^6 \text{sec}^{-1}$. The actual rate of reaction of triplet acetone with 0.38 *M* stannane is 3.2×10^8

sec^{-1} . If the rate of intersystem crossing (isc) of acetone is $4 \times 10^7 \text{sec}^{-1}$,⁹ and if singlet acetone were just as reactive as triplet acetone, then a quantum yield of unquenchable singlet photoreduction equal to 0.89 ought to be observed. However, since $\Phi_s < 0.01$, even at 1.5 *M* stannane concentration, $k_{1h} < 0.01 k_{isc}$. Borkman and Kearns estimated k_{isc} as $4 \times 10^7 \text{sec}^{-1}$ from the integrated absorption intensity of acetone and from their measured fluorescence quantum yield in solution of 0.01.⁹ Hecklen and Noyes have reported that the quantum yield of acetone fluorescence in the gas phase at 40° is 0.002.¹⁰ There is no reason to suspect that the radiative lifetime estimated from the integrated absorption intensity is in error by more than a factor of 2,¹¹ and thus it does not seem likely that k_{isc} for acetone exceeds $2 \times 10^8 \text{sec}^{-1}$. Nor does it seem possible that the stannane might be producing a heavy-atom enhancement of k_{isc} , since theory predicts¹² and experiment confirms¹³ that n, π^* excited states are not very susceptible to heavy-atom effects. If k_{1h} were to equal k_{ah} , k_{isc} would have to equal at least 10^{11}sec^{-1} . It seems much more likely that the lack of singlet-state reaction is caused by k_{1h} being smaller than $10^6 M^{-1} \text{sec}^{-1}$, so that it must be concluded that *excited singlet acetone is appreciably less reactive than triplet acetone*.

If excited singlet acetone is only $1/1000$ as reactive as triplet acetone in hydrogen-abstraction reactions, such should be the case with other aliphatic ketones, in which case the already mentioned intermediacy of both excited states in type-II processes^{4,5} requires a new explanation. From the measured singlet-state quantum yields and triplet-state lifetimes of 2-pentanone and of 2-hexanone,^{4,5} an assumption of equal reactivity in both states yields an estimate of $3 \times 10^9 \text{sec}^{-1}$ for k_{isc} . This value is larger than what might have been extrapolated from the published value for acetone⁹ but convincingly smaller than the value for acetone which results from the assumption of equal singlet and triplet state reactivity. Fortunately, it remains highly possible that type-II photoelimination may proceed by different mechanisms in the two excited states, namely by a concerted six-center process in the singlet and by a perhaps faster intramolecular hydrogen abstraction in the triplet.

There is no good theoretical explanation for n, π^* excited states of different multiplicities having different reactivities, and as long ago as 1958 Robinson predicted from a high-resolution spectroscopic investigation of formaldehyde that the two states should have similar reactivities.¹⁴ The prediction was based on the very similar electronic distribution in the two excited states. However, with a little hindsight it might be noted that triplet formaldehyde—and presumably other carbonyl compounds—comes much closer to assuming a pyramidal (tetrahedral) geometry than does the singlet state.¹⁴ Walling and Gibian have demonstrated the close parallel between the reactivities of

(6) R. E. Rebbert and P. Ausloos, *J. Am. Chem. Soc.*, **87**, 5569 (1965).

(7) R. F. Borkman and D. R. Kearns, *ibid.*, **88**, 3467 (1966).

(8) F. Wilkinson and J. T. Dubois, *J. Chem. Phys.*, **39**, 377 (1963).

(9) R. F. Borkman and D. R. Kearns, *ibid.*, **44**, 945 (1966).

(10) J. Hecklen and W. A. Noyes, Jr., *J. Am. Chem. Soc.*, **81**, 3858 (1959).

(11) E.g., W. R. Ware and B. A. Baldwin, *J. Chem. Phys.*, **40**, 1703 (1964).

(12) M. A. El-Sayed, *ibid.*, **41**, 2462 (1964).

(13) P. J. Wagner, *ibid.*, **45**, 2335 (1966).

(14) G. W. Robinson and V. E. DiGiorgio, *Can. J. Chem.*, **36**, 31 (1958).

e triplet states and of alkoxy radicals,¹⁶ and the simple minded appraisal might suggest that the y radical character of the triplet ketone is closely ated with its tetrahedral geometry.

nowledgment. Grants from the American Chemistry Petroleum Research Fund and the National Foundation provided financial support for work, and Dr. William Reusch provided useful sion.

C. Walling and M. J. Gibian, *J. Am. Chem. Soc.*, **87**, 3361

Peter J. Wagner

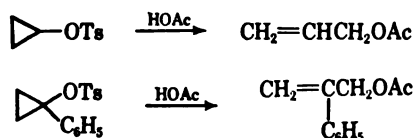
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Received February 11, 1967

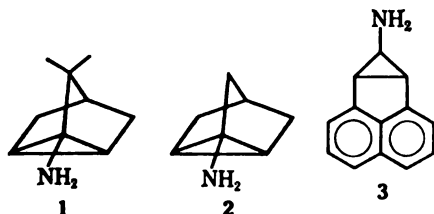
robicyclopropyl. Evidence for the Formation of a propanol during the Hydrolysis of a propyl Halide

wish to report unprecedented examples of sol- of a simple cyclopropyl derivative which result ducts that arise from the attack of solvent on an mediate ion in which the cyclopropane ring is itact.

ause of the facile rearrangement of the cylo- l to the allyl carbonium, ion, the only products have ever been observed in the solvolyses of isly substituted cyclopropyl derivatives have been en-chain allylic structures.^{1,2}



hough reports have appeared that the nitrous leamination of apotricyclylamine (1),³ 1-amino- cyclene (2),⁴ and 3-amino-1,2-cyclopropanoace- hene (3)⁵ resulted in unrearranged products, the



D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034

a) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiede- *ibid.*, **87**, 4006 (1965); (b) C. H. DePuy, L. G. Schnack, and *ausser, ibid.*, **88**, 3343 (1966).

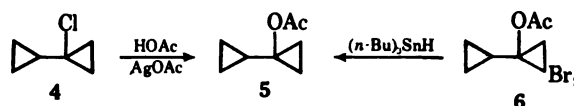
. Lipp and C. Padberg, *Chem. Ber.*, **54B**, 1316 (1921).

f. Hart and R. H. Martin, *J. Am. Chem. Soc.*, **82**, 6362 (1960).

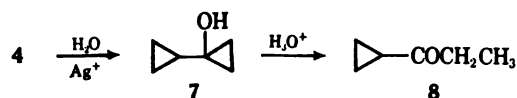
l. Pettit, *ibid.*, **82**, 1972 (1960).

explanation for the lack of rearrangement has been based either on considerations of orbital symmetry during the electrocyclic transformation to the allylic structure^{2b,6} or on the assumption that the mechanism may have been free radical in nature⁷ rather than involving a carbonium ion.⁸

In the present study, 1-chlorobicyclopropyl (4) was prepared in an over-all yield of 30–44% by vapor phase chlorination of the parent hydrocarbon followed by distillation of the monochloride product fraction which contained about 89% of the desired material.⁹



The acetolysis of chloride 4 in the presence of silver acetate at 115° for 72 hr produced a mixture of products from which a 42.6% component was isolated and identified as the unrearranged 1-acetoxycyclopropyl (5). A direct infrared spectral comparison with a sample prepared by the addition of dibromocarbene to the enol acetate of methyl cyclopropyl ketone, followed by reduction of the resulting dibromoacetate 6 with tri-*n*-butyltin hydride, confirmed the assignment of structure.¹⁰ In a similar experiment, the silver ion assisted hydrolysis of 4 (65°, 24 hr) produced a mixture of several compounds, of which the major component (65%) was identified as ethyl cyclopropyl ketone (8) by spectral comparison of the collected peak (vpc) with an authentic sample. No other single component of the product mixture represented more than 24%.¹¹ In view of the acetolysis results, the



presence of ketone 8 as the major product can be readily explained by assuming that 1-bicyclopropanol (7) is formed initially and then undergoes an acid-catalyzed ring opening to the ketone, the latter reaction having been well established for a variety of 1-substituted cyclopropanols.¹² If instead of undergoing an attack by water, the initially formed carbonium ion had opened to produce the allylic ion, a process of the type which occurs to the exclusion of all others during the solvolyses of other cyclopropyl derivatives, the expected product would have been β -cyclopropyl-allyl alcohol, a compound which may yet be identified as a minor constituent of the product mixture.

(6) S. J. Cristol, R. M. Sequeira, and C. H. DePuy, *ibid.*, **88**, 4007 (1966); R. B. Woodward and R. Hoffman, *ibid.*, **87**, 395 (1965).

(7) K. V. Scherer, Jr., and R. S. Lunt, III, *ibid.*, **88**, 2860 (1966).

(8) In the original explanation of the behavior of 2 and 3 by Hart,⁴ it was assumed that the unrearranged product formed from the collapse of a diazonium ion pair directly to the product.

(9) Chloride 4 gave the correct analysis for C_6H_9Cl and an nmr spectrum consistent only with the assigned structure.

(10) The nmr spectrum of 5 showed only complex multiplets from τ 8.0 to 8.6 and 9.0 to 9.9 and a sharp singlet at 8.1.

(11) Several other products have only been tentatively identified and will be discussed in detail in a subsequent publication.

(12) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Am. Chem. Soc.*, **88**, 3347 (1966), and references cited therein.

That the ion formed initially during the hydrolysis of 4 had considerable charge delocalization is suggested by considering a comparison of the solvolysis rate of 4 in aqueous ethanol¹³ with that of cyclopropyl chloride (Table I). Although a direct comparison of

Table I. Solvolysis Rates of Selected Cyclopropyl Derivatives

Compound	Temp, °C	Solvent	k, sec ⁻¹
Cyclopropyl chloride	95	50% EtOH	2.5×10^{-10} ^a
1-Chlorobicyclopropyl	95	50% EtOH	1.58×10^{-4} ^b
Cyclopropyl bromide	130	50% EtOH	2.6×10^{-6} ^c
1-Methylcyclopropyl bromide	130	50% EtOH	1.05×10^{-4} ^c
Cyclopropyl tosylate	108	HOAc	1.5×10^{-7} ^d
1-Phenylcyclopropyl tosylate	108	HOAc	1.93×10^{-3} ^e

^a Extrapolated data from ref 1; see J. A. Landgrebe and D. E. Applequist, *J. Am. Chem. Soc.*, **86**, 1536 (1964). ^b This work. ^c E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 2719 (1961). ^d Extrapolated from data in ref 1. ^e Reference 2b.

all the numerical values in the table is not possible because of the variety of solvents, temperatures, and leaving groups employed by various workers, it seems clear that the introduction of a cyclopropyl group into the 1 position of cyclopropyl chloride has a very large accelerating effect compared with the introduction of a 1-methyl or even a 1-phenyl group on cyclopropyl bromide and tosylate, respectively. Extensive charge delocalization in the ion formed initially during the solvolysis of 4 would be expected on the basis of the well-known behavior of the cyclopropyl-carbinyl system¹⁴ and is undoubtedly responsible for the unique solvolysis behavior of chloride 4. Further studies on systems of this type are in progress.¹⁵

(13) A substantial amount of ketone 8 was also formed during the solvolysis of 4 in 50 vol. % aqueous ethanol, i.e., under the conditions of the kinetic study. Most if not all of the other silver ion assisted hydrolysis products appear to be present as products of the aqueous ethanolysis.

(14) P. von R. Schleyer and G. W. Van Dine, *J. Am. Chem. Soc.*, **88**, 2321 (1966), and references cited therein.

(15) NOTE ADDED IN PROOF. Recent evidence for trapping a cyclopropyl cation in very low yield has been reported by W. Kirmse and H. Schütte, *ibid.*, **89**, 1284 (1967).

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The Synthesis of Ajmaline¹

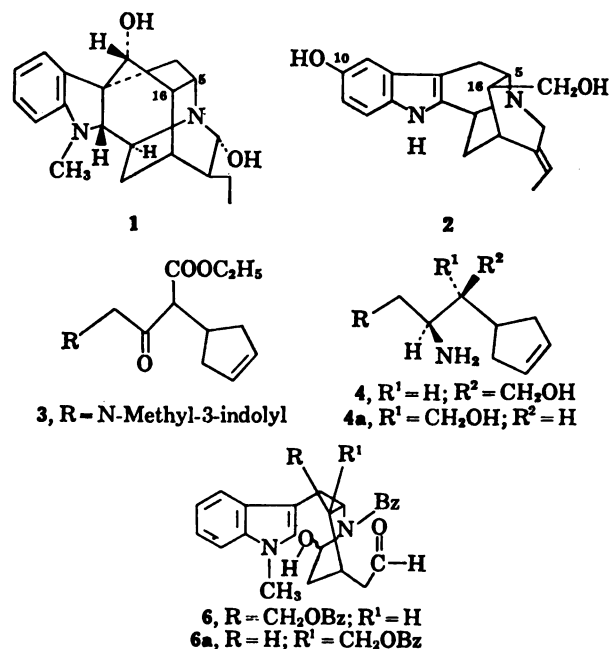
Sir:

Numerous naturally occurring ajmaline-sarpagine type alkaloids² are structurally characterized by the presence of the quinuclidine ring and the C₅ and C₁₅

(1) This work was presented before the Chemical Institute of Canada Symposium, Banff, Alberta, Canada, Aug 31–Sept 2, 1966.

(2) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin, Germany, 1964, p 67.

bond linkage, e.g., ajmaline (1) and sarpagine (2).¹ Since the structural elucidation of ajmaline by Woodward^{4a} and Robinson,^{4b} the unique features of the alkaloids have presented a considerable challenge to synthetic organic chemists. We describe herein the first total synthesis of ajmaline.



Condensation⁵ of the magnesium chelate of ethyl hydrogen Δ^3 -cyclopentenylmalonate⁶ with N-methyl-3-indolacetyl chloride, mp 9–11°, provided in 80% yield a keto ester (3), mp 20–23°. Reaction of 3 with methoxyamine followed by lithium aluminum hydride afforded in 70% yield an approximately 2:1 mixture of readily separable epimeric α,γ -amino alcohols 4 [diacetyl derivative, mp 140–141°; dibenzoyl derivative 5, amorphous] and 4a, mp 113.5–114.5° [diacetyl derivative, mp 117–118°; dibenzoyl derivative 5a, mp 170–172°]. These epimeric series of compounds are both useful for the synthesis of natural products, and they are interconvertible at a later stage of the synthesis (*vide infra*). Treatment of 5 and 5a with osmium tetroxide and then sodium metaperiodate afforded quantitatively aldehydes 6 and 6a,⁷ which were warmed with acetic acid at 50° for 1 hr to give tetracyclic aldehydes 7 and 7a in 40 and 50% yield, respectively. Structures 7 and 7a were compatible with spectral data⁸ of the respective compounds and

(3) W. I. Taylor, *Alkaloids*, **8**, 785 (1965).

(4) (a) R. B. Woodward, *Angew. Chem.*, **68**, 13 (1956); (b) R. Robinson, *ibid.*, **69**, 40 (1957).

(5) R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 2907 (1959).

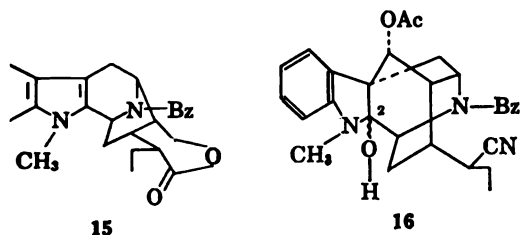
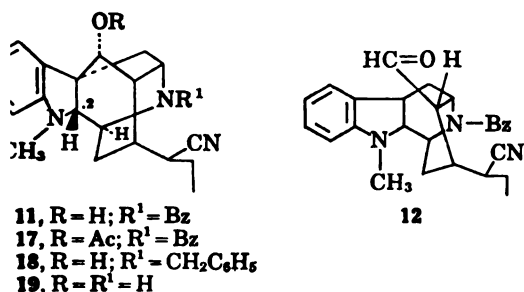
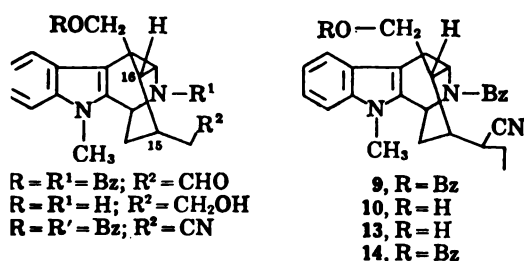
(6) Prepared from the corresponding diethyl ester: C. C. Lee and E. W. C. Wong, *Tetrahedron*, **21**, 539 (1965).

(7) The preparation of dialdehydes by this procedure was utilized in earlier indole alkaloid syntheses: (a) E. E. van Tamelen, M. Sharma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich, *J. Am. Chem. Soc.*, **80**, 5006 (1958); (b) E. E. van Tamelen, L. J. Dolby, and R. G. Lawton, *Tetrahedron Letters*, No. 19, 30 (1960).

(8) Spectral data included ultraviolet, infrared, nmr, and mass spectra. Compounds with no description of melting points have been amorphous. These compounds were purified until each gave a single spot on thin layer chromatography, using several solvent systems. All new crystalline compounds gave satisfactory elemental analyses.

characterized by converting them in more than one way into the corresponding dihydroxy secondary amine 7', mp 208–209°, and 7a', mp 162–163°, with aluminum hydride and then catalytic hydrogenation.

Conversion of 7 into the cyano compound 8 was achieved by treatment with hydroxylamine hydrochloride and benzoyl chloride in warm pyridine. The reduction of 8 (triphenylmethylsodium-tetrahydrofuran complex) with excess ethyl iodide to provide in 70% yield monoethyl compounds, from which a pure ethyl compound 9⁸ was isolated in 60–70% yield. Treatment of 9 with sodium methoxide removed the benzoyl group from the ester to give a hydroxy compound (10), mp 202.5–204.5°. Similarly, 8a was reduced into 9a⁸ and 10a.⁸ Spectra⁸ of 9, 10, 9a, and 10a were identical with those of the corresponding natural products of ajmaline, as shown below.



Compounds 7a, 7a', 8a, etc., are epimeric at C₁₄ with 7, 7', 8, respectively. Compounds 9 and 10 are racemates; 13 and 14 are *d* (or *l*) isomers.

Treatment of ajmaline oxime⁹ with benzoyl chloride in warm pyridine followed by sodium hydroxide afforded a cyanobenzamide (11), mp 265–266°. Reduction of 11 with lead tetraacetate³ followed by neutralization afforded an aldehyde (12), mp 219–220°, τ 0.45 (CHO) and 6.46 (N-CH₃), ν 1650 (C=O), ν 2200 (CN), ν 3400 (OH), ν 3000 (NH), ν 1500 (C=N), ν 1450 (C=C), ν 1350 (C=C), ν 1250 (C=C), ν 1150 (C=C), ν 1050 (C=C), ν 1000 (C=C), ν 950 (C=C), ν 900 (C=C), ν 850 (C=C), ν 800 (C=C), ν 750 (C=C), ν 700 (C=C), ν 650 (C=C), ν 600 (C=C), ν 550 (C=C), ν 500 (C=C), ν 450 (C=C), ν 400 (C=C), ν 350 (C=C), ν 300 (C=C), ν 250 (C=C), ν 200 (C=C), ν 150 (C=C), ν 100 (C=C), ν 50 (C=C).

A. L. Anet, D. Chakravarti, R. Robinson, and E. Schlittler, *J. Am. Chem. Soc.*, **76**, 1242 (1954). All compounds containing the benzamide group showed temperature-dependent nmr spectra.

corresponding hydroxy compound 13, mp 228–230° and 261–262°, O-benzoate (14).¹⁰ In the presence of alumina 12 was equilibrated with its epimer, 12a; nmr (CDCl₃, 60°)¹⁰ τ 0.32 (CHO) and 6.54 (N-CH₃), in a 3:7 ratio in favor of 12a. Thus 12 and 12a were interconvertible. The sodium borohydride reduction of 12a provided a hydroxy compound (13a) which was converted with hydrochloric acid to a lactone (15), mp 312–313°. Compounds 13 and 13a were oxidized with dimethyl sulfoxide and acetic anhydride (or carbodiimide)¹¹ to afford 12 and 12a, respectively. Identity of spectral data⁸ of 13, 14, 13a, and 14a with those of 10, 9, 10a, and 9a, respectively, established the structures and stereochemistry of synthetic intermediates.

Compound 12 upon treatment with hydrochloric acid in acetic acid and acetic anhydride underwent cyclization to afford in 65% yield compound 16, which was hydrogenated with platinum catalyst in 6 *N* hydrochloric acid to yield in 60% yield compound 17, mp 202–204°, and the corresponding 2 epimer in 30% yield.^{12,13} Reduction of 17 with lithium triethoxyaluminum hydride provided the corresponding benzyl derivative 18, mp 170.5–171.5°, which was in turn hydrogenolyzed to a secondary amine (19), mp 260–262°. Since 19 has already been converted into 1 with lithium aluminum hydride,⁹ we have completed the first synthesis of ajmaline.¹⁴

Acknowledgment. The authors are grateful to the National Research Council of Canada for financial support.

(11) A. H. Fenselau and J. G. Moffatt, *J. Am. Chem. Soc.*, **88**, 1762 (1966), and references cited therein.

(12) Compound 16 existed exclusively in the indoleninium form under these conditions: $\lambda_{\text{max}}^{\text{HCl}}$ 294 m μ (ϵ 7200), 244 (11,700), and 236 (13,200).

(13) Catalytic hydrogenation of 21-deoxyajmalal-A³ and 2-hydroxyvincedine under acidic conditions proceeded from the α side of the compounds to yield 2-*epi* series of ajmaline type compounds [J. Gosset-Garnier, J. Le Men, and M.-M. Janot, *Bull. Soc. Chim. France*, 676 (1965)]. Dreiding models of these compounds reveal that the α and β sides present only a slight difference in steric hindrance toward hydrogenation. The exclusive α attack reported above was presumably due to the presence of the protonated nitrogen atom in the α side. In accord with this view, 16, in which the amine was benzoylated, provided predominantly a compound of the normal series.

(14) Compound 15 was readily converted into N-methyl-10-desoxydihydrosarpagine³ through a sequence of four steps in 35% over-all yield.

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Received February 10, 1967

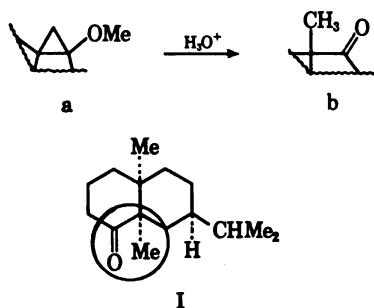
The Stereospecific Introduction of a Vicinally Functionalized Angular Methyl Group. A Synthesis of *l*-Valeranone

Sir:

The molecular rearrangement accompanying the transformation of β -diketones and related substances into monoketones by the action of zinc and acid has been interpreted in terms of reductive formation of cyclopropanols followed by acid-induced ring cleavage.¹

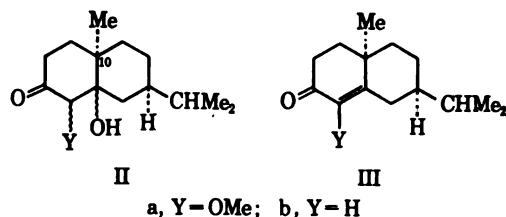
(1) (a) E. Wenkert and E. Kariv, *Chem. Commun.*, 570 (1965); (b) B. R. Davis and P. D. Woodgate, *J. Chem. Soc.*, 2006 (1966), and references therein.

The high specificity of protolysis of a fused, polycyclic methoxycyclopropane recently isolated from a Clemmensen reduction (in methanol solution) which had been quenched at an early stage ($a \rightarrow b$)² strongly recommended the use of cyclopropyl ethers in organochemical synthesis in general and for the construction of quaternary carbon sites next to oxygenated carbon centers in particular. We now wish to report a seven-step synthesis of *l*-valeranone (I)³ whose biosynthetically anomalous α -methylketo moiety (encircled structural unit in I) made this sesquiterpenic ketone an ideal object for exploitation of the new synthetic procedure.⁴

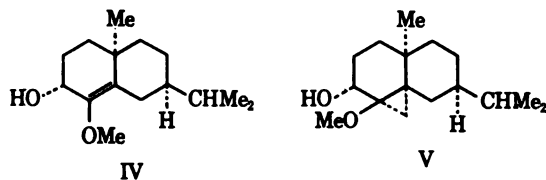


Condensation of *d*-carvomenthone with 1,4-dimethoxy-2-butanone,⁵ the *in situ* precursor of methoxymethyl vinyl ketone,^{6,7} under the influence of ethanolic potassium hydroxide in ether solution⁸ produced a mixture of ketol and isomeric enones, predominating (4.5:1) in the 10α -methyl configuration, from which the liquid ketol IIa [36%; infrared (neat): 2.90 (OH, m), 5.81 μ (C=O, s); pmr (CDCl₃): one-proton singlet at δ 3.99 (methoxymethine), three-proton singlet at δ 3.50 (methoxyl), 1.25 (angular Me), six-proton broad doublet at 0.83 (J = 6.0 cps, isopropyl methyls). *Anal.* Found: C, 70.94; H, 10.40] could be isolated. The structure of this ketol was determined by its conversion into the demethoxy derivative IIb [79%; infrared (neat): 2.84 (OH, m), 5.85 μ (C=O, s). *Anal.* Found: C, 74.37; H, 10.70] on lithium-ammonia reduction, followed by transforma-

tion of the latter on acid-induced dehydration⁹ into the unsaturated ketone IIIb (91%, mp 28–28.5°) whose optical rotatory dispersion curve was the mirror image of the known enantiomer.¹⁰ The ketones IIb and IIIb also were the products of a base-catalyzed condensation⁸ of *d*-carvomenthone and methyl vinyl ketone.



Treatment of the ketol IIa with ethanolic potassium hydroxide yielded the enone IIIa [78%; $[\alpha]^{21}_D -163^\circ$ (c 1.0, CHCl₃); infrared (neat): 5.96 (C=O, s), 6.21 μ (C=C, m); λ_{max} (EtOH) 257 m μ (ϵ 8500); pmr (CDCl₃): three-proton singlet at δ 3.61 (methoxyl), 1.27 (angular Me), six-proton pair of doublets at 0.97, 0.87 (J = 5.5 cps, isopropyl methyls). *Anal.* Found: C, 76.21; H, 10.15] whose lithium aluminum hydride reduction produced the alcohol IV [94%; $[\alpha]^{24}_D +25.7^\circ$ (c 1.2, CHCl₃); infrared (neat): 2.99 (OH, m), 6.01 μ (C=C, m); pmr (CDCl₃): one-proton multiplet at δ 4.44 (hydroxymethine), three-proton singlet at 3.58 (methoxyl), 1.14 (angular Me), six-proton pair of doublets at 0.94, 0.85 (J = 6.0 cps, isopropyl methyls). *Anal.* Found: C, 75.95; H, 10.71]. Simmons-Smith reaction¹¹ of this allyl alcohol¹² led to the cyclopropane derivative V [91%; $[\alpha]^{21}_D -38.9^\circ$ (c 0.8, CHCl₃); infrared (neat): 2.90 (OH, m), 3.25 μ (probably cyclopropyl H, w); pmr (CDCl₃): one-proton multiplet at δ 4.34 (hydroxymethine), three-proton singlet at 3.36 (methoxyl), 0.92 (angular Me), six-proton broad doublet at 0.83 (J = 5.5 cps, isopropyl methyls), one-proton doublets at 0.66, 0.21 (J = 6.0 cps, cyclopropyl methylene). *Anal.* Found: C, 76.33; H, 11.12].



Jones oxidation of V produced the ketone VIa [54%; mp 40.5–42.0°; $[\alpha]^{20}_D -39.8^\circ$ (c 0.8, CHCl₃); infrared (neat): 3.30 (probably cyclopropyl H, w), 5.92 μ (C=O, s); pmr (CDCl₃): three-proton singlet at δ 3.47 (methoxyl), 1.12 (angular Me), six-proton pair of doublets at 0.83, 0.81 (J = 5.5 cps, isopropyl methyls). *Anal.* Found: C, 76.96; H, 10.21] whose

(2) E. Wenkert and J. Zylber, unpublished observations.

(3) H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), 13, 1408 (1965), and references therein.

(4) J. A. Marshall, W. I. Fanta, and G. L. Bundy, *Tetrahedron Letters*, 4807 (1965), have executed a synthesis of *d*-valeranone along traditional lines.

(5) G. F. Hennion and F. P. Kupiecki, *J. Org. Chem.*, 18, 1601 (1953).

(6) While neither this vinyl ketone nor the keto diether appears to have found use in Robinson annulation reactions heretofore, the condensation of 2-methyl-3-hydroxy-2-cyclohexenone with a mixture of 3-methoxy-4-diethylamino-2-butanone and 1-methoxy-4-diethylamino-2-butanone (also an *in situ* precursor of methoxymethyl vinyl ketone), derived from a Mannich condensation of methoxyacetone, formaldehyde, and diethylamine, is on record [J. Szmuszkovicz, *ibid.*, 19, 1424 (1954)].

(7) Even though the Robinson ring annulation reaction is nowadays part of the standard repertoire of organochemical synthesis, the choice of the all-important vinyl ketone component in the Michael condensation is limited usually to compounds with no more daring structural variation than different alkyl substituents. The recent utilization of carbomethoxymethyl vinyl ketone in an annulation process was of immense value in diterpene synthesis [E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, 86, 2038 (1964)]. Methoxymethyl vinyl ketone or its equivalents can be expected to assume similar importance in the future.

(8) Cf. N. C. Ross and R. Levine, *J. Org. Chem.*, 29, 2341 (1964).

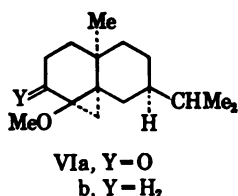
(9) Cf. E. Wenkert and T. E. Stevens, *J. Am. Chem. Soc.*, 78, 2318 (1956).

(10) C. Djerassi, J. Burakevich, J. W. Chamberlin, D. Elad, T. Toda, and G. Stork, *ibid.*, 86, 465 (1964).

(11) H. E. Simmons and R. D. Smith, *ibid.*, 81, 4256 (1959).

(12) W. G. Dauben and G. H. Berezin, *ibid.*, 85, 468 (1963); W. G. Dauben and A. C. Ashcraft, *ibid.*, 85, 3673 (1963).

Wolff-Kishner reduction yielded the tricyclic ether VIb [80%; $[\alpha]_D^{25} -55.6^\circ$ (c 0.8, CHCl_3); infrared (neat): 3.30μ (probably cyclopropyl H, w); pmr (CDCl_3): three-proton singlet at δ 3.25 (methoxyl), 0.91 (angular Me), six-proton doublet at 0.86 ($J = 6.0$ cps, isopropyl methyls), one-proton doublets at 0.30 and 0.16 ($J = 5.0$ cps, cyclopropyl methylene). *Anal.* Found: C, 81.49; H, 11.94]. Exposure of the latter to aqueous, methanolic hydrochloric acid afforded a quantitative yield of *L*-valeranone (I), identical in all respects with the natural plant product.¹³



(13) The authors are indebted to Dr. T. Takemoto (Tohoku University) for a gift of natural *L*-valeranone and to the National Science Foundation for partial support of this work.

(14) Public Health Service predoctoral fellow, 1965-.

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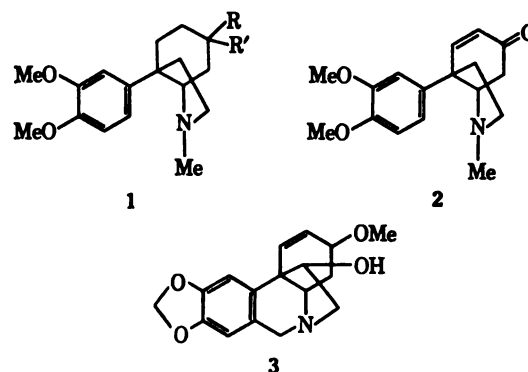
Received February 24, 1967

Biosynthesis of Mesembrine. The Incorporation of One-Carbon Units and the Origin of the C₆ Unit¹

Sir:

The alkaloid mesembrine (1, R = R' = O) along with several congeners, mesembrinol (1, R = OH; R' = H) and mesembrinine (2), occur in several plants of the *Aizoaceae* family.² The biosynthesis of these alkaloids is of interest since the skeletal framework would appear to contain a C₆-C₂-N unit, which in the case of mesembrine is comprised of the cyclohexanone ring and the attached C₂-N bridge, and a C₆ unit represented by the aromatic ring. The presence of an isolated C₆ unit is an unusual structural feature, and its biosynthetic origin is therefore of interest. We report the results obtained which provide information on a precursor to this unit and also the results obtained from the incorporation of the label from methionine-S-methyl-C¹⁴ into mesembrine.

The labeled compounds were fed to *Sceletium strictum* L. Bol.,³ and after periods ranging from 3 to 22 days the plants were harvested and the mesembrine isolated by using inactive mesembrine as a carrier. The results are summarized in Table I and are for mesembrine of constant activity. When the mesembrine derived



from the methionine feeding experiment was demethylated to give the activities for the O-methyl and N-methyl groups separately, the total activity was, within the limits of experimental error, the same as in

Table I. Incorporation of Radioactive Compounds into Mesembrine^a

Precursor	In- jected, μcuries	Iso- lation, days	Incor- poration, %
Methionine S-methyl-C ¹⁴	50	3	0.75
Tyrosine-3-C ¹⁴	50	10	0.051
Phenylalanine-2-C ¹⁴	50	10	<0.001
Phenylalanine [uniformly labeled in the ring with C ¹⁴]	50	22	0.059
	50	10	0.053

^a Samples were counted on a Nuclear Chicago Unix scintillation counter in toluene or dioxane-methanol-water scintillator solutions. ^b This figure may be regarded as a minimum since it was calculated on the basis of the weight of inactive mesembrine added to the plant extract.

the alkaloid. Furthermore, the ratio of the activities for the two methoxyls and the N-methyl group was 2:1. This suggests that each of these one-carbon sites makes an equal contribution to the total activity, in accordance with expectation for the result of a transmethylation process involving the S-methyl group of methionine.⁴

These results were independently confirmed by the degradation of radioactive mesembrine to veratric acid and demethylation of the latter to protocatechuic acid. The relative activities of the products of the degradation sequence are shown in Table II.

Radioactive mesembrine derived from phenylalanine [C¹⁴-ring labeled] was converted to veratric acid which was degraded further to protocatechuic acid. The relative activities of the degradation products indicate that the aromatic ring of phenylalanine is incorporated intact into the aromatic ring of mesembrine and that the label is restricted to this portion of the molecule. These results, when considered in conjunction with the results of the incorporation of radioactivity from tyrosine-3-C¹⁴ and the lack of activity in the mesem-

(1) Supported by National Science Foundation Grant GB-4361 and a grant-in-aid from Eli Lilly Co.

(2) A. Popelak, E. Haak, G. Lettenbauer, and H. Spengler, *Naturwissenschaften*, **47**, 150, 231 (1960); E. Smith, N. Hosansky, M. Shamma, and J. B. Moss, *Chem. Ind. (London)*, 402 (1961); M. Shamma and H. Rodriguez, *Tetrahedron Letters*, 4847 (1965).

(3) We are indebted to Mr. H. Herre, Stellenbosch, South Africa,

for supplying these rare botanicals, and to Mr. J. N. McQuay, Botany Department, Duke University, for invaluable help with their cultivation.

(4) See R. N. Gupta and I. D. Spenser, *Can. J. Chem.*, **43**, 133 (1965).

Table II. Relative Activities of Mesembrine and Its Degradation Products

	Methionine-S-methyl-C ¹⁴	Phenylalanine (C ¹⁴ -ring labeled)
Mesembrine	1.00	1.00
Veratric acid	0.64	1.00
Protocatechuic acid	<0.01	1.01
Methoxyls ^a	0.58	...
	0.64 ^b	
N-Methyl ^a	0.36	...

^a The activity on the carbons of the methoxyls and the N-methyl group in mesembrine was determined by the Zeisel method in which the liberated methyl iodide was trapped as (CH₃)₄NI and converted to the chloride on Dowex AG 1-X8 before counting.

^b Figure obtained from demethylation of veratric acid.

brine derived from phenylalanine-2-C¹⁴, indicate (1) that phenylalanine is not converted to tyrosine before incorporation into mesembrine, (2) phenylalanine can serve as the precursor of the aromatic C₆ unit of the alkaloid, and (3) further suggest but do not prove that

tyrosine may serve as a precursor of the C₆-C₂-N unit.¹

The results on the incorporation of these precursors into mesembrine are reminiscent of those obtained for the *Amaryllidaceae* alkaloids of the structurally related crinine series; cf. haemanthamine (3).⁶ Experiments to test the possibility that mesembrine is biosynthesized by a route which may be considered as an extension of that known to occur⁷ in the crinine series are in hand.

(5) Degradation studies designed to determine the position of the label in the mesembrine derived from tyrosine-3-C¹⁴ which would establish this are in progress.

(6) A. R. Battersby, H. M. Fales, and W. C. Wildman, *J. Am. Chem. Soc.*, **83**, 4098 (1961); P. W. Jeffs, *Proc. Chem. Soc.*, **80** (1962); W. C. Wildman, H. M. Fales, and A. R. Battersby, *J. Am. Chem. Soc.*, **84**, 681 (1962); D. H. R. Barton, G. W. Kirby, J. B. Taylor, and G. M. Thomas, *J. Chem. Soc.*, 4545 (1963); R. J. Suhadolnik and J. Zulalian, *Proc. Chem. Soc.*, 216 (1963).

(7) For a summary, see A. R. Battersby, *ibid.*, 189 (1963); D. H. R. Barton, *ibid.*, 293 (1963).

(8) NSF Undergraduate Research Participant, 1964-1965.

(9) NASA Fellow, 1965 to present.

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Book Reviews

Electrophilic Additions to Unsaturated Systems. By P. B. D. DE LA MARE, M.Sc. (New Zealand), D.Sc. (London), F.R.I.C. Professor of Chemistry, Bedford College, University of London, Regent's Park, London N.W.1, and R. BOLTON, B.Sc. (W. Australia), Ph.D. (Hull), Lecturer in Chemistry, Bedford College, University of London, Regent's Park, London, N.W.1. American Elsevier Publishing Co., 52 Vanderbilt Ave., New York, N. Y. 1966. x + 284 pp. 14.5 × 21.5 cm. \$14.50.

There is a tremendous amount of useful information in this relatively small book, which is primarily concerned with acid-catalyzed additions to olefinic double bonds. The additions of electrophilic hydrogen (water, weak and strong acids), halogens, oxygen, sulfur, nitrogen, phosphorus, arsenic, and the elements of groups I-IV are covered in Chapters 3-10. In the last three chapters one finds a treatment of electrophilic additions to acetylenes and allenes (Chapter 11), conjugated double bonds and aromatic hydrocarbons (Chapter 12), multiple bonds between carbon and other atoms, and also the N=N and S=O double bonds (Chapter 13). The text is well written in a clear, uncomplicated manner. Although there is too much material covered to expect all of it to be presented critically, the authors do a good job of analyzing the validity of the results they review.

Books which contain discussions of so many isolated experiments often lack continuity, but Drs. de la Mare and Bolton somehow manage to avoid that pitfall. The only criticism I have to make is that Chapter 2, titled "The Chemistry of Carbonium Ions" (despite the claim on the dust jacket that it is an important chapter), could better have been omitted, for it is an attempt in 19 pages to review all other carbonium ion processes not included in electrophilic additions to unsaturated molecules. Such material has been so well covered elsewhere that it is unnecessary here, and, further, it cannot be adequately treated in so brief a manner.

The authors, however, have provided a gold mine of information for professors who give graduate courses in physical organic chem-

istry, because their effort has produced a competent and critical survey of a field which has not previously been well reviewed. This last fact alone is enough to make "Electrophilic Additions to Unsaturated Systems" a popular monograph, for it fills a glaring gap in the literature of carbonium ions.

Although the subject matter is probably too specialized to be of much use to the average undergraduate, most practicing organic chemists can profit by reading this book.

(1) Operated by the U. S. Atomic Energy Commission under contract with the Union Carbide Corp.

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Knoxville, Tennessee

The Peptides. Volume II. Synthesis, Occurrence, and Action of Biologically Active Polypeptides. By EBERHARD SCHRÖDER and KLAUS LÜBKE, Hauptlaboratorium der Schering AG, West Berlin, Germany. Translated by ERHARD GROSS, National Institutes of Health, Bethesda, Maryland. Academic Press Inc., 111 Fifth Ave., New York, N. Y. 1966. xxvii + 632 pp. 16 × 23 cm. \$30.00.

This admirable book is a thorough, well-written compilation of information on biologically active peptides as it existed at the end of 1964. Together with the companion volume on synthesis, it will undoubtedly become the standard reference on peptides.

In common with most books designed to give a large amount of information in concise form, this book will not be exciting reading—

at least to the nonexpert. Its presentation is well organized, direct, and clear. The translation from the original German by Dr. E. Gross is excellent, and typographical errors are almost nonexistent.

The authors indicate in the Introduction that the book is written for the peptide chemist. Therefore, a critical comparison of different syntheses for a naturally occurring peptide could be expected, and indeed could be the most valuable contribution. Although some criticism is made, it is not enough. Take the example of oxytocin. The synthesis of this hormone by du Vigneaud and associates in 1953 is generally regarded as the first milestone in modern peptide synthesis. The importance of this synthesis is mentioned only in the Introduction. Reading on to the synthesis of oxytocin by Boissonnas and associates, we find a statement that their approach is more rational, but no reason is given why. Then, further on, the stepwise *p*-nitrophenyl ester synthesis by Bodanszky and du Vigneaud is given without any indication of its importance as the first significant synthesis by the now very popular active-ester approach.

There are many other places where the authors, who are well qualified by their own important contributions, could have given valuable critical appraisal as to the possibility of racemization, superiority of one synthesis over another in yields, etc. Generally speaking, the peptide chemist must still go back to the original literature for these comparisons, but Schröder and Lübke have given him a fine starting point.

This book will be useful to anyone interested in structure-activity relationships of peptides. Excellent tables for comparison are given; for instance, the table for oxytocin derivatives and analogs summarizes testing results on 67 compounds. The authors, of course, could only give results as reported in the literature, and, since biological testing results vary from one laboratory to another, absolute comparisons are not possible.

Since the peptide field is a broad one, including hormones, pressor and depressor substances, antibiotics, and even enzymes by an extension of the definition, it is unquestionably important. A few synthetic peptides are becoming available as drugs (oxytocin, angiotensin, ACTH derivatives), and undoubtedly there will be more. The work reported by Schröder and Lübke was mostly done in the past ten years, a testimony to improved methodology and increased interest. The next few years should bring even greater advances.

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Molecular Biology of Human Proteins with Special Reference to Plasma Proteins. Volume 1. Nature and Metabolism of Extracellular Proteins. By H. E. SCHULTZE, Formerly Scientific Director of the Behringwerke AG, Marburg/Lahn, Germany, and J. F. HEREMANS, Professor of Internal Medicine, University of Louvain, Belgium. American Elsevier Publishing Co., Inc., 52 Vanderbilt Ave., New York, N. Y. 1966. xii + 904 pp. 18 × 25 cm. \$52.50.

The first of two volumes on "Molecular Biology of Human Proteins" is a veritable encyclopedia. It is extremely heavily documented, having over 5500 references, and will serve as an excellent starting point for becoming familiar with almost any aspect of the subject. A unique feature is a comprehensive large chart relating the sedimentation coefficients of the various serum proteins with their behavior on paper and starch gel electrophoresis and on immunoelectrophoresis, followed by a table listing 93 different proteins found in serum and 43 tables giving additional data on those which have been obtained in purified form. A general introduction to structure and molecular and genetic variation in proteins is followed by sections on analytical methods in protein chemistry, the data on the various serum proteins mentioned above, methods of fractionation, synthesis and turnover of plasma proteins, and exchange between mother and child. The final section contains 10 chapters on proteins of extravascular fluids including intestinal fluids, urine, cerebrospinal fluid, saliva, milk, and colostrum, etc.

Both authors have had extensive experience in working with serum proteins, and one finds useful critical comments in their presentation of the subject matter. As with all encyclopedic works it tends to be sketchy in some areas; for example, it is doubtful that

one can learn much about the principle of electron spin resonance from the little more than a page devoted to it without consulting the references. A most objectionable feature is not the fault of the authors but of the publisher who used a very glossy paper so that one is constantly disturbed by reflection and glare while reading by artificial light. All in all the book is of great value and should be widely consulted.

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BOOKS RECEIVED, March 1967

U. W. ARNDT and B. T. M. WILLIS. "Single Crystal Diffraction." Cambridge University Press, Cambridge, England. 1966. 331 pp. \$15.00.

T. M. BIRSHTEN and O. B. PITTSYN. "Conformations of Macromolecules." Interscience Publishers, John Wiley and Sons, Inc., 605 Third Ave., New York, N. Y. 1966. 350 pp. \$14.50.

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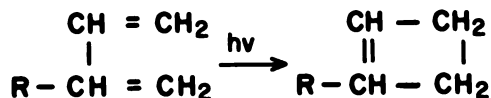
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A synthetic organic chemist may choose to ignore the quantum yield and concentrate his attention on the chemical yield which after all spells out the utility of a photochemical reaction. But the unfortunate fact about most photochemical reactions is that the time it takes to direct enough photons into the reaction vessel usually introduces another factor which cannot be ignored. The duration of a photochemical reaction is invariably measured in hours, frequently in days. This time is costly if the research worker has to watch the irradiation equipment constantly. It is no longer possible to leave a sealed ampoule of the material on the roof of the laboratory for six months in the hope that sunlight which is both cheap and plentiful (in certain latitudes) will make the reaction go.

The photoisomerization of 1, 3-dienes is a useful synthetic method for the preparation of the relatively rare cyclobutenes.¹



The chemical conversion in the reaction is essentially 100 per cent if a very dilute solution

(1-3 per cent) of the diene is used. The one exception among the simple dienes is 1, 3-butadiene which gives about 85 per cent of cyclobutene and 15 per cent of bicyclobutane.² But these isomerizations have very low quantum yields which range from 0.1 to 0.01. To convert 2 moles of 1, 3-butadiene would require 200 einsteins of photons of the right wavelength. The RPR-208 reactor gives 120 watts of uv light at 254 mμ which is highly suitable for irradiating 1, 3-dienes including 1, 3-butadiene. Yet its power input is only 500 watts. It requires no external cooling nor any special high-voltage power supplies so that it needs virtually no attention while in operation.

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1. K. J. Crowley, *Tetrahedron*, 21, 1001 (1965).
2. R. Srinivasan, "Advances in Photochemistry" Interscience (New York) 1966, Vol. IV, p. 118.

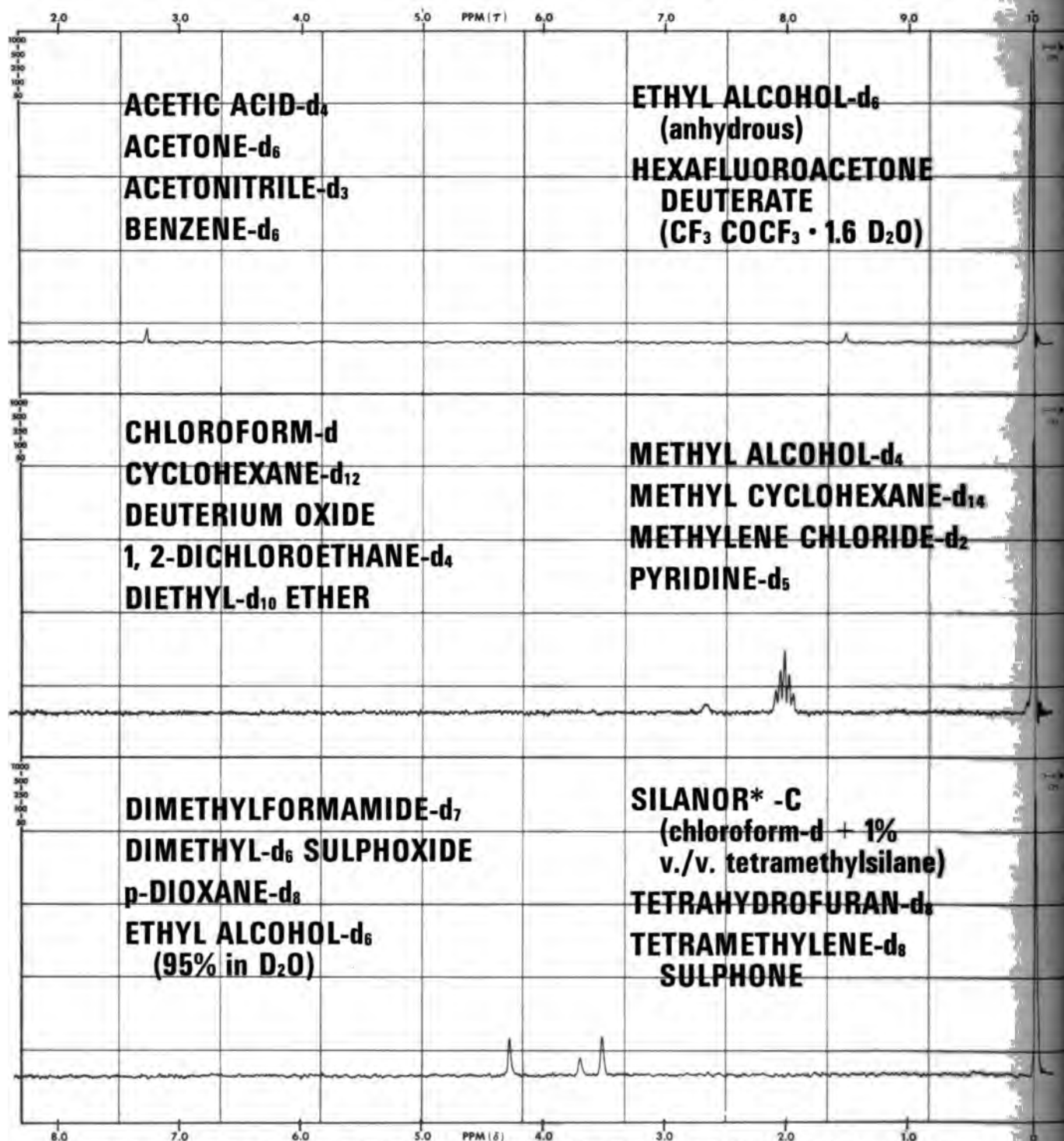
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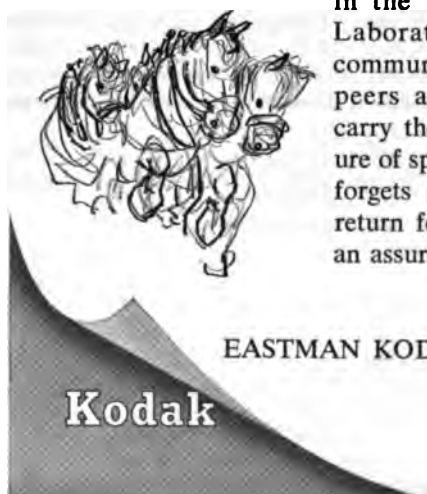
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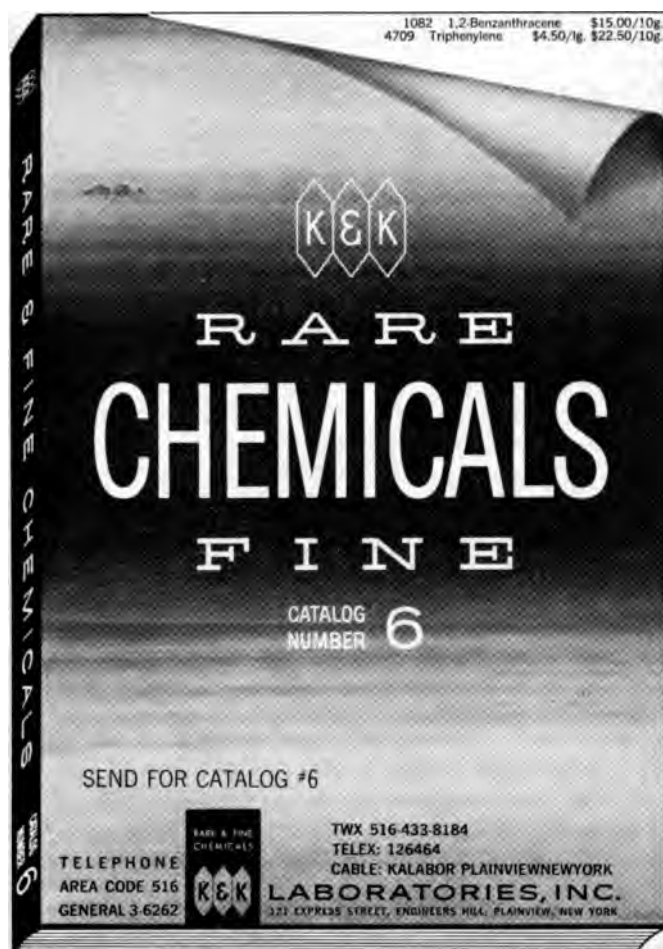
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Solute-Solvent Interactions. I. Evaluations of Relative Activities of Reference Cations in Acetonitrile and Water

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Abstract: Extrathermodynamic methods that have been used to split solvation energies of electrolytes into the ionic components and to compare single ion activities in different solvents are reviewed critically. In this work, the application of the Born equation is restricted in such a manner that the probable reliability of the comparisons is improved significantly. The free energy of transfer from acetonitrile to water associated with potentially useful reference couples, including the rubidium, thallium, ferrocene, and ferroin systems, is evaluated. The relative advantages of these couples are discussed.

It is well known that the properties of electrolytic solutes quite generally are modified substantially by interaction with the solvent. However, quantitative information about this important process is limited. In order to assess the relative extent of such interactions in various solvents, it is necessary to estimate single ion activities in different solvents relative to a common standard state.

The basic problem of evaluating single ion activities and Galvani potentials, and the related ones of comparing potentials in different solvents and splitting the solvation energies of electrolytes into the ionic components, constitute classical dilemmas of chemistry which have received much attention.³⁻⁵ The essential point is that, since the problem is not accessible to exact thermodynamics, it is necessary to follow extrathermodynamic procedures. Perhaps the most promising approach at present is based on an assumed ideal (nonspecific) behavior of certain solutes with respect to their oxidation-reduction or their solubility properties. Thus various authors have assumed that the standard

potentials of couples such as rubidium ion-rubidium amalgam,^{6,7} ferricinium ion-ferrocene,⁸ or the iron-(III-II) complexes of the phenanthrolines^{9,10} are relatively insensitive to specific solvation effects and therefore should be reasonably constant in different solvents. In a related approach, Popovych¹¹ has estimated single ion solvation energies from solubility data by assuming that in any given solvent the cation and anion of an appropriate reference electrolyte, such as triisoamylbutylammonium tetraphenylboride, will have equal free energies of solvation. These assumptions all suffer from certain limitations. Thus, the assumed equality of the free energy of solvation of the ions of the above reference electrolyte is based on the transport properties of the ions, specifically the approximate equality of the Stokes radii in methanol and water.¹² However, no simple correlation necessarily exists between the transport properties and the free energy of solvation of an

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ion, because other factors also affect transport properties. One such factor is the additional frictional force produced as a result of the dielectric relaxation induced by ionic motion in a polar medium;¹³ another is the change in local viscosity produced by the structure-making and structure-breaking properties of ions in a solvent such as water;¹⁴ and, finally, the size and effective "number" of the solvent molecules accompanying the ion during its migration also enter into its transport properties. This problem would persist even if a more ideal reference electrolyte, such as tetraisoamylammonium tetraisoamylboride,¹⁵ were used. The uncertainty would be particularly large in a dipolar aprotic solvent, such as acetonitrile, which solvates anions (except those that are highly polarizable) much more poorly than cations. For such solvents, splitting solvation energies of electrolytes on any basis involving directly or even indirectly the properties of an anion probably should be avoided. Furthermore, reference electrolytes of the type under discussion have quite high solubilities in dipolar aprotic solvents, and the required activity coefficients for the saturated solutions may be difficult to measure. Nevertheless, Popovych's approach may be eminently suitable for comparisons among solvents of similar relative solvating power for cations and anions, such as the water-methanol pair actually studied.¹¹

As far as the use of reference redox couples for the comparison of potentials in different solvents is concerned, desiderata include the lowest and most shielded charge possible, maximum size and symmetry, and minimum polarizability. Other factors to be considered are listed in ref 8. The high-charge type of the iron(III-II)-phenanthroline couples presents a serious problem; the Born equation (see below) predicts that for equal effective radii the free-energy difference associated with a III-II couple will be five times as large as that for a I-0 couple. This problem persists even after due allowance has been made for the effect of ionic strength on the formal potentials in both solvents (through activity coefficients and possible incomplete electrolytic dissociation). Furthermore, specific solvation effects generally are magnified with ions of high-charge type.

For the reasons mentioned above, we prefer to base our comparisons on I-0 couples, such as the rubidium (or cesium) and the ferrocene systems. The latter has the important advantage of considerably greater size, but a serious uncertainty comes from the fact that the reduced form of the couple is also present in solution, so that its solvation energy is involved, and this may vary considerably from one solvent to another (see below). For this reason we place prime emphasis on the rubidium scale, adjusted by a suitable modification of the Born equation, as described in this paper. The thallium(I-0) potential is then placed on this scale, and from the solubilities of thallium(I) salts the relative activities of anions in acetonitrile and water are evaluated, as described in the next paper.

Experimental Section

Preparation and Purification of Chemicals. Matheson Coleman and Bell practical grade acetonitrile was purified as described

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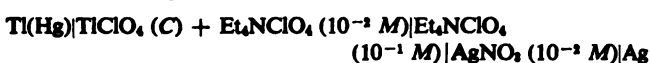
before.¹⁶ Thallium(I) perchlorate was prepared by treating 10 g of Fisher Purified thallium(I) nitrate with 40 ml of 3 M perchloric acid, evaporating to dryness, and then recrystallizing three times from water and drying at 120°. Tetraethylammonium perchlorate was prepared as described elsewhere.¹⁷ Thallium amalgam was prepared by adding Fisher Purified thallium metal to Bethlehem Apparatus Co. triple-distilled mercury and heating with an infrared lamp under a nitrogen atmosphere. Analysis of the amalgam by acidimetric titration¹⁸ showed that it contained 0.74 mole % of thallium. It was stored under 0.01 M aqueous sulfuric acid.

Potentiometric Experiments. Measurements were made with a Leeds and Northrup Model 8687 precision potentiometer. An H-type cell was constructed with 10-mm diameter fritted glass disks of fine porosity inserted 5 cm apart in the horizontal (salt bridge) section of the cell. Between the two disks a vertical tube was provided for the introduction or removal of salt bridge solution. In all experiments, one working (vertical) compartment of the all-acetonitrile cell contained an Ag(0.01 M AgNO₃) electrode as reference.¹⁹ The salt bridge compartment contained 0.1 M tetraethylammonium perchlorate. In the measuring compartment a thallium amalgam electrode dipped into deaerated 0.01 M tetraethylammonium perchlorate containing varying amounts of thallium(I) perchlorate. Immediately before use the thallium amalgam was washed twice with deionized water and then twice with acetonitrile, after which it was introduced into a J-tube electrode.²⁰ An atmosphere of nitrogen saturated with acetonitrile was maintained during all measurements.

Results and Discussion

In Table I the crystallographic radii and polarographic half-wave potentials of the alkali metals in acetonitrile and water are compared.^{7,21,22} In Table II the standard reduction potentials of various couples in the same solvents are compared.^{8,10,23-25}

Standard Potential of Thallium. From the results of three different series of experiments with 0.74 mole % thallium amalgam in the following cell



plots of emf vs. log *C* were linear with slopes near the theoretical value of 59 mv for values of *C* in the range 10⁻³ to 10⁻⁴ M. Extrapolation to *C* = 0 gave a formal potential (on the molar scale) *E*' for the particular amalgam used in 10⁻² M Et₄NClO₄ of -0.521 ± 0.003 v vs. the Pleskov reference electrode, hereafter designated as PE.

The Debye-Hückel equation for the rational activity coefficient, *f*_±, of a 1:1 electrolyte in acetonitrile is

$$-\log f_{\pm} = \frac{1.64S^{1/2}}{1 + (0.485aS^{1/2})} \quad (1)$$

where *S* represents the ionic strength. Rational and molal activity coefficients in acetonitrile are related as follows through the molality, *m*, of the electrolyte and the molecular weight, *M*, of acetonitrile.

$$\gamma_{\pm} = f_{\pm}/(1 + 2 \times 10^{-3}mM) = f_{\pm}/(1 + 0.082m) \quad (2)$$

It is evident that at molalities below 0.1 the two scales

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Table I. Comparison of Polarographic Half-Wave Potentials of Alkali Metal Ions in Acetonitrile (AN) and Water (W)

Ion	r_+ ^a	$-(E_{1/2})_{AN}^{b,c}$	$(E_{1/2})_{AN}^d$	$-(E_{1/2})_W^{b,c}$	$(E_{1/2})_W^e$	$\Delta E_{1/2}^{f,g}$	$\Delta E_{1/2}^{f,g}$ calculated ^h
Li ⁺	0.60	1.95	0.03	2.33 ^a	-0.20	0.23	0.25
Na ⁺	0.95	1.85	0.13	2.12	0.01	0.12	0.11
K ⁺	1.33	1.96	0.02	2.14	-0.01	0.03	0.02
Rb ⁺	1.48	1.98	0.00	2.13	0.00	0.00	0.00
Cs ⁺	1.69	1.97	0.01	2.09	0.04	-0.03	-0.02

^a Crystallographic radius, Å; ref 21. ^b Volts vs. aqueous sce. ^c Reference 7. ^d Volts vs. $(E_{1/2})_{AN}$ of Rb⁺. ^e Volts vs. $(E_{1/2})_W$ of Rb⁺. ^f $\Delta E_{1/2} = (E_{1/2})_{AN} - (E_{1/2})_W$. ^g Values of $\Delta E_{1/2}$ calculated from the modified Born equation with r_+ values of 0.81 and 0.72 for AN and W, respectively; see text. ^h Reference 22.

Table II. Comparison of Standard Reduction Potentials in Acetonitrile (AN) and Water (W) Based on an Adjusted Rubidium Molal Scale

Couple	Measured in AN, v vs. Ag/0.01 M AgNO ₃ (AN)	Derived for AN, v vs. nhe (W)	Value in W, v vs. nhe (W)
Rubidium(I-0)	-3.282 ^a	-2.779 ^d	-2.928 ^e
Thallium(I-0)	-0.648 ^b	-0.145	-0.336 ^f
Ferrocene(I-0)	+0.074 ^c	+0.577	+0.394 ^c
Ferrocene(III-II)	+0.846 ^c	+1.349	+1.120 ^c

^a Computed from amalgam potential given in ref 19; see text. ^b This work. ^c Reference 10; also see ref 8 and 35. ^d Born correction of +0.149 applied to value for water. On this basis the Ag/0.01 M AgNO₃ (AN) reference electrode has a potential of +0.503 v referred to nhe (W); see text. ^e Reference 23. ^f Reference 24.

differ by less than 1%. Salts such as Et₄NClO₄, which contain relatively "ideal" ions, are completely dissociated in acetonitrile at concentrations which are as low as 10⁻² M;¹⁸ hence $S \sim 10^{-2}$. Assuming that the ion-size parameter a can be approximated by the Stokes radii¹⁸ for Et₄N⁺ (2.79 Å) and ClO₄⁻ (2.29 Å), it is found that $a \sim 5$ Å and hence $\gamma_{\pm} \sim f_{\pm} = 0.74$. The formal potential, E_0' , is related to the standard (reduction) potential, E_0 , as

$$E_0' = E_0 + 0.059 \log f_{Tl}/(fx)_{Tl(Hg)} \quad (3)$$

where x is the mole fraction of thallium in the amalgam. Assuming that for the very dilute amalgam used $f_{Tl(Hg)} = 1$, it is found that $E_0 = -0.639$ v vs. PE. Applying the small correction of -0.0025 v for the free energy of amalgamation of thallium,²⁵ a final value of $E_0 = -0.642$ v vs. PE is obtained. Since the density of acetonitrile is equal to 0.777 g ml⁻¹, the corresponding value of E_0 on the molal scale is $-0.642 - 0.006$ or -0.648 v vs. PE.

Standard Potential of Rubidium. Pleskov¹⁹ measured an emf of 2.3275 v for the following all-acetonitrile cell with 0.54 mole % amalgam.



The Stokes radii of Rb⁺ and I⁻ are 2.75 and 2.33 Å, respectively. Hence, assuming a value of 5 Å for the ion-size parameter for RbI, we calculated from eq 1 that $f_{\pm} = 0.74$. Lewis and Argo²¹ determined the free energy of amalgamation of Rb by measurements on the following cell: Rb(Hg)|RbI in EtNH₃ containing 7.9 mole % NH₃/Rb. With 0.54 mole % amalgam (the same concentration as that used later by Pleskov), the emf was 1.0745 v. Consequently the standard potential of Rb in acetonitrile (on the molal scale) is given by

$$E_0 = -2.3275 - 0.059 \log (0.74 \times 10^{-2}) -$$

$$1.0745 - 0.006 = -3.282 \text{ v vs. PE}$$

Rubidium Potential Referred to the Water Scale. Modification of the Born Equation. The main purpose of this paper is to refer the potentials measured in acetonitrile vs. PE (listed in the second column of Table II) to that of the normal hydrogen electrode in water. Our reasons for selecting the rubidium potential for this purpose have been given in the introductory section.

The change in electrostatic free energy occurring when a mole of electrolyte is transferred from the gas phase to a medium of dielectric constant D is given as a first approximation by the Born equation

$$\Delta G_{\pm}^{\circ} = -\frac{N\epsilon^2}{2} \left(1 - \frac{1}{D} \right) \left(\frac{z_+^2}{r_+} + \frac{z_-^2}{r_-} \right) \quad (4)$$

where r_+ and r_- are the crystallographic radii of the cation and anion, respectively, and other symbols have their customary meaning. However, it is well known that the Born equation has the serious limitations that it recognizes neither specific solvation nor dielectric saturation. For the relatively ideal solutes considered here, specific solvation effects are likely to be unimportant, but the same is not true of the differences in dielectric saturation that may be expected in water and acetonitrile. There is no consensus about the quantitative aspects of dielectric saturation in water,²⁶ although a modification of the Born equation which explicitly allows for this perturbation has been used with apparent success to calculate free energies of transfer from water to deuterium oxide²⁷ and to water-alcohol mixtures.²⁸ Too little is known about dielectric saturation in acetonitrile to allow a quantitative treatment here. However, from a rough comparison of the known polarizability of the C≡N bond in HCN (31 Å³)²⁹ and the average polarizability of the water molecule (14 Å³),³⁰ it can be predicted qualitatively that dielectric saturation may be even more pronounced in acetonitrile than in water. (The dipole moments of acetonitrile and water are 3.37 and 1.84 D., respectively.)

In the absence of a reliable estimate of the effective dielectric constants of water and acetonitrile, the only practical approach is the well-known one introduced by Latimer, Pitzer, and Slanski,³¹ in which the effective

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radii of the solute ions, rather than the dielectric constant of the solvent, are corrected.

$$\Delta G_{\pm}^{\circ} = -\frac{Ne^2}{2} \left(1 - \frac{1}{D} \right) \left(\frac{1}{r_+ + r_+'} + \frac{1}{r_- + r_-'} \right) \quad (5)$$

A single pair of values for the correction terms r_+' and r_-' gives a fairly self-consistent match of calculated and experimental solvation energies for the alkali metal halides in water. This self-consistency provides some justification for the use of eq 5 to split solvation energies into the ionic components. Strehlow and his co-workers⁸ have carried out such a split for acetonitrile by comparing the solubilities (S) of the alkali metal halides in water (W) and acetonitrile (AN)

$$\Delta G_{\pm}^{\circ} \text{AN} = \Delta G_{\pm}^{\circ} \text{W} + 2RT \ln \frac{S_W}{S_{\text{AN}}} \quad (6)$$

and then fitting the $\Delta G_{\pm}^{\circ} \text{AN}$ values to eq 5. Omitting activity coefficients (which are unknown), the results lead to average correction terms r_+' and r_-' of 0.72 and 0.61 Å for acetonitrile, as compared to Latimer, Pitzer, and Slanski's values (subsequently revised; see below) of 0.85 and 0.25 Å, respectively, for water. However, the fluctuations in these values for the individual salts in acetonitrile are quite large. Furthermore, the smaller value of r_+' in acetonitrile means that the alkali metal ions are more strongly solvated in that solvent than in water, which is the opposite of what polarographic and other data unambiguously show to be the case. For example, the second last column of Table I shows that the half-wave potentials of the smaller alkali metal ions referred to that of rubidium or cesium are more negative (corresponding to more difficult reduction of the ion) in water than in acetonitrile, and that this negative shift increases smoothly with decreasing size of the ion. It is clear that all of these ions must be more strongly solvated in water than in acetonitrile. The stronger solvation of cations by water, as compared to that by acetonitrile, is not restricted to the alkali metals. In particular, high-charge type ions [e.g., Eu(III)] show large positive shifts in half-wave potential in acetonitrile,⁷ and spectrophotometric and a host of other data show that the proton is solvated much more strongly by water than by acetonitrile.³²

We now assume that the Born equation can be modified empirically according to the approach of Latimer, Pitzer, and Slanski to account for this negative shift in water. This is done with due cognizance of the demonstrated limitations of the Born equation in predicting absolute values of the electrostatic free energy of transfer of ions from the gas phase to water. However, by restricting the use of the equation to the difference between water and acetonitrile, and by imposing *still another restriction* by comparing this difference for rubidium with those for the other ions, many of the uncertainties inherent in the Born treatment should be eliminated. We assume that the "neutral" part of the solvation energy differences is the same in both solvents (zero-energy assumption²¹).

Sample Calculation. The second to last column in Table I shows that the difference between the half-wave potentials of lithium and cesium ions is 0.26 v smaller

in acetonitrile than in water, corresponding to a difference in solvation energy which is $0.26(96,500 \times 10^{-3})/4.18$ or 6.0 kcal mole⁻¹ smaller in the former solvent. From Noyes' recent tabulation,²¹ the average value of r_+' for water is 0.72 ± 0.03 . Equation 5 with $D = 78.5$ then predicts a difference in solvation energy of lithium and cesium of 56.1 kcal mole⁻¹ in water. Hence, in acetonitrile this difference amounts to $56.1 - 6.0 = 50.1$ kcal mole⁻¹. On substituting this value, and $D = 36.0$, for acetonitrile into eq 5, it follows that

$$50.1 = 161 \left(\frac{1}{0.60 + r_+'} - \frac{1}{1.69 + r_+'} \right)$$

from which the value of r_+' for acetonitrile is found to be 0.81 Å. Similar calculations for the pairs Li⁺-K⁺ and Na⁺-K⁺ (for which the differences in solvation energy are reasonably large) give r_+' values of 0.80 and 0.82 Å, respectively. We therefore assume an average value of 0.81, which on substitution into eq 5 leads to calculated positive shifts in the half-wave (or standard) potentials in acetonitrile as compared to water of 0.42, 0.28, 0.19, 0.17, and 0.15 v for Li, Na, K, Rb, and Cs, respectively. The last column of Table I shows an internally consistent agreement between calculated and observed differences in half-wave potentials. Virtually the same differences are calculated if the comparisons are based on the correction factor of Latimer, *et al.*, rather than that of Noyes. For exact comparisons of free-energy values in two different solvents it is necessary to allow for the difference in solvent molality in the two solvents. Such allowance is included in Gurney's J factors³³ and Frank and Rasaiah's "aquamolality" scales.³⁴ A correction of -0.021 v is required for this purpose. Consequently the standard potential of rubidium becomes $0.17 - 0.021 = 0.149$ v more positive in acetonitrile than in water. The standard potentials for the thallium, ferrocene, and ferroin couples in acetonitrile reported in the third column of Table II are based on this value.

In principle it should be preferable to apply the modified Born treatment to standard potentials, rather than half-wave potentials. However, the standard potential of lithium in water is uncertain²⁴ and that reported for lithium in acetonitrile¹⁹ appears to be seriously in error. We have discussed elsewhere⁷ factors to be considered in the comparison of half-wave potentials in different solvents. Many of the uncertainties associated with such comparisons should be minimized here, since only differences among the alkali metal ions are involved. For example, conductance data show that the influence of $M^+ClO_4^-$ ion-pair formation should be similar for all alkali metal ions and is quite small.

The Thallium, Ferrocene, and Ferroin Potentials. The positive shift in the standard potential of the thallium(I-0) couple (0.191 v) is considerably larger than those for rubidium (0.149 v) or potassium (0.169 v), even though its crystallographic radius (1.40 Å) is intermediate between those of the two alkali metals (1.48 and 1.33 Å). We attribute this additional shift to the "abnormally" strong hydration of Tl⁺,²¹ which may be the result of its empty 5f orbital.

(33) R. W. Gurney, "Ionic Processes in Solution," Dover Publications, New York, N. Y., 1953.

(34) J. S. Rasaiah, Ph.D. Thesis, University of Pittsburgh, 1965.

(32) J. F. Coetzee, *Progr. Phys. Org. Chem.*, in press.

the ferrocene potential is 0.18 v more positive in acetonitrile than in water. With $r_+ = 3.8 \text{ \AA}$ ³⁶ and values of 0.72 and 0.81 A for water and acetonitrile, respectively, eq 5 applied to ferricinium ion accounts for 0.12 v of this positive shift. It may appear that the missing 0.12 v must be the result of a lower solvation of ferrocene in water than in acetonitrile. However, the actual ratio of the solubilities of ferrocene in water and acetonitrile is smaller than would be expected on this basis. Kolthoff and Thomas¹⁰ determined a solubility value of $1.7 \times 10^{-6} \text{ M}$ voltammetrically in aqueous 0.1 M Et_4NClO_4 solution; we found a value of $2 \times 10^{-6} \text{ M}$ by extracting a saturated solution of ferrocene in pure water with carbon tetrachloride, evaporating (caution: ferrocene sublimes easily), and weighing. In acetonitrile we found a solubility of $1.5 \times 10^{-6} \text{ M}$. Assuming that in both solvents the activity coefficient of ferrocene is near unity, the expected standard potential resulting from this cause would be 0.24 v, rather than 0.12 v. It is possible that a decrease of 0.12 v in positive shift is caused by hydrophobic repulsion, which would decrease the activity of ferricinium ion in water. Finally, the reversed solubility ratio of ferrocene in the two solvents corresponds to 18 eu, which may be attributed quite reasonably to the reduced entropy expected on the basis of the Frank-Evans model¹⁴ as a result of possible formation of cage structures between ferrocene and ferricinium ion. We conclude that both ferrocene and ferricinium ion may be involved in specific interactions in water, and hence that this couple is unsuitable for our purpose.

The ferroin potential is 0.23 v (or 0.20 v based on the value in ref 36) more positive in acetonitrile than in water. This shift corresponds to an average "effective"

radius term in the Born equation of ca. 2.5 A, a value which is uncertain but not unreasonable. Although the ligand molecules are large, the structure of the iron(III) and iron(II) complexes is quite open, permitting close approach of both water and acetonitrile molecules. An additional complication was reported by Kratochvil and Knoeck.³⁶ Partial molal entropy values for the ferroin couple in acetonitrile indicate, as expected, a greater degree of solvent ordering around the iron(III) than around the iron(II) complex, but in water the situation is reversed. This difference in solvent ordering was attributed to preferential hydrogen bonding of water to localized regions of electronegativity on the iron(II) complex. Clearly specific interactions occur.

It therefore appears that complexes such as ferrocene and ferroin, which contain large organic ligands, may be useful for comparisons among relatively similar nonaqueous solvents, but not for comparisons with water, which is involved in a variety of specific interactions with such ligands, the details of which at present are incompletely understood.

In conclusion, it is likely that application of the Born equation in the restricted manner described in this communication results in a significant improvement in the reliability of comparisons of potentials in water and acetonitrile. However, it should be stressed that unambiguous proof of the validity of any split of solvation energies in any solvent is impossible at present.

Acknowledgments. We are indebted to Professor Henry S. Frank of this department for stimulating discussions on the interaction of solutes with the structure of water. This work was supported by the National Science Foundation under Grant No. GP-1479.

) D. R. Stranks, *Discussions Faraday Soc.*, **29**, 73 (1960).

(36) B. Kratochvil and J. Knoeck, *J. Phys. Chem.*, **70**, 944 (1966).

Solute-Solvent Interactions. II. Relative Activities of Anions in Acetonitrile and Water

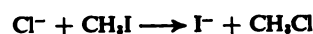
J. F. Coetzee¹ and J. J. Campion²

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213. Received December 12, 1966

Abstract: The free energies of transfer of the halides and of nitrate, perchlorate, and picrate ions from water to acetonitrile have been evaluated. Striking differentiation in the activities of these ions occurs in acetonitrile, to such an extent as to justify the statement that the chemistry of electrolytes in this solvent generally is dominated by differences in the properties of anions. The implications of this statement are discussed.

Considerable circumstantial evidence indicates that in solvents which are dipolar but essentially aprotic, such as acetonitrile, acetone, nitromethane, N,N-dimethylformamide, and dimethyl sulfoxide, anions are solvated more weakly and therefore possess higher activities than is the case in water. Only two examples

will be given here. (a) Bimolecular reactions of anions which pass through large, polarizable transition states containing the anion proceed much more rapidly in aprotic solvents than in others. For example, the relative rates of the following $\text{S}_\text{N}2$ reaction



in methanol, formamide, N-methylformamide, and N,N-dimethylformamide are 1, 12.5, 45.3, and 1.2

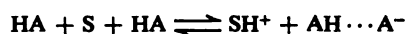
Address all correspondence to this author.
From the Ph.D. thesis of this author, University of Pittsburgh,

Table I. Comparison of Free Energies of Solvation of Anions (X^-) in Acetonitrile and Water Based on Solubility Products of Thallium(I) Salts and Potassium Picrate

Salt	Acetonitrile			Water			ΔpK_{sp}	Log $\mu\gamma_X - i$
	Sol ^a	γ_{\pm} ^c	pK_{sp}	Sol ^a	γ_{\pm}	pK_{sp}		
TlCl	$3.19 \times 10^{-7}^b$	1.00	12.99			3.76 ⁱ	9.23	5.6
TlBr	$4.25 \times 10^{-7}^b$	1.00	12.74			5.47 ⁱ	7.27	3.7
TlI	$8.07 \times 10^{-7}^b$	1.00	12.19			7.19 ⁱ	5.00	1.4
TlSCN	$9.04 \times 10^{-6}^b$	0.97	8.11			3.77	4.34	0.8
TlNO ₃	$5.03 \times 10^{-4}^c$	0.93	6.66	$4.407 \times 10^{-1}^e$	0.497 ^a	1.32	5.34	1.8
TlClO ₄	$3.31 \times 10^{-3}^c$	0.65	3.33	$5.22 \times 10^{-1}^f$	0.525 ^a	1.12	2.21	-1.4
KPi	$1.53 \times 10^{-3}^d$	0.72	3.92	$2.42 \times 10^{-3}^g$	0.88 ^c	3.34	0.58	-2.6

^a Solubility, as molality. ^b This work, results of tracer experiments. ^c This work, results of evaporating and weighing. ^d Kolthoff and Chantooni;⁸ complete dissociation assumed. ^e Molal activity coefficient, calculated from the Debye-Hückel equation with $a = 5$ Å. ^f Arithmetic mean of solubilities at 20 and 30° given in ref 9. ^g Reference 10. ^h Experimental values, ref 11. ⁱ Extrapolated values, ref 12. ^j Based on adjusted rubidium scale, according to which $\log \mu\gamma_X = -\Delta pK_{sp}(TlX) - 3.59 = \Delta pK_{sp}(KX) - 3.22$; see text.

$\times 10^6$, respectively.³ Such striking differences in rates have many important implications in organic chemistry in particular; for details refer to the extensive discussions by Parker and co-workers.^{3,4} (b) Many Brønsted acids dissociate in aprotic solvents, S, according to the following over-all scheme



in which the high activity of A^- results in "homoconjugation" (a term coined by Kolthoff) with the parent acid. Such reactions have been studied extensively in acetonitrile, particularly by Kolthoff and Chantooni,⁵ and also by others.⁶

The chemistry of electrolytes in aprotic solvents generally differs markedly from that in other solvents. Many of the most striking differences are dominated by variations in the activities of anions, such as those described above. However, present knowledge about the quantitative aspects of these variations in activity is unsatisfactory. This communication is concerned with the evaluation of such effects.

It is important to improve our understanding of the chemistry of electrolytes in aprotic solvents, because in such solvents a clearer picture of the intrinsic properties of solutes can be obtained than is possible in a strongly masking solvent such as water. However, for various reasons water must remain a solvent of unique importance, and the complex spectrum of interactions occurring between water and solutes has far-reaching implications in many branches of science. It is evident that comparisons of solute properties in water and in "nonwaterlike" solvents are bound to clarify our understanding of interactions occurring with water.

In the first paper of this series,⁷ we have presented the results of an extrathermodynamic evaluation of the free energy of transfer of certain reference cations, such as rubidium ion and also of thallium(I) ion, from water to acetonitrile. In the present paper the complementary quantities are evaluated for a series of anions from the relative solubilities of the corresponding thallium(I) salts in the two solvents. The results show striking differences in activity of anions in water and acetonitrile.

- (3) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).
- (4) B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Am. Chem. Soc.*, **88**, 1911 (1966), and earlier papers.
- (5) I. M. Kolthoff and M. K. Chantooni, Jr., *J. Phys. Chem.*, **70**, 856 (1966), and earlier papers.
- (6) J. F. Coetzee and G. P. Cunningham, *J. Am. Chem. Soc.*, **87**, 2534 (1965); J. F. Coetzee and G. R. Padmanabhan, *J. Phys. Chem.*, **69**, 3913 (1965).
- (7) J. F. Coetzee and J. J. Campion, *J. Am. Chem. Soc.*, **89**, 2513 (1967).

Experimental Section

Preparation and Purification of Chemicals. Eastman White Label tetraethylammonium chloride and bromide were recrystallized from 2-propanol and dried *in vacuo* at 50°. Tetraethylammonium iodide was prepared by titrating Eastman Yellow Label tetraethylammonium hydroxide solution with Eastman 50% hydrogen iodide. The solution was concentrated by heating, and the crystals were filtered off and recrystallized from ethanol. The product was dissolved in a 1:1 mixture of ethanol and acetone, then precipitated with ether, and finally dried *in vacuo* at 50°. Tetraethylammonium thiocyanate was prepared directly in acetonitrile by treating a solution of tetraethylammonium chloride with a 1% excess of Baker Analyzed Reagent potassium thiocyanate and then filtering off potassium chloride, which is virtually insoluble in acetonitrile. The solution was standardized by titration with silver nitrate. Fisher Purified thallium(I) nitrate was recrystallized from water and dried at 120°. Other chemicals were treated as described.⁷

Potentiometric Experiments. The apparatus was the same as that described previously. Solubility products of the thallium(I) halides and thiocyanate were determined by measuring the potential of a thallium amalgam electrode in a solution prepared by adding 5×10^{-4} to 5×10^{-3} M thallium(I) perchlorate to 5×10^{-3} M tetraethylammonium halide or thiocyanate.

Radioactivity Measurements. All measurements were made with a Geiger counter coupled with a Nuclear Chicago decade scaler (Model 181). Samples were counted on stainless steel planchets mounted on aluminum cards and covered with Mylar. Radioactive thallium(I)-204 nitrate supplied by the Oak Ridge National Laboratory was diluted with water to give an activity of ca. 1 mcurie/ml, and this solution was then used to dissolve an accurately weighed 100-fold excess of inactive thallium(I) perchlorate and to make it up to exactly 10 ml, giving a 0.500 M labeled solution. Precipitates of labeled TlCl, TlBr, TlI, and TlSCN were prepared by treating exactly 1 ml of this labeled solution with exactly 1 ml of 0.525 M reagent quality NaCl, KBr, KI, and NaSCN, respectively. The precipitates were washed at least four times with distilled water, transferred to polypropylene bottles, and dried *in vacuo* at 60°. Acetonitrile was added, and the bottles were sealed with serum caps and shaken for 24 hr. Aliquots then were transferred to polypropylene centrifuge tubes by means of plastic syringes and centrifuged. Aliquots (1 ml) were withdrawn with polypropylene pipets and evaporated on planchets under an infrared lamp. A Duco cement-ethyl acetate mixture (1 ml) was then added to each planchet and also evaporated, after which the samples were counted. Aliquots (1 ml) of 5.00×10^{-4} M labeled TlClO₄ (prepared by diluting the 0.500 M stock solution of TlClO₄) served as standards. It was necessary to use plastic ware, because it was found that glass adsorbed appreciable amounts of thallium. Several measurements were made with each precipitate, with a reproducibility of ca. $\pm 5\%$ in the number of counts.

Results

The solubilities of a variety of thallium(I) salts and potassium picrate in acetonitrile and water are compared in Table I.⁸⁻¹² The values listed for the halides

- (8) I. M. Kolthoff and M. K. Chantooni, Jr., *ibid.*, **87**, 4428 (1965).
- (9) "International Critical Tables," Vol. IV, McGraw-Hill Book Co., Inc., New York, N. Y., 1928, p 220.
- (10) A. Seidell, "Solubilities of Inorganic and Metal Organic Com-

thiocyanate in acetonitrile were obtained by tracer measurements and were checked potentiometrically as described in the Experimental Section. The potentiometric data gave the following pK_{SP} values: $TlCl$, 12.4; $TlBr$, 12.4; TlI , 11.8; and $TlSCN$, 8.0. We used the tracer data, because of the uncertainty involved in estimating the activity coefficients required for the results of the potentiometric experiments, which were primarily designed to detect possible formation of anion complexes. The Stokes radii of I^- are 2.33 and 2.37 Å, respectively,¹³ and that for Br^- is near 2.5 Å, as computed from the approximate data of Walden and Birr.¹⁴ Hence, as before,⁷ we use that $a = 5$ Å in the Debye-Hückel equation. In a typical experiment with a mixture of 5.0×10^{-2} M tetraethylammonium halide and 5.0×10^{-3} M $LiClO_4$, $S \sim 4.5 \times 10^{-2}$, assuming complete dissociation of the quaternary ammonium salt and no significant complexation beyond the first stage. (Actually, no complexation whatever is detected.) We obtain $f_{\pm}^2 = 0.35$, a value which is large enough to introduce considerable uncertainty. For further details, see ref 2.

Medium Activity

Medium Activity. It will be convenient here to refer to the activity coefficient of an ion in acetonitrile to its activity in a very dilute solution in water as standard state. The conversion factor required for this purpose is the medium activity coefficient,¹⁵ $\gamma_{i,AN}$.

$$\gamma_{i,AN} = (\gamma_{i,AN}^0) \gamma_{i,AN} \quad (1)$$

$\gamma_{i,AN}^0$ is the conventional Debye-Hückel activity coefficient of the ion in acetonitrile relative to acetonitrile as standard state,⁷ and $\gamma_{i,AN}$ is the desired over-all activity coefficient. It is clear that the medium activity coefficient simply represents the energy of transfer of the ion from acetonitrile to water.

$$\Delta G_i^0 = G_i^0(AN) - G_i^0(W) = RT \ln \gamma_{i,AN} \quad (2)$$

For further information, refer to the discussions by Robinson and Popovych.¹⁶

Medium activity coefficients are tabulated in the last column of Table I for several anions. The numbers are on $\log \gamma_{i,AN}$ values for Tl^+ and K^+ ions of 3.23 and 3.86, respectively, and a correction term of 0.36 for interconversion with the "aquamolality scale."¹⁷ The immediate significance of medium activity coefficients can be illustrated as follows. Compare the activity of chloride ion in 10^{-2} M solutions of lithium chloride in water and acetonitrile, referred in both cases to an infinitely dilute solution in water as standard state. In water, $\gamma_{Cl^-,W} \sim 0.9$; hence, $\gamma_{Cl^-,W}^0 \sim 9 \times 10^{-2}$. In acetonitrile, $\gamma_{Cl^-,AN}^0 \sim 0.8$ (calculated from the Debye-Hückel equation) and $\gamma_{Cl^-,AN} = 4 \times 10^{-2}$; hence, $\gamma_{Cl^-,AN}^0 \sim 3 \times 10^{-2}$.

¹⁵ Vol. I, 3rd ed, D. Van Nostrand Co., Inc., New York, N. Y., 1970.

¹⁶ R. A. Robinson, *J. Am. Chem. Soc.*, **59**, 84 (1937).

¹⁷ "Stability Constants," Part II, "Inorganic Ligands," The Chemistry, London, 1958.

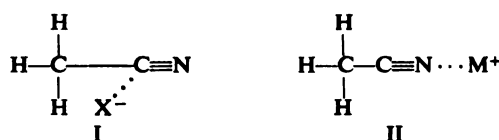
¹⁸ J. F. Coetzee and G. P. Cunningham, *J. Am. Chem. Soc.*, **87**, 1659.

¹⁹ P. Walden and E. J. Birr, *Z. Physik. Chem.*, **114**, 269 (1929).

²⁰ R. G. Bates, "Determination of pH," John Wiley and Sons, New York, N. Y., 1964.

²¹ D. Popovych, *Anal. Chem.*, **38**, 558 (1966).

All anions tested, except perchlorate and picrate ions, favor water over acetonitrile as solvent. In water, anions are stabilized mainly by strong hydrogen bonding as a result of the localized positive charges of the water dipoles. Although the dipole moment of acetonitrile is high (3.37 D.), and in a nitrile the positive pole apparently is localized mainly on the cyanide carbon atom,^{17,18} the charge density there is likely to be less than on the small water protons; in addition, a certain degree of charge delocalization nevertheless is likely to occur. Steric factors probably also impede solvation of anions by acetonitrile. Thus, because of the vicinity of the electron cloud of the $C \equiv N$ bond, an anion probably will be forced to take up the specific position indicated in structure I, resulting in loss of freedom of rotation. Furthermore, solvation of a (small) anion by more than one acetonitrile molecule then becomes improbable. The same is not true for the cylindrically symmetrical solvate of a cation, indicated in structure II.



Direct measurement of the medium activity coefficient of fluoride ion is likely to be prone to large errors. Fluoride ion should be a very strong base in acetonitrile, and traces of acidic impurities (such as water) should cause a large increase in the solubility of sparingly soluble fluorides. However, it may be possible to estimate an approximate value for its medium activity coefficient from those of the other halide ions. A plot of $\log \gamma_{i,AN}$ vs. the reciprocal of the crystallographic radius is linear (Figure 1), which on extrapolation to $r = 1.36$ Å gives $\log \gamma_{F^-,AN} \sim 14$. The corresponding value for potassium ion, which has virtually the same radius (1.33 Å), is only 2.86, or 11 units smaller. On the other hand, iodide ion and a hypothetical alkali metal ion of the same radius should have approximately the same medium activity coefficient. These estimates illustrate one aspect of the strong differentiation in the properties of electrolytic solutes occurring in acetonitrile.

The two intercepts in Figure 1 predict that a hypothetical alkali metal ion with a radius near 13 Å (the exact value is uncertain) should have equal solvation energies in acetonitrile and water, and that for a halide ion the analogous radius is only 2.3 Å. We attribute the fact that neither value is infinity (which may have implications for Izmailov's splits; see below) to the influence of other factors, in addition to that which may be termed a first-order (Born) electrostatic effect. The polarizabilities of the ions, which increase rapidly with increasing radius, may be such an additional effect. The polarizability of a halide ion is greater than that of an alkali metal ion of equal radius, and the difference increases with increasing radius.¹⁹ Hence, it is to be expected that this additional effect will cause equal solvation of a halide ion in the two solvents to occur

(17) F. E. Murray and W. G. Schneider, *Can. J. Chem.*, **33**, 797 (1955).

(18) W. Dannhauser and A. F. Flueckiger, *J. Phys. Chem.*, **68**, 1814 (1964).

(19) E. S. Rittner, *J. Chem. Phys.*, **19**, 1030 (1951).

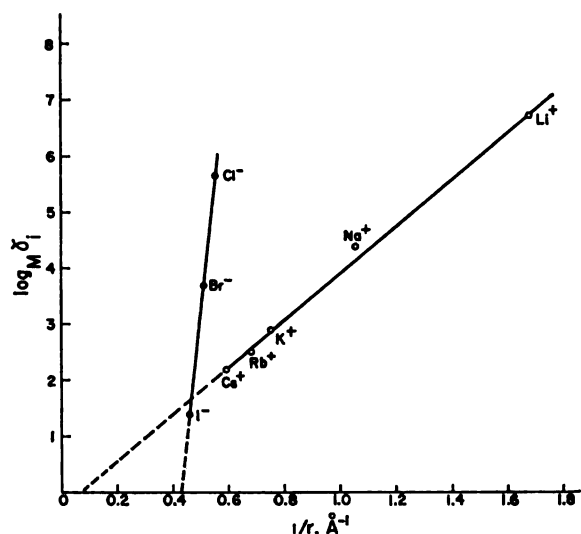


Figure 1. Dependence of medium activity coefficients of halide and alkali metal ions on radii.

at a smaller radius than would be the case for an alkali metal ion, as observed. Another factor which must be involved is the structure-making and structure-breaking properties of the ions in water.⁷

The very polarizable picrate ion is more stable in acetonitrile than in methanol, which has approximately the same dielectric constant, and in which $\log M\gamma_i = -1.1$.¹⁶ This is yet another illustration of the fact that the bulk dielectric constant of the solvent is not a very useful parameter in predicting the properties of solutes. The affinity of perchlorate ion for acetonitrile (or, more likely, its phobia for water) is puzzling.

The well-known fact that the solubility of a salt in acetonitrile (and other aprotic solvents) is particularly sensitive to the nature of the anion is clearly illustrated by the data in Table I.

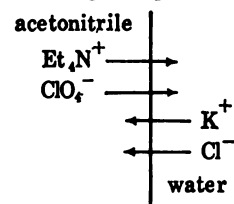
It is obvious that it now becomes possible to calculate the solubilities of numerous salts in acetonitrile from the known values in water, by using the $\log M\gamma_i$ values for anions reported in Table I and those calculated from the shifts in potential given in the previous paper.⁷ This will be true whether or not our original split of solvation energies into the ionic components was accurate. The only requirement is that for a given salt the sum of the two $\log M\gamma_i$ values be accurate.

Our results can be compared to two other estimates based on data appearing in the literature. Izmailov²⁰ split solvation energies of electrolytes into the ionic components by extrapolating plots of the solvation energies of the hydrogen halides, and of the differences in solvation energy between the hydrogen halides and the corresponding alkali metal halides, *vs.* the reciprocal of the radius of the varying ion to infinite radius; or, of appropriate combinations of solvation energies *vs.* the quantity $1/n^2$ to $n = \infty$, where n is the principal quantum number involved. The following $\log M\gamma_i$ values were obtained: Rb^+ , 1.6 (our value is 2.52); Cl^- , 8.0; Br^- , 5.0; I^- , 2.3. This split obviously indicates a greater difference between cation and anion activities than ours does. Izmailov's extrapolation is long and uncertain, a fact which undoubtedly contributes to the discrepancy (also see above).

(20) N. A. Izmailov, *Dokl. Akad. Nauk SSSR*, **149**, 1364 (1963).

Another estimate can be obtained from the solubility data of Pavlopoulos and Strehlow²¹ for the alkali metal halides in acetonitrile. The rubidium halides²² have the following molal solubilities²³ and molal mean activity coefficients,¹¹ respectively, in water: RbCl , 7.77, 0.58; RbBr , 7.04, 0.52; RbI , 7.72, 0.52. For acetonitrile the corresponding solubilities²¹ and activity coefficients (calculated from the Debye-Hückel equation with $a = 5 \text{ \AA}$) are: RbCl , 2.6×10^{-4} , 0.95; RbBr , 2.6×10^{-4} , 0.86; RbI , 8.0×10^{-4} , 0.56. Using our values of 2.52 for $\log M\gamma_{\text{Rb}^+}$ and 0.36 for conversion to the aquamolality scale, we calculate $\log M\gamma_{\text{X}^-}$ values of 5.6, 3.5, and 1.0 for the halides, in reasonable agreement with the numbers in Table I.

Liquid Junction Potentials. Many polarographic measurements in acetonitrile (and other nonaqueous solvents) have been carried out with an aqueous saturated calomel electrode (sce) as reference. Various estimates have been made of the magnitude of the liquid junction potential (see pertinent papers listed in ref 7). Provided the mobilities in both solvents and the medium activity coefficients of all ions involved are known, it should be possible, in principle, to calculate the junction potential *ab initio*. This required information is now available (for Et_4N^+ , we estimate $\log M\gamma_i \sim -0.3$ from the relative solubilities of Et_4NI in water and acetonitrile), but various other factors introduce gross uncertainties into such calculations. Typically we are dealing with the following complex interface



where the water phase may or may not contain agar. Furthermore, the exact profile of the interface is unknown (acetonitrile and water are miscible in all proportions). However, a semiempirical value of the junction potential can be obtained from our derived value of +0.503 v for the potential of the Pleskov electrode referred to the normal hydrogen electrode in water,⁷ *i.e.*, +0.257 v referred to sce, and Iwamoto's experimental value of +0.291 v for the Pleskov electrode *vs.* sce with 0.1 M Et_4NClO_4 as salt bridge.²⁴ The junction potential then is $0.291 - 0.257 = 0.034 \text{ v}$, of such sign as to make all potentials measured directly *vs.* sce too positive by 0.034 v. One may speculate that this relatively small value does not appear unreasonable in view of the marked compensating activity effects occurring across the interface. Thus, the medium activity coefficients of the four ions involved show qualitatively that the net effect is that the water phase is favored by an anion (Cl^-), and the acetonitrile phase also by an anion (ClO_4^-). Finally, it should be noted that, since potentials measured in acetonitrile against the sce certainly are reproducible to within a few milli-

(21) T. Pavlopoulos and H. Strehlow, *Z. Physik. Chem. (Frankfurt)*, **2**, 89 (1954).

(22) We are omitting from consideration those salts which form hydrates and for which comparisons therefore are more prone to error. In addition, the solubility reported for CsBr in acetonitrile appears to be inconsistent with the other data.

(23) Reference 10, pp 1429, 1433, 1437.

(24) R. C. Larson, R. T. Iwamoto, and R. N. Adams, *Anal. Chim. Acta*, **25**, 371 (1961).

volts, a very large value of the junction potential appears to be unlikely.

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Hydration of Undissociated Salts in Acetonitrile¹

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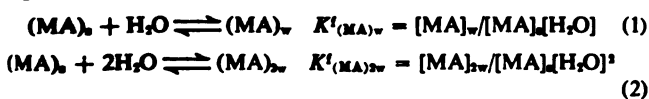
Contribution from the School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455. Received January 6, 1967

Abstract: An equation has been derived to calculate from the total and ionic solubilities of potassium picrate, salicylate, 3,5-dinitrobenzoate, and 3,5-dinitrophenolate in acetonitrile (AN) in the presence of known concentrations of water the individual formation constants $K'_{(MA)_w}$ and $K'_{(MA)_{zw}}$ of dissolved, undissociated mono- and dihydrated salts, $(MA)_w$ and $(MA)_{zw}$. Using these values and the previously determined values of formation constants of hydrated ions in AN, it has been possible to calculate the concentration of all species present in saturated solutions of the above salts in the presence of water. This allowed the calculation of the ionic dissociation constant $K^d_{(MA)_w}$ which was found to be greater than $K^d_{(MA)_s}$ (unhydrated salt). Unexplained is the result that $K^d_{(MA)_w}$ of potassium salicylate was found smaller than the corresponding constant of the anhydrous salt. In the presence of water the dissociation constant of the anhydrous salt was found to be virtually unaffected up to a water concentration of 0.6 *M*. The red solid salt, potassium 3,5-dinitrophenolate, changes into a yellow solid in the presence of small concentrations of water in AN. This solid was found to be a monohydrate. No hydrated solid was formed with the other salts used. The ionic dissociation constant of the monohydrate was found greater than that of the anhydrous salt, while the constant of the dihydrate was found considerably greater than that of the monohydrate.

In a previous paper² the equilibrium constant of the hydration of several monovalent ions I^\pm was determined. In that study it was not necessary to consider a reaction between the dissolved undissociated anhydrous salt, $(MA)_s$ (M^+ and A^- both being monovalent ions), and water.

In the present investigation the formation constants of the hydrates of the potassium salts of picric, salicylic, and 3,5-dinitrobenzoic acids and 3,5-dinitrophenol were determined. The potassium ion forms only a monohydrate with a formation constant of 1, while the sodium ion is much more strongly hydrated and forms at least a mono- and a dihydrate. For this reason sodium salts have not been used in the present study as they are expected to form higher hydrates than those of potassium. On the basis of the uncertainty in the assumptions made and in the experimental results, the hydration and dissociation constants calculated for sodium salts would be considerably more uncertain than those of hydrated potassium salts.

Denoting $(MA)_s$ as the unhydrated potassium salt and $(MA)_{zw}$ as the hydrated salts, the following equilibria can be written



From the total molar solubility, s_t , and the total ionic solubility, i_t , in presence of known concentrations of water eq 3 results, $[MA]_s$ being the solubility of undissoci-

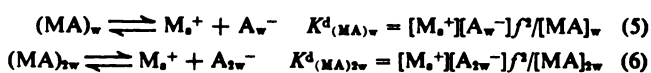
$$s_t = i_t + [MA]_s + [MA]_{zw} \quad (3)$$

ated anhydrous salt in absence of water and $[MA]_{zw}$ the total concentration of hydrated undissociated salts in presence of water. From the experimentally determined values of s_t , i_t , and $[MA]_s$, $[MA]_{zw}$ is readily obtained. Assuming that the ratio of the solubility product and dissociation constant of $(MA)_s$, $K_{sp}/K^d_{(MA)_s}$, equal to $[MA]_s$, does not change with water content, the values of the individual formation constants K' of the hydrates (eq 1 and 2) are found from the relation

$$\frac{s_t - i_t - [MA]_s}{[MA]_s[H_2O]} = \frac{[MA]_{zw}}{[MA]_s[H_2O]} = K'_{(MA)_w} + [H_2O]K'_{(MA)_{zw}} \quad (4)$$

which is derived by combining eq 1-3. A plot is made of $s_t - i_t - [MA]_s/[MA]_s[H_2O]$ vs. $[H_2O]$. If the slope of the linear plot is zero or close to zero, it is safe to conclude that $y = 1$ and only a monohydrate is formed. When the linear plot does not have a slope of 0, $y = 2$, the intercept being equal to $K'_{(MA)_w}$ and the slope $K'_{(MA)_{zw}}$.

From the experimental data it was also possible to calculate the dissociation constant of the salt $(MA)_w$ and of $(MA)_{zw}$ (eq 5 and 6). The over-all dissociation constant $K^d_{z(MA)_{zw}}$ (eq 7) is calculated in the follow-



tion constant $K^d_{z(MA)_{zw}}$ (eq 7) is calculated in the follow-

$$K^d_{z(MA)_{zw}} = i_t^2 f^2 / s_t = \frac{[M_s^+][M_{zw}^+][A_w^-][A_{zw}^-]}{[MA]_s + [MA]_{zw}} f^2 \quad (7)$$

(1) This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research, under Grant AF-AFOSR-28-65.

(2) M. K. Chantooni, Jr., and I. M. Kolthoff, *J. Am. Chem. Soc.*, **89**, 1582 (1967).

ing way. First $[M_s^+]$ is calculated from the ionic solubility, i_t , taking the value of $K_{K^+}^t$ equal to 1.0³. Then $[A_s^-]$ is found from the solubility product, K_{sp} ($K_{sp} = [M_s^+][A_s^-]^2$). From the values of $[A_s^-]$ and the individual formation constants² $K_{A_w^-}^t$ and $K_{A_{2w}^-}^t$

$$K_{A_w^-}^t = [A_w^-]/[A_s^-][H_2O]$$

$$K_{A_{2w}^-}^t = [A_{2w}^-]/[A_s^-][H_2O]^2$$

$[A_w^-]$ and $[A_{2w}^-]$ become known, while $[MA]_w$ and $[MA]_{2w}$ are calculated from the values of $K_{(MA)_w}^t$ and $K_{(MA)_{2w}}^t$ (eq 1 and 2) and $[MA]_s$. Finally $K_{(MA)_w}^d$ and $K_{(MA)_{2w}}^d$ are evaluated from eq 5 and 6.

Experiments have been carried out to check the assumption that the ionic dissociation constant of the unhydrated salt $(MA)_s$ does not change in the presence of relatively small concentrations of water. For this purpose, water in known concentrations was added to a saturated solution of potassium salicylate in AN and the conductance measured. Using previously determined constants, $K_{(MA)_s}^d$ could be calculated, writing in eq 3 the total concentration C_s of the salt instead of s_t . From the relations

$$[K_s^+] = \frac{i_t}{1 + K_{K^+}^t[H_2O]} \quad (8)$$

$$[A_s^-] = \frac{i_t}{1 + K_{A_w^-}^t[H_2O] + K_{A_{2w}^-}^t[H_2O]^2} \quad (9)$$

and

$$[MA]_s = \frac{C_s - i_t}{1 + K_{(MA)_w}^t[H_2O] + K_{(MA)_{2w}}^t[H_2O]^2} \quad (10)$$

we obtain $K_{(MA)_s}^d$ in the presence of water

$$K_{(MA)_s}^d = \frac{i_t^2(1 + K_{(MA)_w}^t[H_2O] + K_{(MA)_{2w}}^t[H_2O]^2)}{(C_s - i_t)(1 + K_{K^+}^t[H_2O])(1 + K_{A_w^-}^t[H_2O] + K_{A_{2w}^-}^t[H_2O]^2)} \quad (11)$$

Experimental Section

Chemicals. Acetonitrile was purified and dispensed as described previously.⁸ Potassium picrate,⁴ 3,5-dinitrobenzoate,⁵ and 3,5-dinitrophenolate³ were used previously while potassium salicylate was prepared in a similar way as the sodium salt.⁴

The monohydrate of potassium 3,5-dinitrophenolate was prepared and analyzed in the following way. Approximately 0.5 g of the red anhydrous salt was introduced into 10 ml of AN, the solution made 1.6 M in water, and the mixture shaken until equilibrium was obtained. The orange-yellow solid was collected by filtering with suction on a sintered-glass filter crucible and left exposed to the air until constant weight was attained (2 hr). The water content of the salt was determined by heating 412.2 mg at 110° to constant weight. The loss in weight corresponded to $KA \cdot 0.96H_2O$. A blank experiment in the absence of water gave a loss in weight of 0.7 mg for 402.0 mg of air-dried salt. Under the same conditions as above, 947.2 mg of air-dried potassium salicylate lost 0.6 mg upon drying at 110°, while in the blank experiment 902 mg of air-dried salt lost 0.2 mg. Apparently undissociated potassium salicylate is not hydrated in acetonitrile containing 1.6 M water.

Ionic and Total Molar Solubility. Ionic solubilities were obtained from the conductance of the saturated solutions as described previously.²

The total molar solubility, s_t , was found by taking a 1-ml aliquot of the saturated solution containing water, after filtering, evaporating to dryness under an infrared lamp, dissolving the residue in

0.3 ml of anhydrous acetic acid, adding 3 ml of AN, and titrating with 0.450 M perchloric acid in acetic acid using dibromothymol benzein as indicator. A very sharp color change from yellow to red was obtained at the end point.⁷

Results

Ionic Mobilities and Dissociation Constants of Salts. The mobilities of the following ions were previously reported in AN; potassium, 86;⁸ 3,5-dinitrobenzoate, 100;⁸ 3,5-dinitrophenolate, 96;⁹ salicylate, 78;⁶ and picrate, 78.⁸ It was found that with the exception of the picrate ion, the mobilities of the above ions did not change with the addition of water up to a concentration of at least 1.5 M.² The following values of the mobility of the picrate ion in the presence of water have been reported:² 0.55 M H_2O , 80; 1.94 M H_2O , 84; 2.13 M H_2O , 84; and 3.14 M H_2O , 84.

The dissociation constants and solubility products in anhydrous AN of the salts in Table I are: potassium picrate,^{4,8} 6.7×10^{-3} , 2.8×10^{-6} ; 3,5-dinitrobenzoate,⁵ 2.6×10^{-4} , 5.3×10^{-8} ; 3,5-dinitrophenolate,³ 3.6×10^{-3} , 6.7×10^{-6} ; and salicylate, 1.4×10^{-3} , 9.6×10^{-6} , respectively. The dissociation constants of the latter two salts were estimated from the Fuoss and Kraus plot of conductivity data in Table II.

Viscosity of AN in the Presence of Water. The viscosity of AN solutions containing water² is 0.352 cp in 0.46 M H_2O ; 0.356 in 0.91 M H_2O ; 0.366 in 1.88 M H_2O ; and 0.382 in 3.13 M H_2O . All reported conductivities in the presence of water were corrected for viscosity.

Total and Ionic Solubility of Salts. Table I lists the total molar solubility, s_t , and total ionic solubility, i_t , at various concentrations of water up to 2 M in

saturated solutions of the various salts. From the experimental data $K_{(MA)_w}^t$, $K_{(MA)_{2w}}^t$, $K_{(MA)_w}^d$, $K_{(MA)_{2w}}^d$ (the latter only for potassium salicylate), and $K_{Z(MA)_{2w}}^d$ (eq 7) were calculated as described in the introductory section, and the results are given in Table I. Values of $K_{A_w^-}^t$ and $K_{A_{2w}^-}^t$ reported in Table I have been taken from a previous publication.²

Of the salts in Table I potassium 3,5-dinitrophenolate is the only one which becomes hydrated in the solid phase. This occurs when the water concentration is equal to or greater than about 0.2 M. The product $[M_s^+][A_s^-]^2$ then becomes smaller than K_{sp} . With the monohydrate as the solid phase, values of $[M_s^+]$, $[M_w^+]$, $[A_s^-]$, $[A_w^-]$, and $[A_{2w}^-]$ were found from the total ionic solubility, i_t , and the reported hydration constants of the ions, using eq 8 and 9, while $[MA]_s$ was calculated from the experimentally determined value of $s_t - i_t$ and the known value of $K_{(MA)_w}^t$ using eq 10. The molarity of water reported in Table I has been calculated in all instances from the amount of water added and that removed by the various hydrated species.

Table III presents the conductance of solutions obtained by adding water to a saturated solution of potassium salicylate in anhydrous AN. The last column

(3) I. M. Kolthoff, S. Bruckenstein, and M. K. Chantooni, Jr., *J. Am. Chem. Soc.*, **83**, 3927 (1961).

(4) I. M. Kolthoff and M. K. Chantooni, Jr., *ibid.*, **87**, 4428 (1965).

(5) I. M. Kolthoff and M. K. Chantooni, Jr., *ibid.*, **85**, 426 (1963).

(6) I. M. Kolthoff and M. K. Chantooni, Jr., *J. Phys. Chem.*, **70**, 856 (1966).

(7) Details of the titration of carboxylates in AN with perchloric acid will be described elsewhere.

(8) P. Walden and E. J. Birr, *Z. Physik. Chem.*, **144**, 269 (1929).

(9) I. M. Kolthoff, M. K. Chantooni, Jr., and S. Bhowmik, *J. Am. Chem. Soc.*, **88**, 5430 (1966).

Table I. Hydration Constants of Salts and Dissociation Constants of Hydrated Salts^a

[H ₂ O], M	α_0 , M × 10 ³	i_0 , M × 10 ³	[K ₂], M × 10 ³	[K ₂], M × 10 ³	[A ₂], M × 10 ³	[A ₂], M × 10 ³	[A ₂], M × 10 ³	f^b	[MA] ₀ , M × 10 ³	[MA] ₀ , M × 10 ³	$K^d_{(MA)_0}$, × 10 ³	$K^d_{(MA)_0}$, × 10 ³
Potassium Picrate, $K_{sp} = 2.8 \times 10^{-4}$, $K^d_{(KPF)} = 6.7 \times 10^{-4}$, $K^d_{(KPF)} = 0$												
0	11.9	7.7						0.52	0	0		
0.55	14.1	10.0						0.50	0	0		
1.09	19.0	15.0						0.43	0	0		
Potassium Salicylate, $K_{sp} = 9.6 \times 10^{-4}$, $K^d_{(KSA)} = 1.4 \times 10^{-4}$, $K^d_{(KSA)} = 6.6 \times 10^{-4}$, $K^d_{(KSA)} = 4$, $K^d_{(KSA)} = 1.3$, $K^d_{(KSA)} = 7.6$												
0	10.5	3.9	3.9	0	3.9(3.9) ^b	0 ^b	0 ^b	0.65(0.68) ^b	0	0	...	1.4(1.5) ^b
0.089	14.5	5.0	4.6	0.4	3.4(3.4)	1.2(1.2)	0.1	0.65(0.66)	0.76	0.4	...	1.6(1.8)
0.176	17.4	5.75	4.9	0.8	3.34(3.3)	2.3(2.3)	0.4	0.59(0.65)	1.5	1.6	4.4(4.9)	1.7(1.9)
0.275	21.9	7.2	5.65	1.55	3.0(2.8)	3.5(3.1)	1.05(1.0)	0.58(0.61)	2.4	3.8	4.7(4.5)	2.0(2.2)
0.495	35.4	10.4	6.95	3.45	2.8(2.5)	5.6(5.0)	2.7(2.4)	0.49(0.54)	4.2	12.2	4.5(4.5)	2.1(2.4)
0.77	59.4	15.8	8.94	6.9	2.56(2.2)	7.9(6.8)	6.05(5.2)	0.42(0.49)	6.6	29.5	4.5(4.5)	2.4(2.8)
1.28	134	29.7	13.0	16.7	2.4(1.8)	12.2(9.1)	15.6(14.6)	0.31(0.42)	11.0	82	4.5(4.5)	2.6(3.5)
Potassium 3,5-Dinitrobenzoate, $K_{sp} = 5.3 \times 10^{-4}$, $K^d_{(KDNB)} = 2.6 \times 10^{-4}$, $K^d_{(KDNB)} = 2.1 \times 10^{-4}$, $K^d_{(KDNB)} = 6.4$, $K^d_{(KDNB)} = 5.4$, $K^d_{(KDNB)} = 2.5$												
0	0.47	0.25	0.25	0	0.25	0	0	0.87	0	0		0.26
0.55	1.21	0.82	0.52	0.30	0.13	0.44	0.21	0.82	(0.29) ^b		(0.64) ^b	1.4
1.32	3.01	2.14	0.92	1.2	0.080	0.67	0.76	0.72	(0.69)		(0.64)	3.8
1.54	3.68	2.76	1.1	1.66	0.071	0.70	0.93	0.69	(0.81)		(0.64)	5.7
Potassium 3,5-Dinitrophenolate, $K_{sp} = 6.7 \times 10^{-4}$, $K^d_{(KDNPF)} = 3.6 \times 10^{-4}$, $K^d_{(KDNPF)} = 1.9 \times 10^{-4}$, $K^d_{(KDNPF)} = 7$, $K^d_{(KDNPF)} = 6$, $K^d_{(KDNPF)} = 4$												
Anhydrous Solid Phase												
0	5.10	3.20	3.20	0	3.20	0	0	0.67	0	0		3.6
0.058	6.41	4.09	3.86	0.23	2.72	1.11	0.05	0.64	0.44	6		3.6
0.091	7.08	4.47	4.07	0.41	2.66	1.69	0.13	0.62	0.69	6		4.7
0.151	8.36	5.23	4.53	0.69	2.46	2.60	0.33	0.59	1.14	6		5.1
Monohydrate Solid Phase												
0.31	7.25	5.20	3.97	1.2	1.30	3.1	0.80	0.60	1.14 ^d	7		7.9
0.53	8.00	6.20	4.0	2.2	0.91	3.7	1.6	0.58	1.14 ^d	6		12.4

^a $K^d_{(K_2)^+}$ taken as 1.0. ^b Values in parentheses obtained by using the extended Debye-Hückel expression (see Discussion). ^c Values very uncertain. ^d $[KDNB]_0 = 0.87 \times 10^{-3} M$. ^e $[KDNB]_0 = 0.56 \times 10^{-3} M$. ^f Total solubility. ^g Ionic solubility.

Table III. Effect of Water Added to Saturated Solutions of Potassium Salicylate on Conductivity and $K^d_{(KA)}$.

[H ₂ O], M	C_{∞} , M × 10 ³	Specific conduct- ance, L	i_0 , M × 10 ³	$K^d_{(KA)}$, × 10 ³
0	1.19	6.1	141	4.32
0.33	1.19	7.3	139	5.22
0.54	1.18	7.9	138	5.69
0.81	1.17	8.4	137	6.15
1.10	1.17	9.1	135	6.76
$K^d_{(K_2)^+} = 1.0$, $K^d_{(A_2)^-} = 4$, $K^d_{(KA)} = 1.3$, $K^d_{(KA)} = 7.6$				

Table II. Conductance of Salts

Potassium 3,5-dinitrophenolate M × 10 ³	— Potassium salicylate — M × 10 ³	— Potassium salicylate — Λ
1.28	134	1.70
2.04	126	2.55
2.55	118	4.10
5.11	100	5.10
Δ ₀ = 181		10.2
Δ ₀ = 180		

lists the calculated values of $K^d_{(KA)_s}$ in the presence of water (cf eq 10).

Discussion

From the data in Table I it appears that undissociated potassium picrate does not become hydrated, at least up to a water concentration of 1 *M*. The most extensive study has been carried out with potassium salicylate. The solubility of this salt is great enough to determine the formation constants $K^i_{(KA)_w}$ and $K^i_{(KA)_{2w}}$ with reasonably accuracy. In the presence of 0.5 *M* or higher concentrations of water, the values of $[MA]_w$ and especially $[MA]_{2w}$ become considerably greater than the concentration of the unhydrated salt $[MA]_s$. It was expected that the ionic dissociation constants of the hydrated salts would be greater than that of the anhydrous salt due to the separation of center of charge on the cation and anion resulting from interposing one or two water molecules between them. This was found to be true for the monohydrate of potassium salicylate, its constant being of the order of 4.5×10^{-3} as compared to 1.4×10^{-3} for that of the anhydrous salt. Unexpectedly, the constant for the dihydrate was found to be 0.8×10^{-3} and smaller than that of the anhydrous salt. All calculations of the activity coefficients had been made using the limiting Debye-Hückel expression, which should yield only approximate values at the relatively high ionic strength of the solutions. All calculations were repeated using the extended Debye-Hückel expression

$$-\log f = \frac{1.53\sqrt{\mu}}{1 + (4.7 \times 10^7)a\sqrt{\mu}}$$

Using Kielland's¹⁰ values in water for the ionic size *a* of potassium, 3×10^{-8} cm, and of salicylate, 6×10^{-8} cm, we obtain $-\log f_{K^+} = 1.53\sqrt{\mu}/(1 + 1.41\sqrt{\mu})$ and $\log f_{Sal^-} = 1.53\sqrt{\mu}/(1 + 2.82\sqrt{\mu})$.

The values in parentheses in Table I refer to those calculated with the aid of the extended Debye-Hückel expression. The values of $K^d_{(MA)_s}$, $K^d_{(MA)_w}$, and $K^d_{(MA)_{2w}}$ remained unchanged. The data in Table III indicate that $K^d_{(MA)_s}$ remains practically unchanged up to a water concentration of 0.6 *M*. All calculations in Table I were repeated taking into account the small effect of water on $K^d_{(MA)_s}$. The values obtained were almost the same as those reported in Table I up to a water concentration of 0.8 *M*. Considering the experimental uncertainty in the values of the four constants needed for the calculation of the dissociation constants and also the uncertainty in the assumptions made (especially that $[MA]_s$ remains unaffected by water), the values for the dissociation constants of the hydrated forms of potassium salicylate are no more reliable than to within 50%. However, it is fair to conclude that the ionic dissociation constant of the

dihydrate is relatively small since its formation constant is large and the value of the "over-all" dissociation constant of potassium salicylate, reported in the last column of Table I, increases only very slightly with increasing water content because of formation of relatively large concentrations of the dihydrate. In the presence of 1.3 *M* water, the "over-all" dissociation constant is only twice as large as that of the unhydrated salt, while a similar "constant" of potassium 3,5-dinitrobenzoate was found to increase 15 times when the water concentration was 1.3 *M*.

The solubility product and the ionic dissociation constant of potassium 3,5-dinitrobenzoate in anhydrous AN are much smaller than those of the salicylate. In order to obtain results from eq 4 which are reasonably accurate it is necessary that $s_t - i_t - [MA]_s = [MA]_{2w}$ be considerably greater than corresponds to the experimental error in the determination of s_t , i_t , and $[MA]_s$. This is not found to be the case with potassium 3,5-dinitrobenzoate. The sum of the concentrations of the three un-ionized hydrated forms $[MA]_{2w}$ is so small that the formation constant of each hydrate cannot be calculated. Only the "over-all" dissociation constant is found with good accuracy; it is found to increase very much with increasing water concentration (last column, Table I). The solubility product and ionic dissociation constant of anhydrous potassium 3,5-dinitrophenolate are of the same order of magnitude as the corresponding constants of the salicylate. At the low water concentrations where the solid phase is anhydrous salt, formation of undissociated dihydrated salt can be neglected, as its concentration is proportional to $[H_2O]^2$. At the three lowest water concentrations used a constant value of $K^d_{(MA)_w}$ of 6×10^{-3} is found as compared to 3.6×10^{-3} for the anhydrous salt.

In saturated solutions, the monohydrate being the solid phase, $[MA]_s$ is no longer constant, but it decreases with increasing concentration of water. On the other hand, $[MA]_w$ is now a constant and equal to 1.14×10^{-3} *M* (Table I). Knowing $K^d_{(MA)_w}$ and $[K^+_s]$, the value of $[A^-_w]$ is readily obtained and found equal to 2.8×10^{-3} *M* at a water concentration of 0.55 *M*. From $K^i_{(MA)_w}$ we obtain $[MA]_s = 5 \times 10^{-4}$ and from $K^d_{(MA)_s}$, $[A^-_s] = 0.9 \times 10^{-3}$. From eq 3 we get that $[MA]_{2w}$ is 2×10^{-4} *M*. This small value is highly uncertain, but its order of magnitude should be correct. Using this value of $[MA]_{2w}$ we obtain for $K^d_{(MA)_{2w}}$ a value of the order of 3×10^{-3} , which is considerably greater than $K^d_{(MA)_s} = 3.6 \times 10^{-3}$. The formation constant of the dihydrate is of the order of 1.

The large increase of the "over-all" dissociation constant (last column, Table I) with increasing water concentration substantiates the conclusion that the dissociation constant of the dihydrate must be considerably greater than that of the anhydrous salt and greater than that of the monohydrate.

(10) J. Kielland, *J. Am. Chem. Soc.*, **59**, 1675 (1937).

Very Low-Pressure Pyrolysis. I. Kinetic Studies of Homogeneous Reactions at the Molecular Level

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Abstract: Gases have been pyrolyzed in a very low-pressure environment in which attention has been given to the establishment of uniform temperature conditions, and energy transfer is predominantly *via* gas-wall collisions. We have compared the observed low-pressure and theoretical high-pressure decomposition rates of molecules of widely different chemical and structural character. Complicated molecules with small activation energies are pyrolyzed into simpler products at a rate which is close to the high-pressure rate. Simpler molecules decompose more slowly at rates which become controlled by energy transfer. Wall catalysis is relatively unimportant in the process. Studies of the unimolecular decomposition of isopropyl iodide have given information on: (1) the energy accommodation between wall and molecule, (2) the effective number of Kassel oscillators deduced from a simple theoretical treatment of the data, and (3) the effects of wall conditioning on the decomposition rate. The kinetic equations for the steady-state condition in a stirred flow reactor at very low pressures are evaluated explicitly. These include the effects of induction periods due to "mixing" and to lack of attainment of a steady-state internal energy distribution. Preliminary results on isopropyl iodide indicate that about 80 wall collisions are needed to attain steady state at 900°K.

Number of authors¹⁻⁶ have pyrolyzed complex molecules at sufficiently low pressures that there are very few gas-phase collisions, and most collisions take place with the walls of the vessels. The results of these studies have been useful as a means of producing free radicals and, in one or two isolated instances, have given information about the initial molecular structure or isomerization. However, quantitative interpretation of the kinetics has proven difficult. Numerous reasons can be cited for this difficulty, but the principal reasons have been that the Boltzmann equilibrium has not been achieved in the reacting gas and the wrong equations have been applied to the data and have resulted in incorrect interpretation of the data. It is the purpose of the present and succeeding papers to describe a variant of these experimental techniques which lends itself to quantitative interpretation and thus provides a new kinetic tool for quantitative study of the details of unimolecular reactions, energy transfer, and bimolecular reactions in the gas phase. It can also be used to study heterogeneous reactions.⁷ It is useful to refer to the technique as "very low-pressure pyrolysis" or "VLPP."

Experimental Section

Materials and Procedure. The gas to be studied is stored in a reservoir at a few torr pressure. The gas passes through an

adjustable leak valve at a rate of from 10^{14} to 10^{16} molecules/sec and into the reactor through a short length of small bore capillary tube which prevents back diffusion from the reactor. Pyrolysis occurs in a cylindrical fused silica reactor approximately 9 cm long and 2.2 cm i.d. The ratio of internal surface area to exit aperture area gives the average number of gas-wall collisions Z , made by a molecule while in the reactor. We have a number of reactors whose exit apertures are in the range of 0.8 to 0.008 cm². A typical vessel is shown in Figure 1. A pair of 1-cm³ fused silica baffles interrupt the direct path between the gas injection capillaries and the exit aperture. The pyrolysis vessel temperature is maintained to better than $\pm 10^\circ$ up to 1000°. Heating is by means of a pair of 4-in. long clam shell heaters⁸ with temperature "trimming" elements (each consisting of a coil of nichrome heating element) placed at the upper and lower parts of the furnace. Six chromel-alumel thermocouples monitor temperature at various parts of the vessel. The low thermal inertia system is lagged with Microquartz fiber to exclude drafts. (Microquartz⁹ is a fabric composed of short, fine, quartz fibers; its properties are essentially unaffected by a Bunsen flame.) We have arranged for a sharp temperature gradient at the point of gas injection in order to heat the injected molecules as fast as possible. It is very important to avoid pyrolysis of the gas in the higher pressure region above this injection capillary. Gas density in the reactor depends on the area of the pyrolysis chamber exit aperture, on the degree of molecular decomposition achieved, and on factors such as molecular throughput, temperature, and molecular weight.

Gases which effuse from the reactor pass to the ionization chamber of a quadrupole mass spectrometer.¹⁰ A schematic drawing of the apparatus is given in Figure 2. The spectrometer is located in a large (10-in. i.d. by 18-in. long) cylindrical aluminum chamber. Electrical connections are made by means of Kovar glass seals which are epoxied (using Epon 828 vacuum epoxy) to the aluminum support plate. An NRC HS4-750 pump (5-in. diffusion pump), using DC704 pump oil, evacuates the chamber through an ambient-cooled baffle and a 4-in. Temescal manifold gate valve. The base pressure of the system is about 10^{-6} torr; a slight air leak gives peaks at 28 and 32 amu, and other residual gases give interference at 17, 18, 73, 77, 78, 91, and 135 amu and, less importantly, at numerous other places in the mass spectrum. A correction is applied when interference occurs. Ordinarily such interference is serious only when H₂O, O₂, or N₂ are produced and have to be measured explicitly. The effective pumping speed is about 60–80 l./sec in the

¹ J. Sinke, G. A. Pressley, A. B. Baylis, and F. E. Stafford, *J. Phys.*, **41**, 2207 (1964); A. B. Baylis, G. A. Pressley, Jr., and F. E. I., *J. Am. Chem. Soc.*, **88**, 2428 (1966).

² LeGoff, A. Cassuto, and A. Pentenero, *Ind. Chim. Belge*, **29** (4), 64; paper presented at the 12th ASTM Conference on Mass Spectrometry and Allied Topics, Montreal, Canada, 1964.

³ P. Fisher, J. B. Homer, B. Roberts, and F. P. Lossing, material presented at the Ottawa Symposium on Pyrolysis, Sept 1964. They use a carrier to produce high space velocities and thus had many fewer gas collisions but almost no secondary reactions.

⁴ F. Thomas and D. F. Swinehart, 150th National Meeting of American Chemical Society, Atlantic City, N. J., Sept 1965, p 65-V.

⁵ P. Fehlner and W. S. Koski, *J. Am. Chem. Soc.*, **87**, 409 (1965).
⁶ Collin, "Pyrolysis Studies by Mass Spectrometry," EUR2114e—Report obtainable from Presses Academiques Europeennes, Musée de Charleroi, Brussels 6.

⁷ D. McKinley, *J. Chem. Phys.*, **40**, 120 (1964).

⁸ Hevi Duty Type 73 KS designed for operation at up to 1200° with 210-w input power, manufactured by the Hevi Duty Electric Co., Watertown, Wis.

⁹ Obtainable from Western Asbestos Co., Brisbane, Calif. 94005.

¹⁰ Further details regarding the operating characteristics of the mass spectrometer will be supplied by the authors on request.

mass spectrometer chamber. The mass spectrometer consists of an ionizer, rod system, and particle multiplier tube fed by appropriate power supplies. Data are recorded by an oscilloscope-Polaroid camera combination.

The electronics which supply the quadrupole analyzer rods were designed by members of the Engineering Department of Stanford Research Institute.¹¹ The radiofrequency generator operates at a fixed frequency, and the mass spectrum is scanned by variation of applied voltage. A sawtooth signal from a waveform generator (Tektronix, Type 162) drives a dc amplifier and a coupled radio-frequency generator and, in addition, the signal drives or triggers

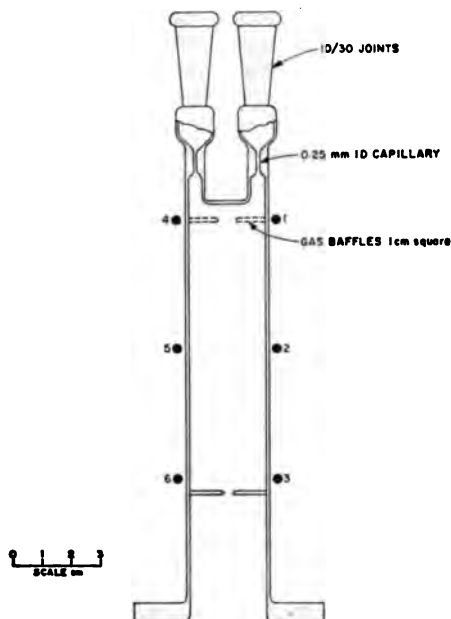


Figure 1. Very low-pressure pyrolysis fused silica reactor. Thermocouple locations are indicated by the numbers 1-6.

the horizontal sweep of the recording oscilloscope (Tektronix 535A). Linearity of mass-filtered *vs.* instantaneous voltage of the sawtooth gives a linear mass spectrum on the oscilloscope screen. The radiofrequency/dc ratio has to be maintained accurately in order to obtain a stable mass spectrum. Under normal operating conditions the electrical inputs to the analyzer rod system are adjusted until we get a mass spectrum whose relative peak heights are almost unchanged as the radiofrequency/dc ratio control (or resolution) is changed.

We have found it necessary to keep the electronics running at constant sweep rate in order to avoid drift effects¹² which appear when the quadrupole electronics are operated at fixed output (*i.e.*, when attempting to measure the intensity of a single peak). This has so far limited our precision to about $\pm 5\%$. We have found that best accuracy can be achieved by measuring adjacent or close-spaced mass peaks. For this reason, for example, work on *i*-PrI decomposition to C_3H_6 and HI has been followed most easily by monitoring the peaks 39, 40, 41, 42, and 43. We think that our analytical methods cause errors of less than about 5% (in midrange) in the rate constants.¹³

(11) We are grateful to members of the Applied Physics group of Stanford Research Institute for the use of their designs of various parts of the quadrupole spectrometer and electronics.

(12) These drift effects seem to have been eliminated in a new set of electronics recently acquired from Electronic Associates Inc., Palo Alto, Calif.

(13) Other errors such as the determination of the escape rate constant of the reactor are comparable with this. A referee has pointed out that perhaps 10% of the material emerging from a 100-collision reactor will reenter the vessel and be subjected to further pyrolysis. All quoted rates for reactors of 93, 110, and 120 collisions should be reduced by about 10%.

For the work reported in this paper, no effective trapping had been provided between the diffusion pump and the mass spectrometer. It was thus necessary to heat the ionizer to a temperature of about 200° in order to maintain ionizer operation for as long as several days.

The ionizer is mounted approximately 7 cm from the furnace exit aperture. We estimate that less than 1.6% of the gas concentration in the ionizer is due to species which have arrived there from the reactor without making any collisions. The electron beam is directed at right angles to the analyzer rod system axis. Typically, operating pressures in the spectrometer chamber are below 10^{-4} torr, and satisfactory signals are obtained with an electron beam current of about 2 ma at 70 ev. Interruption of the path between

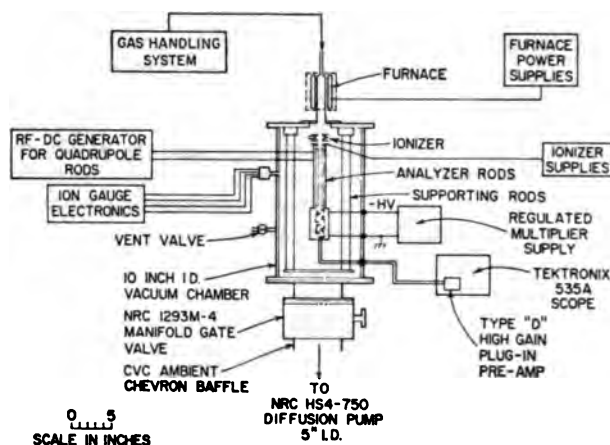


Figure 2. Schematic of low-pressure pyrolysis apparatus.

furnace and ionizer by means of a beam flag has shown that only about 15-30% of the signal of the detector is due to gases which have just emerged from the reactor into the volume between the reactor exit aperture and the ionizer. These gas molecules will have already made a number of collisions with walls in the neighborhood of this volume. The bulk of the signal is given by gases which have made many collisions with the walls of the spectrometer chamber and have thus cooled to a low temperature. We do not, therefore, make any $(T/M)^{1/2}$ correction to adjust for changing sensitivities for substances of different mass.

We have also noted that after a rapid change is made in the nature of the gases injected into the mass spectrometer, the spectrum may take some minutes to readjust to its new values. For example, when equimolar amounts of *i*- C_3H_7I and C_3H_8 are injected, several minutes must elapse after their introduction before reproducible runs are obtained. Similarly, when furnace temperature is raised so that the amount of decomposition is changed appreciably, a waiting time must be allowed for equilibration.

Some free-radical products such as CH_3 cannot be detected directly with the present instrument, although their presence has been established by titration with NO_2 . We are well aware of the problems attaching to direct detection of free radicals with mass spectrometers¹⁴ and have not attempted to surmount them in this work.

Results

A. Pyrolysis of Selected Compounds. The extent of decomposition of the reactant listed in Table I was followed by measuring the ratio of reactant peaks to product peaks. Where available, API¹⁵ sensitivity data were used to estimate decomposition. When they were not available, estimates were made from the re-

(14) F. P. Lossing in "Mass Spectrometry," C. A. McDowell, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1963, p 442.

(15) American Petroleum Institute Project 44, Collection of Mass Spectral Data, Carnegie Institute of Technology, Pittsburgh, Pa., June 30, 1959.

Table I. Comparison of VLPP Data for Some Selected Compounds with High-Pressure Rates,* Nominal 110-Collision Vessel

Reaction	Log k_{∞}^b	T_{20}	k_u^{20}	k_{∞}^{20}	T_{60}	k_u^{60}	k_{∞}^{60}
$\text{CH}_3\text{I} \rightarrow \text{CH}_3 + \text{I}$	14.5-56/ θ^c	>1100	<44	>2500	>1100		
$\text{CHCl}_3 \rightarrow \text{CCl}_3 + \text{HCl}$	11.4-47/ θ^d	>1370	<53.5	>8000	>1370		
$\text{CH}_2\text{CCl}_2 \rightarrow \text{CH}_2\text{CCl} + \text{HCl}$	14.0-54/ θ^e	~1370	50.6	2.5×10^4	>1370	<303	$>2.5 \times 10^4$
$n\text{-C}_3\text{H}_7\text{Cl} \rightarrow \text{C}_3\text{H}_7 + \text{HCl}$	13.0-54/ θ	~1270	63.6	5000	>1370	<365	$>2.4 \times 10^4$
$i\text{-C}_3\text{H}_7\text{I} \rightarrow \text{C}_3\text{H}_7 + \text{HI}$	13.0-43.5/ θ	1070	39.6	1.3×10^4	1220	254	1.6×10^4
$\text{CH}_3\text{COOEt} \rightarrow \text{CH}_3\text{COOH} + \text{C}_2\text{H}_4$	12.0-46/ θ	~1020	53.8	215	~1120	338	1000
$t\text{-BuOH} \rightarrow t\text{-C}_4\text{H}_9 + \text{HOH}$	13.5-60/ θ	~1120	61.6	63	~1220	385	630
toluene $\rightarrow \text{C}_6\text{H}_5\text{CH}_2 + \text{H}$	14.8-84/ θ^f	>1370	<61.0	>25	>1370		
$(\text{C}_2\text{H}_5)_2 \rightarrow 2\text{C}_2\text{H}_5^g$	13.0-33.7/ θ	~620	34.2	13	~730	223	830
$[(\text{CH}_3)_3\text{CO}]_2 \rightarrow 2(\text{CH}_3)_3\text{CO}$	15.6-37.5/ θ^h	~620	32.6	240	~690	195	6300

* Literature values of Arrhenius parameters are given in the second column. The temperatures (or their limits) at which 20 and 60% decomposition was observed are listed in the columns headed T_{20} and T_{60} . The terms k_u^{20} and k_u^{60} are the apparent first-order rate constants at T_{20} and T_{60} . (From the stirred flow reactor equations we have $k_u^{20} = 0.2(1 - 0.2)^{-1}k_{\infty}$, where k_{∞} is the escape rate constant for the reactor.) The terms k_{∞}^{20} and k_{∞}^{60} are high-pressure rate constants at T_{20} and T_{60} , respectively. The ratio of k_u to k_{∞} gives a measure of the fall-off. ^b Arrhenius parameters taken from compilation by S. W. Benson, "Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960. Units are sec^{-1} for all rate constants. ^c Estimated from back-reaction and thermal data. $\theta = 2.303RT$ in kcal/mole. ^d A. E. Shilov and R. D. Sabirova, *Russ. J. Phys. Chem.*, **34**, 408 (1960). ^e D. H. R. Barton and P. F. Onyon, *J. Am. Chem. Soc.*, **72**, 988 (1950). ^f S. J. Price, *Can. J. Chem.*, **40**, 1310 (1962). ^g L. Batt and S. W. Benson, *J. Chem. Phys.*, **36**, 895 (1962). ^h $\text{C}_3\text{H}_8 = 1,3\text{-cyclopentadiene}$.

duction in parent peak intensity, using eq 17 of the Appendix. Species like di-*t*-butyl peroxide give unstable *t*-BuO radicals, which decompose completely in our system to acetone + CH_3 . This makes them useful as sources of CH_3 radicals. Extent of decomposition was determined from measurement of the ratio of mass peaks at 146 and 73 amu (parent compound) to that at 58 amu (acetone). Preliminary data on some of the reactions we have studied in a nominal 110-collision vessel are shown in Table I. Rather than give the entire decomposition curves, we have listed the temperatures at which we have observed 20 and 60% decomposition. For comparison we have given the high-pressure rate constants, using literature values for the Arrhenius parameters. We have used the equations for a stirred flow reactor to derive the apparent first-order rate constants from the per cent reaction. Details of the application of these equations to our system are developed in the Appendix.

In the cases of CH_3I , CHCl_3 , and toluene, we observed no measurable decomposition in this vessel up to the highest temperatures listed.

The mean molecular residence time in the vessel was about $16(M/T)^{1/2}$ msec, where M is the mass in amu. For *i*-PrI, for example, this was about 6.5 msec at 1000°K .

B. Isopropyl Iodide. In order to check the validity of the results of VLPP for measurements of kinetics and energy exchange, we have studied the unimolecular decomposition of *i*-PrI in a number of vessels of different nominal collision numbers.

The unimolecular decomposition of isopropyl iodide and the inverse reaction (addition of HI to propene) have been thoroughly investigated by several groups of workers, and there is satisfactory agreement on the rate constants of the reactions.^{16,17} For reaction i, $k_{\infty} = 10^{12.96-42.5/\theta} \text{ sec}^{-1}$, where $\theta = 2.303RT$ (kcal/mole).



The error limits on $\log A_1$ are ± 0.5 and on E are

(16) H. Teraniishi and S. W. Benson, *J. Chem. Phys.*, **40**, 2946 (1964); S. W. Benson and A. N. Bose, *ibid.*, **37**, 1081 (1962).

(17) W. Tsang, *ibid.*, **41**, 2487 (1964), and references cited therein.

± 1.0 kcal/mole; k_{∞} refers to the high-pressure rate constant.

Isopropyl iodide was pyrolyzed in our fused silica vessels at very low pressures. Gas flows were typically 3×10^{15} to 5×10^{15} molecules sec^{-1} ; except for the 9000-collision vessel, molecules made very many more collisions with the wall than with other molecules. For the 9000-collision reactor the mean free path for gas-gas collision was 4 cm compared with about 2 cm for gas-wall collisions. The decomposition rate was measured as a function of temperature for several vessels whose collision numbers Z_r were 93, 110, 630, 1100, and 9000.¹⁸ The relative heights of the fragment peaks at 43 and 41 amu give an accurate measure of the amount of decomposition. These mass peak heights were measured after steady state had been reached at each temperature. The fraction of undecomposed material was calculated from our measurements of the relative sensitivities of these peaks, the parent compound, and propylene. (There is a small but important contribution to the 43 peak from $\text{C}^{13}\text{-C}^{13}\text{H}_6^+$.) A slight error is introduced into our results, since we cannot be sure that parent molecules will contribute to peaks 43 and 41 in the same way when the furnace is at a high temperature as they do when it is cold. This error could be significant when decomposition is less than 5%, but the approximation which ignores this correction should be satisfactory when decomposition is in excess of this amount.

From the kinetic equations which have been derived for the VLPP conditions, we compute apparent first-order rate constants $k = k_e \delta$, where δ is the ratio of product to reactant fluxes and k_e is the known first-order rate constant for escape from our reactor.¹⁹ Figure 3 shows $\log k$ as a function of temperature for the different reactors (k is in sec^{-1}). Included for comparison is k_{∞} calculated from the Arrhenius parameters.

Individual points in Figure 3 are averages of three or more observations. Each observation was made

(18) Collision number is given by the ratio of internal surface area to exit aperture area. All vessels were cylinders of 2.2 cm internal diameter and length about 9 cm.

(19) We estimate that for *i*-PrI in our vessels, $k_e = 8.5A_h\sqrt{T} \text{ sec}^{-1}$, where A_h cm² is the exit aperture area.

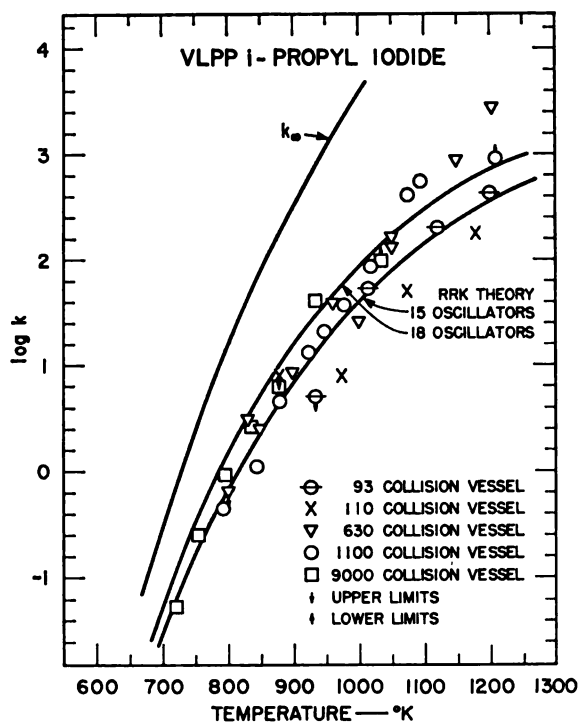


Figure 3. Apparent first-order rate constant for isopropyl iodide decomposition. The dimensions of k are sec^{-1} .

after short-term (*i.e.*, ~ 15 min) reproducibility was obtained. Long-term (*i.e.*, on a day-to-day basis) reproducibility was generally fairly good on well-conditioned vessels. These included the 110-, 1100-, and 9000-collision reactors. The effect of history is illustrated for the less well-conditioned 630-collision reactor. Reactor temperature ($^{\circ}\text{K}$) was increased in steps as follows: 300, 700, 800, 830, 898, 958, 1000, 1050, again 1050 after 90 min at temperature, 1148, and 1203. The temperature was then reduced to 1000 and then to 848 $^{\circ}\text{K}$. (Except for the second run at 1050 $^{\circ}\text{K}$, readings were ordinarily taken after 15 min at temperature.) Results for the 93-collision vessel are included for interest, although this reactor was previously unused. No conditioning studies were possible with this reactor, since it broke during a run at 1300 $^{\circ}\text{K}$. Its "freshness" could account for the apparently fast rates compared with the 110-collision reactor.

A well-conditioned vessel differs visually from a fresh one; it is slightly darker in color. HF solution acts on the walls, causing a thin, dark (presumably carbonaceous) film to peel off. We have estimated that the percentage of material decomposing *via* carbon and other products is less than 10%.

Discussion

The high-pressure rate constants approximately describe the observed results for the more complex molecules but are inadequate for the simpler ones in the 110-collision vessel. Further confirmatory work is required to clarify some of the data, particularly the fate of the radical species in the case of di-*t*-butyl peroxide decomposition. It is clear from the slowness of the rates found from the experimental data that

the walls are not "catalyzing" the reactions of the reactant molecules listed in Table I. The principal value of the work on the pyrolysis of this wide range of compounds was to eliminate our fear that wall reactions would seriously interfere with the pyrolysis. However, we would like to know the magnitudes of the relative roles of low-pressure falloff effects and of slowness of energy equilibration, for example. We have some indication of the importance of the latter process for *i*-PrI, but a comprehensive survey of all of these molecules would be of considerable general interest.

In order to unravel the various kinetic features from one another, we have developed, in the Appendix, a treatment of the theory of the method which we think is able to explain the data quantitatively.

Comparison of k_{∞} for *i*-PrI with the observed rates confirms that energy transfer to the molecules limits the rate of decomposition.

Equations derived from the theory in the Appendix permit us to evaluate k from the classical Arrhenius parameters and from n , the effective number of internal oscillators in *i*-PrI. These theoretical values are shown in Figure 3 for $n = 15$ and 18 and appear to bracket the experimental data very well except at the highest temperatures. It may be that the precision of our data warrants the more accurate RRKM²⁰ quantum theory, and we are exploring this possibility.

The difference in the rate constants for the 110- and for the 630- and 1100-collision vessels arises from the slowness of energy accommodation between wall and molecule which introduces an induction period, appreciable only for the smaller collision-number reactors. At 900 $^{\circ}\text{K}$ the energy required by an *i*-PrI molecule to undergo breakup in about $10^{-4.3}$ sec is of the order of 60 kcal/mole or $\sim 30RT$. Accommodation to this energy seems to occur in 80 ± 30 collisions.²¹

Wall-conditioning appears to be associated with the formation of a carbonaceous coating. The conditioning process could be associated with different energy-transfer processes between wall and reactant as the wall is progressively coated. The alternative view which cannot yet be ruled out is that the wall gives rise to catalytic decomposition of parent molecules. The occurrence of coating obviously implies that wall-promoted reactions can occur. Their rates are small, however, on our time scale, and it is more likely that these reactions are taking place with products than with reactants.

We are continuing our investigations of the nature of wall-conditioning effects and will report on these subsequently.

Application of the Method

The possible applications of the low-pressure pyrolysis technique to chemical kinetics are manifold. By covering a large temperature range, we are able to measure apparent unimolecular rate constants k_d whose values range in each case over 4 to 6 decades (*e.g.*, $10^{-2} < k_d < 10^{3.5} \text{ sec}^{-1}$). For most molecules studied, this carries k into the region well below the high-pressure limit rate constant k_{∞} , and energy trans-

(20) D. W. Placzek, B. S. Rabinovitch, G. Z. Whitten, and E. Tschui-kow-Roux, *J. Chem. Phys.*, **43**, 4071 (1965).

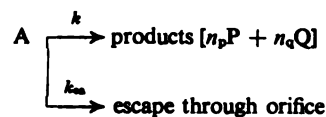
(21) Calculated from theory presented in Appendix, eq 24.

s rate controlling. Using the theory with the experimental data, it is possible to obtain the Arrhenius parameters for k_{ea} and the details of energy transfer, or with the walls or with added carrier gases. Studies of the induction times in low-collision-number cells yield values for the rates at which the upper rotational levels of complex molecules relax in collisions. Such studies are now under way. Perhaps the most important use for VLPP is in the study of the direct products of primary thermal reaction in unimolecular decomposition. Thus we have found that both 1- and 2-nitropropane decompose to give²² $C_3H_6 + HNO_2$, rather than the much discussed n - or isopropyl radical + NO_2 . We hope to distinguish the paths $CHCl_3 \rightarrow CHCl_2 + Cl$ (or $CH_2 + HCl$) in $CHCl_3$ pyrolysis. Present data²³ indicate that carbene formation is important. We note that the activation energy exceeds 56 kcal.²⁴ Finally, the system lends itself extremely well to studies of the kinetics and stoichiometry of molecule-surface reactions, and we are now beginning studies of this type for suitable molecules with various catalytic and metal surfaces.

Appendix. Treatment of Data

The experimental technique of very low-pressure pyrolysis (VLPP)²⁵ consists of permitting a steady flow of reactant molecules to pass into a thermodynamic reaction cell under conditions of such low pressure that most collisions of reactant (or product) molecules take place with the vessel walls and not in the gas phase. For our usual reactors this corresponds to pressures $P \leq 10^{-2}$ torr. Once in the cell, reactant molecules may decompose, escape from the cell, or, in special cases, react chemically with added carrier gases or products. In conditioned quartz vessels, the rates of heterogeneous reactions have turned out to be small (less than 10% of the observed rates). This is not necessarily the case in metal vessels. The apparent first-order rate constants measured in the system fall considerably below those obtained at higher pressures in static systems. In the following sections we shall develop the appropriate equations which permit us to interpret our data and explain qualitatively the falloff in rate constants in our system in similar ones.

Flow Kinetics. The conditions in VLPP correspond closely to those in a stirred flow reactor.^{26,27} The important difference between the usual stirred flow reactor equation and those applicable here will emerge directly. We can represent the mechanism by the following set of kinetic equations in which A represents reactant molecule and B represents an added carrier gas (e.g., NO_2) or product molecule which can react with A (or the products of A).



where n_i is the stoichiometric number of moles of product formed per mole of A decomposing.

$(A)_{ss}$, the steady-state concentration of A in the reactor, is determined by the rate of introduction N_A in moles/second (essentially the steady-state flow rate) and the various depletion processes. From the above we find

$$(A)_{ss} = \frac{N_A}{[k_{ea} + k + k_b(B)_{ss}]V} \quad (2)$$

where V is the reactor volume in liters and concentrations are in units of moles/liter. The steady-state concentration of species in the reactor thus depends on k_{ea} and $k_b(B)_{ss}$. These terms depend in turn on an average molecular speed, and there is thus this important difference between the stirred flow reactor equations for high and for very low pressures.

The flux of unreacted A in the exit stream is given by

$$Vk_{ea}(A)_{ss} = \frac{N_A k_{ea}}{[k_{ea} + k + k_b(B)_{ss}]} \quad (3)$$

The exit flux of product molecules P at steady state is

$$Vk_{ep}(P)_{ss} = k(A)_{ss}n_p V \quad (4)$$

where k_{ep} is the first-order escape rate constant for P.

The mass spectrometer is calibrated by passing known fluxes of products and reactants through the system. From the observed signals at two or more mass peaks, we can determine the relative fluxes of product and reactant. From eq 4, this relative flux δ_p or δ_q for product P or Q is given by

$$\delta_p = \frac{k_{ep}(P)_{ss}}{k_{ea}(A)_{ss}} = \frac{kn_p}{k_{ea}} \quad (5)$$

$$\delta_q = \frac{k_{eq}(Q)_{ss}}{k_{ea}(A)_{ss}} = \frac{kn_q}{k_{ea}} \quad (6)$$

where δ_p and δ_q are the ratios of the observed signals of P and Q, respectively, to A. We can write similar equations for δ_r and δ_s , the relative fluxes of R and S. From kinetic theory²⁸ the escape rate constant through a thin aperture is²⁹

$$k_{ea} = \frac{1/4 \bar{c}_A A_h}{10^3 V} \text{ sec}^{-1} \quad (7)$$

where A_h is the hole area in cm^2 and \bar{c}_A is the mean molecular speed of A. From kinetic theory $\bar{c}_A = 1.46 \times 10^4 (T/M_A)^{1/2}$ cm/sec. M_A is the mass of A in amu. Hence, from eq 5 and 7

$$k = \frac{3.65 A_h \delta_p T^{1/2}}{V n_p M_A^{1/2}} \quad (8)$$

Using the relation $Z_r = A_v/A_h$, we can, if we wish,

(28) S. Dushman, "Vacuum Technique," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 90. Equation 7 is derived from Dushman's eq 2.36 by dividing the pumping speed of the aperture by the vessel volume in liters.

(29) We may note that the escape rate constant is independent of gas pressure. This means that the volume effect treated by, for example, G. M. Harris (*J. Phys. Colloid Chem.*, 51, 505 (1947)) does not apply to VLPP conditions.

- (1) G. N. Spokes and S. W. Benson, manuscript in preparation.
- (2) S. W. Benson and G. N. Spokes, paper submitted to the 11th Symposium on Combustion, Berkeley, Calif, Aug 1966.
- (3) Assuming an A factor of $10^{13.5} \text{ sec}^{-1}$ and a Kassel n of 7.5.
- (4) VLPP may be defined as "pyrolysis in a reactor at low pressure such that energy transfer from an external heat source is primarily by means of gas-wall interactions. Gas flow is chiefly free molecular flow. Temperature history of average molecules is well characterized."
- (5) M. Bodenstein and K. Wolgast, *Z. Physik. Chem.*, 61, 422 (1908).
- (6) K. Denbigh, "Chemical Reactor Theory," Cambridge University Press, Cambridge, Mass., 1965.

rewrite k in terms of the vessel collision number Z_r and the internal surface area of the vessel A_v (cm²)

$$k = \frac{3.65\delta_p A_v T^{1/2}}{V n_p M_A^{1/2} Z_r} \quad (9)$$

Now

$$\frac{\delta_p}{n_p} = \frac{\delta_q}{n_q} = \frac{f}{(1-f)} \quad (10)$$

where f is the fraction of unimolecular decomposition of A in the reactor.

From eq 5 and 10

$$k = k_{ea} \frac{f}{(1-f)} \quad (11)$$

From eq 9 and 10

$$k = \frac{3.65 A_v T^{1/2}}{Z_r V M_A^{1/2}} \left[\frac{f}{(1-f)} \right] \quad (12)$$

It will be noted that eq 11 and 12 bear a formal similarity to the equations for a stirred flow reactor.³⁰

If f' represents the fraction of A disappearing by chemical reaction with B, we can show that

$$k_b(B)_{ss} = \frac{3.65 A_v T^{1/2} [f'/(1-f')]}{Z_r V M_A^{1/2}} \quad (13)$$

Here $f'/(1-f')$ is a direct experimental observable and is equal to δ_r/n_r or δ_s/n_s .

Since our experimental data give $f/(1-f)$ and $f'/(1-f')$ directly, we can immediately use eq 12 and 13 to give first-order and second-order rate constants.

Some experiments are not directly amenable to the foregoing treatment. For example, we may sometimes not be able to measure the relative sensitivities of a parent molecule and its free-radical decomposition products. For such experiments we must measure the absolute flux of parent molecules under the various experimental conditions.

The mass spectrometer signal I_A is closely proportional to the flux of species A. If we denote the constant of proportionality (or sensitivity) by α_A , then (with eq 2)

$$I_A = \alpha_A k_{ea}(A)_{ss} = \frac{N_A k_{ea} \alpha_A}{k + k_{ea} + k_b(B)_{ss}} \quad (14)$$

We can determine α_A by calibration.³²

In this type of measurement N_A , the mass flow rate, is kept constant and the temperature range is scanned. At low temperatures where no reaction takes place, we observe a signal $I_A^0 = N_A \alpha_A$ (from eq 4) so that we can eliminate N_A and α_A and write

$$\frac{I_A}{I_A^0} = \frac{k_{ea}}{[k + k_{ea} + k_b(B)_{ss}]} \quad (15)$$

(30) Equation 12 can be transformed to eq 10 of ref 31 by the substitutions $k/k_w = b$, $f = B$, and $Z_r = \nu_w$. k_w is the wall-collision frequency where $k_w = 3.65 A_v T^{1/2} / (V M_A^{1/2}) \text{ sec}^{-1}$.

(31) P. LeGoff, *J. Chim. Phys.*, 359 (1956).

(32) One must correct for the effect of oven temperature on α_A when working with molecular beams. This problem has been studied by O. Osberghaus and R. Taubert, *Z. Physik. Chem. (Leipzig)*, B516, 264 (1955); H. Ehrhardt and O. Osberghaus, *Z. Naturforsch.*, 13a, 16 (1958); 15a, 575 (1960). The mass spectrometer experiments described earlier in this paper were not beam experiments and most of the molecules were cooled to close to ambient temperature prior to entering the ionizer.

Solving for k , the apparent first-order rate constant for decomposition of A, we find

$$k = k_{ea} \left[\left(\frac{I_A^0}{I_A} \right) - 1 - \frac{k_b(B)_{ss}}{k_{ea}} \right] \quad (16)$$

In the absence of any secondary reactions by B, we have

$$k = k_{ea} \left[\left(\frac{I_A^0}{I_A} \right) - 1 \right] = k_{ea} \left(\frac{I_A^0 - I_A}{I_A} \right)$$

or, alternatively

$$k = k_{ea} \frac{f}{(1-f)} \quad (17)$$

2. Induction Periods. Two types of induction times must be considered in our system. The first, τ_m , corresponds to a "mixing" time and arises because reactant molecules are introduced at one end of a cylindrical vessel and escape from an orifice at the opposite end. The probability of escape is lower for these molecules than for the average molecule, and one can make a simple estimate that in time τ_m , Z_m collisions are required to bring these molecules to an "average" position in our cell. For a cylinder of length l cm and radius r cm, $Z_m \sim (l/2r)^2$. Z_m is estimated on the basis of a random walk of step size r cm. For our system Z_m is about 4 to 6 and generally negligible.

The second induction period is related to the time τ_i necessary to reach the stationary population of the upper vibrational levels of the reactant molecules. Since internal energies of average reacting molecules are in the range of $40RT$, one would imagine that on the order of at least 40 and possibly $(40)^2$ wall collisions would be required to establish such stationary states.

We can examine the effect of this internal energy relaxation by considering the fate of a number of molecules $V(\Delta A)$ introduced into the reactor at time $t = 0$ in a time interval $\Delta\tau$ which is very short compared to the mean residence time τ_r in the reactor. Note that $\tau_r = 1/(k_{ea} + k)$.

Ignoring the complications of secondary reactions with B, the rate of depletion of the group ΔA in the reactor is given by

$$\frac{-d(\Delta A)}{dt} = (k + k_{ea})(\Delta A) \quad (18)$$

where k is now some monotonic function of time. If we wish to take account of the mixing time τ_m , we can easily do so by saying that k_{ea} is a step function, $k_{ea} = 0$ for $0 \leq t \leq \tau_m$, and $k_{ea} = k_{ea}$ for $t \geq \tau_m$, with $\tau_m = Z_m \tau_w$ where τ_w is the mean time between wall collisions.

Integrating eq 18 between limits 0 and t , we find

$$-\ln \left[\frac{(\Delta A)}{(\Delta A)_0} \right] = k_{ea}(t - \tau_m) + \int_0^t k dt \quad (19)$$

$$= k_{ea}(t - \tau_m) + \langle k \rangle t \quad (20)$$

where $\langle k \rangle$ is the average of k over the time interval t and is a function of t as defined by eq 19 and 20.

Now the rate of unimolecular reaction is given by

$$-\left[\frac{d(\Delta A)}{dt} \right]_{\text{chem}} = k(\Delta A) \quad (21)$$

and, on eliminating (ΔA) with the aid of eq 20

$$\frac{-1}{(\Delta A)_0} \left[\frac{d(\Delta A)}{dt} \right]_{\text{chem}} = k \exp\{-[k_{\text{ea}}(t - \tau_m) + \langle k \rangle]\} \quad (22)$$

The total fraction of chemical reaction f which occurs in the group ΔA is obtained by integrating eq 22 between limits $0 \leq t \leq \infty$. We find

$$f = \exp(k_{\text{ea}}\tau_m) \int_0^\infty k \exp[-(k_{\text{ea}} + \langle k \rangle)t] dt \quad (23)$$

This can be integrated if we have an explicit form for $k(t)$. As a simple case which is probably not far from reality, we may assume that k is a step function such that $k = 0$ for $0 < t < \tau_i$ and $k = k$ for $t \geq \tau_i$. τ_i is then an induction time for energy relaxation. Under these conditions f becomes

$$f = \frac{k \exp\{-k_{\text{ea}}(\tau_i - \tau_m)\}}{(k_{\text{ea}} + k)} = \frac{k/\beta}{(k_{\text{ea}} + k)} \quad (24)$$

with $\beta \equiv \exp\{k_{\text{ea}}(\tau_i - \tau_m)\}$ and generally $\beta \geq 1$.

Solving for k we find a result similar to eq 11

$$k = \frac{k_{\text{ea}}f\beta}{(1 - f\beta)} \quad (25)$$

where $f\beta$ can be interpreted as a corrected fraction of decomposition.

In vessels with very small apertures where $k_{\text{ea}}(\tau_i - \tau_m) \ll 1$, eq 11 and 25 are identical, and we can ignore the induction times. This permits us to solve for k from calculations of k_{ea} (eq 7) and measurement of f . We can then solve for the induction parameters (from eq 24) by measuring f at the same temperatures in a series of vessels of different k_e where $k_e(\tau_i - \tau_m) \approx 1$.

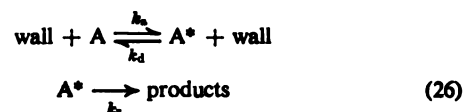
From preliminary results reported here, it appears as though for isopropyl iodide, at about 1000°K, $(\tau_i - \tau_m) \sim 4$ msec in a conditioned quartz vessel. This would correspond to about 80 wall collisions for the average i -PrI molecule to pick up about $40RT$ of internal energy. If we assume an oversimple Brownian process of energy exchange between the walls and i -PrI molecules, this corresponds to about $4.5RT = 9$ kcal/mole transfer of energy per wall collision, essentially a "strong" collision mechanism.³³

3. RRK Theory of the Unimolecular Rate Constant k_u . The Rice-Ramsperger-Kassel (RRK) theory of unimolecular reactions assumes that molecules are activated and deactivated by collisions and that a stationary population of vibrationally excited species is produced by these processes together with the process of spontaneous unimolecular decomposition. The rate constant falls off from its high-pressure limit when spontaneous decomposition depletes the upper energy states responsible for reaction faster than collisional deactivation does.

Normally, one studies such effects by measuring the apparent first-order rate constant at fixed temperature but successively lower pressures. In the VLPP technique, the frequency of wall collisions is essentially fixed by the dimensions of the vessel. As one goes to higher and higher temperatures, the rate of spontaneous decomposition increases, and at sufficiently high temperatures all unimolecular reactions will fall off from their high-pressure limits.

(33) G. H. Kohlmaier and B. S. Rabinovitch, *J. Chem. Phys.*, **38**, 1692 (1963).

For an arbitrary reactant molecule A, the RRK scheme is³⁴



Here k_a and k_d are rate constants for vibrational energy exchange at the wall, and k_r is the specific decomposition rate of a critically energized molecule with internal energy $E \geq E^*$, the activation energy for reaction at 0°K. The observed apparent first-order rate constant k is then

$$k = \int_{E^*}^\infty \frac{k_a k_r}{k_d + k_r} dE \quad (27)$$

Using the classical RRK forms for k_r and k_a/k_d , it can be shown that the integrand in eq 27 has a simple sharp maximum at $E = E_m$ where $E^* \leq E_m \leq E^* + (n - 1)RT$, and n is the effective number of classical oscillators in the molecule A. If the half-width of the integrand is ΔE_m around the maximum, then we can write

$$k = \frac{k_a(E_m)k_r(E_m)(\Delta E_m)/RT}{[k_d(E_m) + k_r(E_m)]} \quad (28)$$

It can be further shown that this maximum occurs very close to the value of E_m that makes $k_d(E_m) \sim k_r(E_m)$, so that eq 28 becomes

$$k \approx \left(\frac{k_a}{2}\right) \frac{(\Delta E_m)}{RT} = \left(\frac{k_a}{k_d}\right) \left(\frac{k_d}{2}\right) \left(\frac{\Delta E_m}{RT}\right) = \frac{1}{2} P(E_m) k_d \frac{\Delta E_m}{RT} \quad (29)$$

where $P(E_m) = k_a/k_d$ is the probability of finding a molecule of internal energy E_m in a system at equilibrium. It is given classically by

$$P(E_m) = \frac{1}{(n - 1)!} \left(\frac{E_m}{RT}\right)^{n-1} \exp\left(-\frac{E_m}{RT}\right) \quad (30)$$

Now $k_d(E_m)$ can be written as $\lambda_d k_w$, where k_w is the frequency of wall collisions, typically $\sim 10^{4.5} \text{ sec}^{-1}$ in our system, and λ_d is the probability that a molecule with internal energy E_m will, on a wall collision, lose enough of this energy that it is not capable of reacting in $10^{-4.5} \text{ sec}$. The amount of energy required is probably of the order of $2RT$ and λ_d is probably of the order of 1. Thus we can set

$$k_r(E_m) = k_d(E_m) \cong k_w \quad (31)$$

while from the RRK theory

$$k_r(E_m) = A \left(\frac{E_m - E^*}{E_m} \right)^{n-1} \quad (32)$$

where A is the Arrhenius A factor in sec^{-1} . From eq 31 and 32

$$1 - \frac{E^*}{E_m} = \left(\frac{k_w}{A} \right)^{1/(n-1)} \quad (33)$$

or

$$\frac{E^*}{E_m} = 1 - \left(\frac{k_w}{A} \right)^{1/(n-1)} \quad (34)$$

(34) S. W. Benson, "Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter XI.

Thus if we know or can choose a value of n and A we can calculate the ratio E^*/E_m for our system.

Having calculated the ratio (E^*/E_m) , one then uses eq 29 and 30 with $\Delta E_m/RT \sim (n-1)^{1/2}$ to calculate E_m at any given temperature.³⁵ This is done numerically, explicit solutions not being possible.

With Stirling's approximation for $(n-1)!$ we have from eq 29 and 30

(35) This approximation for ΔE_m is obtained by use of the method of steepest descents for the integration of eq 29.

$$k = \frac{k_w}{2\sqrt{2\pi}} \left[\frac{eE_m}{(n-1)RT} \right]^{n-1} \exp\left(-\frac{E_m}{RT}\right) \quad (35)$$

which permits us to solve for E_m from the observed value of k and the appropriate value of n .

When the high-pressure Arrhenius parameters A and E^* are known, as is often the case, n is the only unknown parameter and it can be determined accurately.

We have used eq 35 in our theoretical estimates for the rate of decomposition of *i*-PrI.

A Nuclear Magnetic Resonance Study of Steric Effects in *cis*- and *trans*-1,4-Dichloro-2-butene¹

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Contribution from the University of California, Los Alamos Scientific Laboratory, Los Alamos, New Mexico, and the Department of Chemistry, Texas Technological College, Lubbock, Texas. Received December 16, 1966

Abstract: The 60-Mc nmr spectra of *cis*- and *trans*-1,4-dichloro-2-butene are reported and analyzed. A population analysis based upon the observed vicinal couplings indicates that the steric interaction between $-\text{CH}_2\text{Cl}$ groups in the *cis* isomer is at least 170 cal mole⁻¹ larger when the chlorine atom is oriented *trans* with respect to the adjacent vinyl proton.

The nuclear spin-spin coupling between vicinal protons in HC-CH groups of ethane and ethylene-type molecules has been found to be dependent upon the dihedral angle.³ Since internal rotational energy barriers about carbon-carbon single bonds are low, only an average coupling is observed in many cases, but such an average can still be useful to determine which is the more stable rotamer.

The analysis of the complex nmr spectra of *cis*- and *trans*-1,4-dichloro-2-butene was undertaken since the coupling constants obtained from these spectra can be used to infer the conformation of the CH_2Cl groups about the carbon-carbon single bonds. Our primary objective was to see if we could determine the extent of the steric interaction of these groups in the *cis* compound.

The basis for our conformational study rests upon the following considerations. Figure 1 shows the anticipated stable conformation of *trans*-1,4-dichloro-2-butene.⁴⁻⁶ It is assumed that in this case a certain average vicinal coupling between the methyl protons (H_a) and the adjacent vinyl proton (H_b) will be observed, the magnitude of which is determined by the energy difference between the conformation of Figure 1 and others obtained by rotations about the carbon-carbon single bonds. If the same *trans* orientation of an H_a

proton with respect to the adjacent H_b proton persisted in the *cis* isomer, we would expect to observe a rather strong steric interaction between the H_a protons of the different $-\text{CH}_2\text{Cl}$ groups. Of course with the chlorine atoms *trans* with respect to H_b , the steric effect would be even more pronounced. Because of these interactions, conformational stability requirements are altered, and these changes should be reflected in the average proton couplings observed.

This unsaturated system may be regarded as an allylic system, since there is spin-spin coupling between protons separated by one double bond and three single bonds, and also as a homoallylic system, where the coupling between protons is over five bonds with the protons symmetrically placed about the carbon-carbon double bond, i.e., $\text{H}-\text{C}-\text{C}=\text{C}-\text{C}-\text{H}$.⁷

Karplus,⁸ through a valence bond treatment, has had most success in correlating experimental results with theoretical calculations, with respect to both the sign and magnitude of couplings in allylic and homoallylic systems. The proposed mechanism involves hyperconjugation determined by $\sigma-\pi$ configuration interaction.

From the theoretical point of view, the allylic coupling constants are negative in sign with the coupling being transmitted mainly through the π -electron system.⁸ The magnitudes of the allylic coupling constants have been found to vary between 0 and 3 cps.⁹ These coupling constants attain a maximum of approximately 3 cps when the azimuthal angle is 90°, and a minimum when the azimuthal angle is 0 or 180°.

(1) Based in part on work performed under the auspices of the U. S. Atomic Energy Commission.

(2) Author to whom inquiries should be addressed: University of California, Los Alamos Scientific Laboratory, Los Alamos, N. M. 87544.

(3) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(4) M. Barfield and D. M. Grant, *J. Am. Chem. Soc.*, **85**, 1899 (1963).

(5) H. J. M. Bowen, A. Gilchrist, and L. E. Sutton, *Trans. Faraday Soc.*, **51**, 1341 (1955).

(6) A. A. Bothner-By and H. Günther, *Discussions Faraday Soc.*, **34**, 127 (1962).

(7) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

(8) M. Karplus, *J. Chem. Phys.*, **33**, 1842 (1960).

(9) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

In the homoallylic system the coupling also involves the σ - π configuration interaction mechanism.⁸ The theory predicts the sign to be reversed, but there should be no change in the magnitude of the coupling constants on replacing the fragment C=C by C=C-CH. The same stereochemical limitations should apply as for the allylic case.

Experimental Section

Preparation of Compounds. *trans*-1,4-Dichloro-2-butene was obtained from K and K Laboratories Inc. as a 98% pure compound. *cis*-1,4-Dichloro-2-butene was synthesized following the procedure of Babbitt, Amundsen, and Steiner.¹⁰ Attempts to purify these compounds by distillation and fractional crystallization were unsuccessful, but through the courtesy of Dr. G. Perkins, Jr., of Continental Oil Co., both compounds were finally purified using gas chromatography.¹¹ The chromatogram indicated that the *trans* compound was contaminated with about 18% of impurities before purification.

Before observing the nmr spectra of the liquid samples of *cis*- and *trans*-1,4-dichloro-2-butene, these samples were degassed by flushing with nitrogen gas in standard thin-walled cells. Sealed capillaries of benzene were inserted into the sample tubes for use as an external reference standard. There were no bulk susceptibility corrections made.

Instrumentation. The nmr spectra were recorded on a Varian A-60 spectrometer operating at room temperature. The line positions were measured at total peak height with a probable error of ± 0.05 cps.

The spectra were calculated using a computer program written for an IBM 1620 Model II computer having a disk pack. The computer program was written in FORTRAN II following the procedure given by Pople, Schneider, and Bernstein.¹² Values for the chemical shift for each proton plus the coupling constants between the various protons in the molecule are used as parameters to calculate the spectrum. By varying these parameters the experimental spectrum was fairly well reproduced. The probable error for the calculation of the frequencies and intensities is 0.05 to 0.1 cps. Thus we feel that the chemical shifts and coupling constants determined in this way are accurate to at least ± 0.1 cps.

Results

The calculated chemical shifts and coupling constants for the *cis* and *trans* isomers as determined by the methods discussed above are found in Tables I and II, respectively. The results are illustrated in Figures 2 and 3. The field is calibrated in cycles per second from the benzene external standard.

The results obtained are in agreement with the theory as well as with the results obtained by other investigators.⁷ The small but significant differences in the allylic, vicinal, and long-range coupling constants for the two isomers can be used to discuss conformational effects. Since the vicinal coupling is the more straightforward, we will limit our subsequent discussion to it.

A complete conformational analysis is complicated by the fact that much less experimental data are available in the case of orientations about a carbon-carbon single bond which involves sp^3 hybridization on one end and sp^2 hybridization on the other. However, both theoretical¹³ and experimental^{6,14} indications are that the angular dependence of the vicinal coupling constant closely parallels that found for sp^2 - sp^3 hybridization.

(10) J. Babbitt, L. Amundsen, and R. Steiner, *J. Org. Chem.*, **25**, 2231 (1960).

(11) A. B. Carel and G. Perkins, Jr., *Anal. Chim. Acta*, **34**, 83 (1966).

(12) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 103.

(13) J. Rant, *Ann. Phys.*, **9**, 124 (1962).

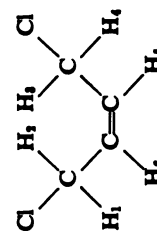
(14) A. A. Bothner-By, C. Naar-Colin, and H. Günther, *J. Am. Chem. Soc.*, **84**, 2748 (1962).

Table I. Chemical Shifts and Coupling Constants for *cis*-1,4-Dichloro-2-butene

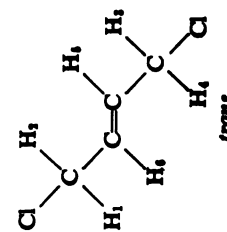
$\nu(1)$	Chemical shifts from benzene, cps				Coupling constants, cps									
	$\nu(2)$	$\nu(3)$	$\nu(4)$	$\nu(5)$	$\nu(6)$	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{23}	J_{24}	J_{25}	J_{26}
14.8	141.8	141.8	141.8	40.0	40.0	0.53	0.53	0.53	1	7.9	0.53	0.53	1	7.9
														10.2

Table II. Chemical Shifts and Coupling Constants for *trans*-1,4-Dichloro-2-butene

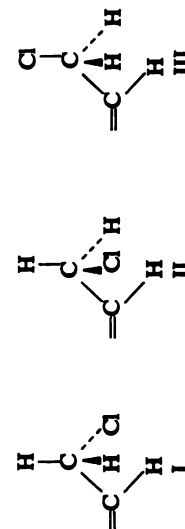
$\nu(1)$	Chemical shifts from benzene, cps				Coupling constants, cps									
	$\nu(2)$	$\nu(3)$	$\nu(4)$	$\nu(5)$	$\nu(6)$	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{23}	J_{24}	J_{25}	J_{26}
147.0	147.0	147.0	147.0	34.0	34.0	...	0.9	0.9	-1.5	7.1	0.9	0.9	-1.5	7.1
														17.0



cis



trans



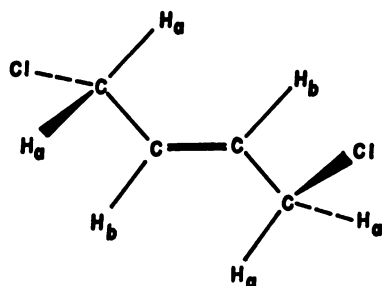


Figure 1. Assumed conformation of *trans*-1,4-dichloro-2-butene.

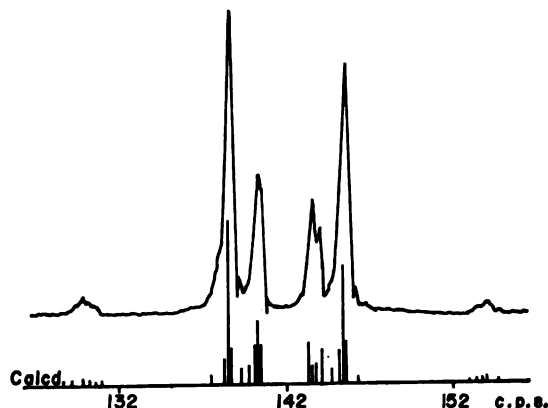


Figure 2. The experimental and calculated 60-Mc nmr spectrum of *cis*-1,4-dichloro-2-butene.

A population analysis based upon the three conformations I-III leads to an average vicinal coupling constant

$$J = p_I J_t + (1 - p_I) J_g$$

where J_t and J_g are the *trans* and *gauche* couplings, and the fractional populations are p_I , p_{II} , and p_{III} ($p_I = p_{II}$, $p_I + p_{II} + p_{III} = 1$).

We assume the values of $J_t = 13.4$ cps and $J_g = 2.4$ cps reported by Bothner-By, *et al.*,¹⁵ for the vicinal *trans* and *gauche* couplings in allyl chloride. Then we find for the *trans* configuration ($J = 7.1$ cps) $p_I = 0.427$, and for the *cis* configuration ($J = 7.9$ cps) $p_I = 0.500$. If we assume, as is usually done,¹⁶ that $\Delta S =$

(15) A. A. Bothner-By, S. Castellano, S. J. Ebersole, and H. Günther, *J. Am. Chem. Soc.*, **88**, 2466 (1966).

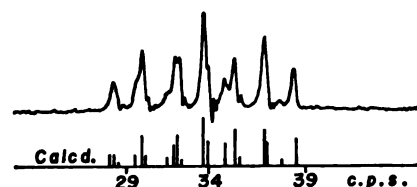
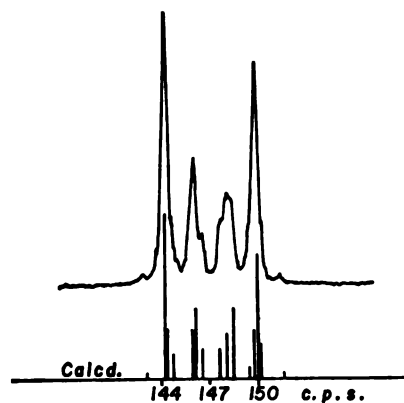


Figure 3. The experimental and calculated 60-Mc nmr spectrum of *trans*-1,4-dichloro-2-butene.

0, then the energy difference in the conformers I or II and III is

$$\Delta H = -RT \ln K_{eq} = -RT \ln \frac{2p_I}{1 - p_I}$$

We find in this way that $\Delta H_{trans} = -237$ cal mole⁻¹ and $\Delta H_{cis} = -411$ cal mole⁻¹. The difference, ~ 170 cal mole⁻¹, represents a lower limit to the difference in energy of interaction of a proton and a chlorine atom in the *trans* orientation (with respect to the vinyl proton) with the average potential of a $-\text{CH}_2\text{Cl}$ group oriented *cis* (with respect to the other $-\text{CH}_2\text{Cl}$ group).

The fact that this figure is but a lower limit is shown by the value of $p_I = 0.5$ for the *cis* compound, which means that $p_{III} = 0$ and $J = (J_t + J_g)/2$. Obviously, all that we can determine is the least amount of interaction energy which is required to drive the system to this limit. It is also possible that there may be some skewing of the stable conformation due to the steric interaction, similar to that reported by Woolfenden and Grant¹⁶ for *o*-methyl groups in aromatic systems. Whether or not this effect is significant should be revealed by a study of the parent compounds, *i.e.*, the *cis*- and *trans*-2-butenes, where no population effects are involved. Such a study is being pursued by us at the present time.

(16) W. R. Woolfenden and D. M. Grant, *ibid.*, **88**, 1496 (1966).

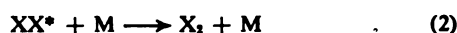
Halogen Atom Complexes. Thermodynamic and Kinetic Properties of the Iodine Atom-*o*-Xylene Charge-Transfer Complex

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Abstract: Thermodynamic and kinetic properties of the transient complex between iodine atoms and *o*-xylene in the liquid phase have been determined by flash spectrophotometry. The formation constant and enthalpy of formation at 25° are reasonably consistent with those inferred from kinetic recombination studies for the gas-phase complex when solvation effects are considered, and show that charge-transfer interactions can lead to both the specificities and observed negative temperature coefficients for relatively efficient third-body species.

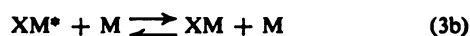
The homogeneous gas-phase recombination of halogen atoms (X) in the presence of a third body (M) is now generally considered¹ to occur either by the energy-transfer mechanism



or the radical-molecule complex mechanism



In these mechanisms, XX^* represents a short-lived diatom with more than sufficient energy to dissociate, and XM is a complex of sufficiently long life to be collisionally deactivated and to participate in step 4, leading to recombination



the over-all rate of recombination in either case being

$$\frac{d[X_2]}{dt} = k_{app}[X]^2[M] \quad (5)$$

The first mechanism satisfactorily describes the recombination of iodine atoms in the presence of atomic or relatively simple molecular third bodies.² In more complex systems, however, the large rate constants cannot adequately be explained by energy transfer alone, and the second mechanism accounts for recombination where the binding energy of XM is greater than kT . Dispersion forces alone, although leading to reasonable binding energies,^{3,4} do not result in the large variations actually observed in third-body efficiencies,⁴⁻⁶ whereas charge-transfer interactions lead to quite large binding energies but reasonable specificities among the donor third bodies.

Following the flash photolysis of molecular iodine, a transient absorption attributed to a strong intermediate complex between a nitric oxide molecule and an iodine atom has been detected in the gas phase.⁷ Similarly, charge-transfer complexes between iodine atoms and aromatic donors have been observed spectrophotometrically in the liquid phase;⁷⁻⁹ the absorption spectra of these relatively weak complexes have not been observed in the gas phase, but formation constants deduced from the gas-phase atom recombination studies are at least an order of magnitude greater than the comparable molecular iodine-aromatic complexes in the liquid phase.¹⁰ A stronger atom complex is, in fact, to be expected, as the electron affinity of the iodine atom is greater than that of the iodine molecule. Although the formation constant for the iodine atom-hexamethylbenzene complex has been shown¹¹ to be somewhat larger than that for the molecular iodine-hexamethylbenzene complex (2.7 and 1.5 l. mole⁻¹, respectively, both at 25°, CCl₄ solvent), this difference is not large enough to account for the at least tenfold difference cited above and may indicate a compensating effect between the standard enthalpies and entropies of formation not present in the gas phase. In addition, however, it has recently been shown¹² that gas-phase molecular iodine complexes are appreciably stronger than comparable liquid-phase complexes (although the enthalpies of formation are approximately the same), the effect diminishing with increasing strength of the complex.¹³

Determination of the thermodynamic properties of the liquid-phase iodine atom-aromatic complexes requires the precise measurement of absorbance changes as a function of temperature and donor concentration at two wavelengths, one of which corresponds to change in molecular iodine concentration only. Accordingly, the flash spectrophotometric apparatus of this laboratory has been modified to permit the simultaneous recording of two absorbance changes as a function of

- (1) S. W. Benson and W. B. DeMore, *Ann. Rev. Phys. Chem.*, **16**, 397 (1965).
- (2) M. Eusuf and K. J. Laidler, *Trans. Faraday Soc.*, **59**, 2750 (1963).
- (3) D. L. Bunker and N. Davidson, *J. Am. Chem. Soc.*, **80**, 5090 (1958).
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- (5) R. Engleman and N. R. Davidson, *J. Am. Chem. Soc.*, **82**, 4770 (1960).
- (6) G. Porter and J. A. Smith, *Proc. Roy. Soc. (London)*, **A261**, 28 (1961).

- (7) G. Porter, Z. G. Szabo, and M. G. Townsend, *ibid.*, **A270**, 493 (1962).
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- (9) R. L. Strong, S. J. Rand, and J. A. Britt, *ibid.*, **82**, 5053 (1960).
- (10) T. A. Gover and G. Porter, *Proc. Roy. Soc. (London)*, **A262**, 476 (1961).
- (11) R. L. Strong and J. Perano, *J. Am. Chem. Soc.*, **83**, 2843 (1961).
- (12) F. T. Lang, and R. L. Strong, *ibid.*, **87**, 2345 (1965).
- (13) J. M. Goodenow and M. Tamres, *J. Chem. Phys.*, **43**, 3393 (1965).

time following flash photolysis, one in the ultraviolet region (due to dissociation of iodine in the molecular iodine-aromatic complex) and the other in the visible region (resulting from the simultaneous dissociation of iodine and formation of the atom complex).

Experimental Section

Flash Apparatus. The flash spectrophotometric apparatus used in this work was a modification of the unit used in previously reported experiments in this laboratory on transient charge-transfer species.⁸ The flash lamp consisted of two parallel quartz tubes (15-mm i.d., 1.5-mm wall thickness), each approximately 15 cm long with either cup stainless steel or 5-mm tungsten rod electrodes 12 cm apart. Semicircular Pyrex manifolds at each end positioned the tubes at a distance of 8 cm from each other and provided for common gas filling of both tubes (Xe, 60–120 mm). The lamp was mounted horizontally on the optical bench in a polished cylindrical reflector, and the reaction cell was positioned midway between the two tubes.

The discharge tubes were connected in series electrically. Two ASEA Type CTUA capacitors (625 joules each) charged in parallel were discharged across the lamp, triggering being effected by a 20–35-kv pulse applied at the midpoint connection between the two tubes. The maximum capacitance voltage possible was 10 kv. However, as with flash units elsewhere,¹⁴ a "saturation effect" was also encountered here; i.e., at low energies the peak light intensity is directly proportional to the electrical energy, but at higher discharge energies the peak intensity becomes roughly constant and the flash duration time (or "tailing") increases. The voltage at which this effect becomes significant apparently is a function of the design of the apparatus and was encountered here at a much lower voltage (ca. 8 kv) than on the unit described previously¹⁴ (23 kv), although the energies dissipated per unit length of discharge path (33 and 42 joules/cm, respectively) are more comparable. For the relatively fast recombination reactions reported here, it was desirable to minimize flash tailing as much as possible consistent with a high peak light intensity, and therefore all measurements were made at not more than 8 kv (800 joules).

Analyzing light from the continuous light source (Osram Type XBO 450W/P xenon lamp, powered by a Sola dc constant wattage supply further stabilized by two parallel 18-v storage battery units) was partially collimated so that it passed through the reaction cell without hitting the sides and was split past the cell with a partially silvered mirror. The transmitted portion (70%) was focused on the entrance slit of a Zeiss MM12 double monochromator and detected by an EMI 9558Q photomultiplier tube; this unit involving the larger fraction of the analyzing beam was used for lower wavelength (ultraviolet) measurements. The reflected light, for measurements in the visible spectral region, was focused on the entrance slit of a Beckman DU monochromator and detected by an EMI 9558B photomultiplier. Voltage outputs developed across load resistors (variable in steps from 10 kilohms to 1 megohm) and shunting capacitors (from 0 to 600 pF) were dc-coupled through 12AU7 cathode followers to the upper and lower 2A63 amplifier plug-in units of a Tektronix Type 565 dual-beam oscilloscope. The two traces were maintained on the cathode ray screen by opposing the dc voltages from the continuous analyzing light with variable dc voltage applied at the negative inputs of the two amplifier sections. The two sweeps were simultaneously initiated by a manual trigger switch, and the gate-out signal from the oscilloscope was used to initiate the high-voltage flash trigger pulse. The rise time of the 2A63 amplifier is 1 μ sec, and this was the limiting factor for fast time resolution. However, the time constant of each detecting assembly could be stepwise increased to a maximum of 600 μ sec by the appropriate combination of load resistor and shunting capacitor in order to give the optimum signal-to-noise ratio consistent with negligible signal distortion.

Reaction Cell. The Pyrex reaction cell was cylindrical (10 cm light path, 2.5 cm i.d.) with evacuated 2-cm cylindrical chambers at each end. Surrounding the cell compartment and approximately three-fourths of each end section was an annular jacket (ca. 1-cm inside thickness) through which was circulated the thermostated aqueous filter solution (1 M CuCl₂·2H₂O + 0.5 M CaCl₂·2H₂O). With this arrangement, temperature control and uniformity over the entire cell was sufficiently precise to prevent any distortion of the

analyzing light beam by density gradients at the highest temperature used.

Purification of Materials. To Eastman *o*-xylene was added a small amount of iodine and the solution illuminated for 36 hr. Excess iodine was removed with sodium sulfite solution; the wet *o*-xylene was shaken with portions of concentrated sulfuric acid until no discoloration of the acid occurred, washed, shaken with a 10% sodium hydroxide solution, washed, and distilled twice over sodium through a 48-cm Vigreux column, the second distillation being at a high reflux ratio. A similar procedure was used for carbon tetrachloride (Fisher reagent grade), except that chlorine was added instead of iodine before illumination, and distillation was performed over phosphorus pentoxide instead of sodium. Iodine (Fisher) was freshly resublimed and used without further purification.

Calculations. At λ_1 , where it is assumed that the changes in absorbance (optical path length d) are due only to changes in total molecular iodine concentration, $\Delta[I_2]$ (either free or complexed)

$$\Delta A_{\lambda_1} = \epsilon_{I_2, \lambda_1} d \Delta[I_2] \quad (6)$$

(Values for the apparent molar extinction coefficient of iodine, $\epsilon_{I_2, \lambda_1}$, were determined at the temperatures and donor molecule concentrations used in this work in independent measurements with a thermostated Beckman DU spectrophotometer using 1-cm quartz absorption cells.) At λ_2 , the other wavelength at which absorbance changes as a function of time are simultaneously measured

$$\Delta A_{\lambda_2} = \epsilon_{C, \lambda_2} d[C] + \epsilon_{I_2, \lambda_2} d \Delta[I_2] \quad (7)$$

where $[C]$ is the concentration of the iodine atom-aromatic complex, and ϵ_{C, λ_2} and $\epsilon_{I_2, \lambda_2}$ are the molar extinction coefficients at λ_2 of the complex and molecular iodine, respectively. The formation constant K_x of the 1:1 complex between an iodine atom and the donor aromatic molecule (mole fraction X_D) is

$$K_x = \frac{[C]}{X_D[I]} = \frac{[C]}{X_D(-2\Delta[I_2] - [C])} \quad (8)$$

Rearrangement of eq 6, 7, and 8 leads to an equation similar to the well-known Benesi-Hildebrand equation¹⁵ in the form suitable in particular to relatively weak complexes¹⁶

$$-\frac{2R_A}{(1 - R_A R_e) \epsilon_{I_2, \lambda_1}} = \frac{1}{\epsilon_{C, \lambda_2} K_x X_D} + \frac{1}{\epsilon_{C, \lambda_2}} \quad (9)$$

where $R_A = \Delta A_{\lambda_1} / \Delta A_{\lambda_2}$ and $R_e = \epsilon_{I_2, \lambda_2} / \epsilon_{I_2, \lambda_1}$.

Trotter and Hanna have recently pointed out¹⁷ that solution non-ideality will lead to different values for ϵ_C depending on the concentration units of the donor, D , although linear plots of the Benesi-Hildebrand equation still result. This will affect also the values for K determined from these plots in addition to the conversion unit factors. In this work, however, within the rather wide experimental errors, no differences were found in ϵ_C for the different concentration scales; mole fraction units have therefore been used throughout for comparison purposes.

Results and Discussion

Iodine-*o*-Xylene System. The transient absorbance changes, present 100 μ sec following initiation of the flash discharge, were measured simultaneously at 350 and 570 m μ as functions of temperature (25, 45, and 65°) and *o*-xylene mole fraction (0.082:1, CCl₄ solvent), but constant (3.9×10^{-5} M) initial molecular iodine concentration. The choice of the former wavelength represents a compromise between maximum ultraviolet absorption by iodine in *o*-xylene (316 m μ)¹⁸ and the increasing noise-to-signal ratio at lower wavelengths; the latter wavelength is the maximum of the *o*-xylene-iodine atom complex.⁹

(15) H. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, **71**, 2703 (1949).

(16) P. R. Hammond, *J. Chem. Soc.*, 479 (1964).

(17) P. J. Trotter and M. W. Hanna, *J. Am. Chem. Soc.*, **88**, 3724 (1966).

(18) L. J. Andrews and R. M. Keefer, *ibid.*, **74**, 4500 (1952).

(14) S. Claesson, L. Lindqvist, and R. L. Strong, *Arkiv Kemi*, **22**, 245 (1964).

The ratios of these absorbance changes are shown in Figure 1 as a function of the reciprocal of the *o*-xylene mole fraction according to eq 9, each point representing the average of at least ten oscillograms. From these plots $\epsilon_{c,\lambda}$ and K_x were calculated from the intercepts and slopes of the best straight lines using the method of least squares. The results are given in Table I and are compared at 25° with those of the molecular iodine-*o*-xylene complex. (In practice, the data were also plotted using the technique of Rose and Drago¹⁹ in order to determine experimental scattering and to verify the validity of the thermodynamic data resulting from the specific range of conditions used; no significant differences resulted using this latter technique.)

Table I. Comparison of Thermodynamic Constants for the Iodine Atom- and Molecular Iodine-*o*-Xylene Complexes in the Liquid Phase

	I complex (λ_{\max} 590 m μ)	I ₂ complex ^a (λ_{\max} 316 m μ)
K_x , mole fraction units		
25°	7.4	2.96
45°	3.5	
65°	2.9	
ΔH°_x , kcal mole ⁻¹	-4.4	-2.0
ΔS°_x , eu	-10.9	-4.9
ϵ_{\max} , l. mole ⁻¹ cm ⁻¹	3400	12,500

^a J. A. A. Ketelaar, *J. Phys. Radium*, 15, 197 (1954).

Since the slopes of the lines in Figure 1 can be determined more accurately than K_x , which depends on both the slope and the intercept (i.e., the extinction coefficient), the enthalpy and entropy of formation at 25° were calculated according to the integrated form of the van't Hoff equation from the reciprocals of the slopes, thereby assuming $\epsilon_{c,\lambda}$ and ΔH°_x are independent of temperature. These thermodynamic properties are also given in Table I.

That the equilibrium constant at 25° for the atom complex is greater than that for the molecular complex is to be expected from Mulliken's treatment of charge transfer²⁰ because of the greater electron affinity of the iodine atom, leading also to the visible shift of the charge-transfer band. The correspondence between enthalpy and entropy is also quite general, the relative values for the iodine atom complex agreeing well with those for a large number of donor species with molecular iodine.²¹ The energy of formation of the complex, *ca.* -4.1 kcal/mole, is essentially the same as the calculated binding energy for a gas-phase, charge-transfer complex according to Mulliken following the method of Eusuf and Laidler.² There is little question, therefore, of the charge-transfer nature of this intermediate.

The third-order, gas-phase recombination rate constant, k_{app} (defined by eq 5), for iodine atoms with *p*-xylene as the third body is approximately 3.3×10^{11} l.² mole⁻² sec⁻¹ at room temperature.⁴ For the recombination mechanism given by eq 3 and 4, $k_{app} = k_4(K_c)_{gas}$, where $(K_c)_{gas} = k_3/k_{-3}$ is the formation constant (in concentration units) for the assumed equilib-

(19) N. J. Rose and R. S. Drago, *J. Am. Chem. Soc.*, 81, 6138 (1959).

(20) R. S. Mulliken, *ibid.*, 74, 811 (1952).

(21) G. Briegleb, "Elektronen-Donator-Acceptor-Komplexe," Springer-Verlag, Berlin, 1961, p 141.

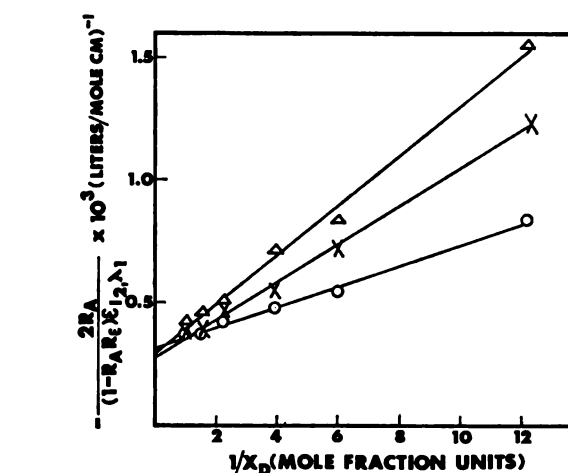


Figure 1. Absorbance changes at 100 μ sec as a function of *o*-xylene mole fraction, plotted according to eq 9: O, 25°; X, 45°; Δ , 65°.

rium between I atoms, xylene, and the charge-transfer complex. The bimolecular rate constant k_4 is easily estimated since this metathetical reaction would be expected to have essentially zero activation energy and therefore should proceed at a rate proportional to collisional frequency, the specific collision number between unlike molecules being given by

$$Z_{12}' = \sigma^2 \left(\frac{8\pi kT}{\mu} \right)^{1/2} \quad (10)$$

where σ is the collision diameter of the I-I pair⁶ (4.3×10^{-8} cm) and μ is the reduced mass of the I-IM pair. The major uncertainty in this calculation is the statistical factor giving the fraction of iodine atom pairs, each atom being in its ground ($^2P_{1/2}$) state, that lead to a stable configuration. Porter and Smith⁶ have used $1/16$ since the total degeneracy of the ground-state iodine atom is 16, whereas the degeneracy of the stable singlet molecular ground state is unity. However, Eusuf and Laidler² point out that 8 of the 16 possible states from combination of two iodine atoms are attractive and can lead to combination if stabilized by collisional deactivation; the appropriate statistical factor is therefore $1/2$. On this basis, $(k_4)_{calcd} = 4.8 \times 10^{10}$ l. mole⁻¹ sec⁻¹ at 25° and $(K_c)_{gas} = 6.9$ l. mole⁻¹. The formation constant in solution for this same intermediate species IM at 25° (Table I) is 7.4 in mole fraction units; in concentration units, $(K_c)_{liquid} = 0.9$ l. mole⁻¹. Agreement between the formation constants in the two phases is considered to be reasonably close in view of the experimental errors associated with the transient absorbance measurements in solution and the uncertainties in the calculation of k_4 . The results do, however, indicate a smaller formation constant in the liquid phase than in the gas phase, in agreement with results for weaker complexes between atomic iodine and ethyl iodide or bromide¹⁰ and between molecular iodine and benzene or diethyl ether.¹² This behavior is presumably due to competition between complexing and solvation of the donor molecule in the liquid phase,²² the disagreement between the formation constants in the two phases decreasing with increasing strength of the complex.¹² (For the stronger complex between molec-

(22) S. Carter, J. N. Murrell, and E. J. Rosch, *J. Chem. Soc.*, 2048 (1965).

ular iodine and diethyl sulfide, the agreement between the two phases is much closer.¹³)

The negative temperature dependence of the gas-phase recombination of iodine atoms with xylene as a third body has not been determined, but certainly is less than that for toluene (-3.4 kcal/mole) and is probably close to the -4.1 -kcal/mole complex formation energy obtained in this liquid-phase work. It is thus quite clear that charge-transfer interactions can account for both the third-body specificities and observed negative recombination temperature coefficients for relatively efficient third-body species.

The formation of molecular iodine in the liquid phase after the dissociation flash intensity has decayed to a negligible value is second order (as shown by linear time plots of $1/\Delta A_{350}$) and is consistent with a bimolecular recombination mechanism involving free or complexed iodine atoms where a third body is essentially in contact in every bimolecular encounter. The second-order rate constant, k , defined by

$$\frac{d[I_2]}{dt} = -\frac{1}{2} \frac{d[I]_{\text{total}}}{dt} = k[I]_{\text{total}}^2 \quad (11)$$

where $(I)_{\text{total}}$ is the total iodine atom concentration (free or complexed) was calculated from the slope of this second-order plot and eq 6 ($[I]_{\text{total}} = -2\Delta[I_2]$) for each oscillogram, and the average values are summarized in Table II for each concentration at 25, 45, and 65°. At 25°, the rate of recombination is in good agreement with the rate of recombination in pure carbon tetrachloride.²³

Table II. Rate of Recombination of Iodine in *o*-Xylene-Carbon Tetrachloride Solutions

[<i>o</i> -Xylene], mole fraction	25° $k \times 10^{-3}, \text{l.}^2 \text{mole}^{-2} \text{sec}^{-1}$	45° $k \times 10^{-3}, \text{l.}^2 \text{mole}^{-2} \text{sec}^{-1}$	65° $k \times 10^{-3}, \text{l.}^2 \text{mole}^{-2} \text{sec}^{-1}$
0.082	5.3	7.1	7.7
0.167	5.4	6.7	7.1
0.255	5.3	6.2	6.4
0.446	5.2	5.6	6.8
0.651	5.4	6.1	6.5
1.00	4.5	5.0	4.7

Combination of the Smoluchowski relation

$$k = \frac{8\pi aDN}{1000} \quad (\text{l. mole}^{-1} \text{sec}^{-1}) \quad (12)$$

which gives the diffusion-controlled recombination rate constant assuming that even on a molecular scale the solvent can be treated as a continuous medium of viscosity η and the Stokes-Einstein equation for the diffusion coefficient

$$D = \frac{kT}{6\pi\eta a_s} \quad (\text{cm}^2 \text{sec}^{-1}) \quad (13)$$

shows that the product $k\eta$ should be a function only of temperature

$$k\eta = \frac{4RTa}{3000a_s} \quad (14)$$

(23) R. L. Strong and J. E. Willard, *J. Am. Chem. Soc.*, **79**, 2098 (1957).

if the encounter diameter in solution ($2a$) pertinent to the recombination process is taken to be the same as the diffusion diameter ($2a_s$). The viscosities for all the *o*-xylene-carbon tetrachloride solutions used in this work were determined at 25, 45, and 65° with an Ostwald viscometer (modified at the top to prevent evaporation of the solution at the higher temperatures) which was calibrated with the two pure liquids *o*-xylene and carbon tetrachloride at 25°; these are tabulated in Table III with the densities (measured at room temperature with a Westphal balance and assumed to be independent of temperature) and values for $k\eta$.

Table III. Values of $k\eta$ for Iodine Atom Recombination in *o*-Xylene-Carbon Tetrachloride Solutions

[<i>o</i> -Xylene], mole fraction	ρ_{25} , g cc ⁻¹	η_{25} , cp	25° $k\eta \times 10^{-7}$ poise l. ² mole ⁻² sec ⁻¹	45° $k\eta \times 10^{-7}$ poise l. ² mole ⁻² sec ⁻¹	65° $k\eta \times 10^{-7}$ poise l. ² mole ⁻² sec ⁻¹
0.00	1.590	0.901			
0.082	1.508	0.886	4.7	5.0	4.4
0.167	1.430	0.875	4.7	5.1	4.1
0.255	1.360	0.860	4.6	4.2	3.6
0.446	1.216	0.831	4.3	3.7	3.7
0.651	1.080	0.803	4.4	3.9	3.4
1.00	0.880	0.753	3.4	3.0	2.3

It is seen that $k\eta$ is, in fact, roughly constant at room temperature but decreases with increasing *o*-xylene concentration at the higher temperatures. Since two iodine atoms must come into close proximity for recombination to occur, the apparent encounter diameter ($2a$) should be approximately constant (or decrease by a steric effect), whereas the average diffusion diameter ($2a_s$) must surely increase with increased extent of complexing, both factors leading to the observed behavior. The net effect, however, is to give an inverse temperature relationship in $k\eta$ at the higher *o*-xylene concentrations, approximately 90% of the iodine atoms being complexed in pure *o*-xylene. A similar effect (or constancy of k , as shown in Table II) in a pure donor has also been observed by Gover and Porter for iodine in benzene¹⁰ and has been interpreted in part as a possible compensation by a temperature dependence of the extinction coefficient, since in the benzene-iodine system only the ratio k/ϵ can be determined. The fact that there is appreciable overlapping of the molecular iodine-iodine atom-benzene complex spectra in the visible region would be expected to lead to just such an effect, but should not be a major factor in measurements made at 350 m μ on the atomic iodine-*o*-xylene complex since presumably there is negligible contribution to the absorbance at 350 m μ of the atomic complex absorption curve. At the lowest concentration, the expected constancy of $k\eta$ is roughly followed and is consistent with the temperature coefficient for the recombination of iodine atoms in carbon tetrachloride.²⁴

Acknowledgment. This research was supported in part by the National Science Foundation, Grant No. GP-2146.

(24) S. Aditya and J. E. Willard, *ibid.*, **79**, 2680 (1957).

The Crystal and Molecular Structure of the Silver Nitrate Complex of *cis,cis,cis*-1,4,7-Cyclononatriene, $C_9H_{12}(AgNO_3)_3$

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Contribution No. 1399 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401. Received October 5, 1966

Abstract: The structure of the silver nitrate π complex of *cis,cis,cis*-1,4,7-cyclononatriene, $C_9H_{12}(AgNO_3)_3$, has been determined by a three-dimensional single-crystal X-ray diffraction investigation. The complex crystallizes in space group $R\bar{3}c$; cell dimensions for the triply primitive hexagonal cell are $a = 16.258$ and $c = 9.556$ Å at approximately -125° . The cyclononatriene ring is in the crown configuration and shows little or no distortion due to the complex formation. Each silver is associated with only one ethylenic bond at divergent ends of the π -bonded p orbitals. The silver ions are distorted 17° in the direction of the *cis* hydrogens.

structure of *cis,cis,cis*-1,4,7-cyclononatriene, H_{12} ,²⁻⁴ is known to have a crown configura-

Silver complexes of olefins are well known⁵ and several⁶⁻¹³ have been investigated by X-ray diffraction techniques. The present study was undertaken to elucidate the geometry of the nine-membered ring system and to compare the bonding in the olefin with that of its silver complex.

Experimental Section

Collection. White needles of $C_9H_{12}(AgNO_3)_3$ were prepared and supplied to us by Dr. Karl Untch. Irregular single crystals approximately $0.2 \times 0.2 \times 0.3$ mm were cleaved and mounted, the first of these with the needle axis along the goniometer axis. Preliminary Weissenberg and precession photographs indicated a rhombohedrally centered hexagonal unit cell, the hexagonal axis corresponding to the needle axis. The conditions for selection, $-h + k + l = 3n$ for hkl and $l = 2n$ for $h0l$, led to the space group to be $R\bar{3}c$ or $R\bar{3}c$. Cell dimensions obtained from film measurements and an approximate density (by flotation) of 2.9 g/cm³ indicated six molecules in the hexagonal unit cell. It was assumed, and later verified, that the molecule had the same symmetry, $3m\bar{C}_2$, as its parent compound. This symmetry condition restricted the space group to $R\bar{3}c$, since $R\bar{3}c$ would have required the molecule to have $3\bar{C}_2$ or $32\bar{D}_3$ symmetry. Three sets of three-dimensional, low-temperature intensity data were collected: initially (a) integrated Weissenberg multiple film using $Cu K\alpha$ radiation, of levels $hki0$ – $hki3$ and $0k0l$ – $8k0l$, later refinement (b) counter-diffractometer data, collected by with $Mo K\alpha$ radiation on a General Electric spectrometer equipped with a single-crystal orienter and scintillation counter. Threefold redundant data were measured for 483 unique intensities and 364 unique counter intensities. The integrated intensities were measured with a Nonius Model I densitometer. Both data sets were collected at low temperature using a conventional liquid vapor cold stream in order to reduce thermal motion and to avoid a gradual surface decomposition of the crystals. Im-hexagonal cell dimensions, obtained by least-squares fit

with diffractometer 2θ data, were $a = 16.258 \pm 0.005$ and $c = 9.556 \pm 0.003$ Å at approximately -125° .

Computations. All calculations were performed on a CDC 3600 computer. The raw data were correlated and corrected for Lorentz and polarization effects using a program written at this laboratory. Standard errors for the film intensities were based on observed deviations during film correlation with a minimum error of $0.05I_{\text{obsd}}$ to avoid accidental agreement. Standard errors for the counter data were based on counting statistics as described by Johnson.¹⁴ Cell dimensions and errors were determined using the least-squares program by Heaton, Gvildys, and Mueller.¹⁵ Patterson and electron-density maps were computed using the Gvildys Fourier summation program.¹⁷ The Busing and Levy full-matrix least-squares program¹⁸ was used for the structure refinement, and their function and error program¹⁹ was used for calculation of bond distances, angles, anisotropic parameters, and their respective standard deviations.

Structure Determination. The structure was solved by the heavy-atom method. The x and y silver atom coordinates were determined from a two-dimensional Patterson map calculated from 40 $hki0$ film intensities. Since there was only one silver atom in the asymmetric unit and the position of the origin along the c axis was arbitrary, we proceeded directly to a three-dimensional least-squares refinement. Two cycles, varying the silver coordinates and the absolute scale factor, decreased the residual, $R = \sum ||F_o| - |F_c|| / \sum |F_o|$, from 0.41 to 0.22. A three-dimensional Fourier map revealed the approximate positions of the carbon ring atoms. After two least-squares cycles refining silver and carbon coordinates, another difference map was computed and the nitrate group atoms were located. Further refinement of all coordinates (except hydrogen), scale factor, and isotropic temperature factors failed to lower R below 0.185. The relatively high value of R at this stage of refinement led us to make a correction for systematic errors in the form of artificial temperature factors. The film data were collected over an extended period of time involving more than one crystal and several interruptions in the operation of the cold stream. It was therefore suspected that the various film packs may have been exposed at somewhat different temperatures and that this would constitute the major systematic error. The original intensities were corrected according to the relation $I_{\text{corrected}} = k_i I_{\text{obsd}} \exp(-B_i \sin^2 \theta / \lambda^2)$, where I_{obsd} 's are the observed intensities for a given film pack, k_i is the correlation scale factor for that pack, and B_i is the individual film pack temperature factor which was fitted by least squares. Two cycles of isotropic refinement with the corrected intensities, followed by two cycles with anisotropic tempera-

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* The F_o 's were obtained from counter data. Columns contain values of h , k , $10F_o$, $10|F_c|$, $10A_c$, and $10B_c$. Unobserved reflections are designated by an asterisk.

At this point the errors in the light-atom coordinates were still large and the set of counter intensity data was collected. Starting

with the previously determined parameters, two cycles of isotropic refinement, followed by two cycles with anisotropic temperature factors for silver, yielded $R = 0.028$ and an acceptable set of standard deviations on the light atoms. The final calculated and

observed structure factors are listed in Table I which, in addition, includes 70 unobserved intensities estimated (at the raw-data level) as half the minimum observed intensity. The unobserved data were not used in the least-squares refinements.

Results

Atom coordinates, isotropic temperature factors, and their standard deviations are given in Table II. Interatomic distances and angles and their errors are given in Table III.

Table II. Atomic Coordinates and Isotropic Temperature Factors

Atom	x/a_1	y/a_2	z/c	$B, \text{\AA}^2$
Ag	0.8717 (1) ^a	0.2823 (1)	0.2441 ^b	...
C ₁	0.7969 (10)	0.3549 (11)	0.3657 (14)	1.08 (28)
C ₂	0.7306 (11)	0.2589 (11)	0.3624 (12)	1.34 (27)
C ₃	0.6398 (12)	0.2111 (12)	0.2741 (14)	0.87 (29)
O ₁	0.2868 (7)	0.3018 (8)	0.1806 (10)	2.03 (22)
O ₂	0.2928 (7)	0.1792 (7)	0.2521 (12)	1.46 (23)
O ₃	0.3825 (8)	0.2645 (8)	0.0805 (11)	2.56 (24)
N	0.3217 (8)	0.2483 (8)	0.1690 (11)	1.24 (22)

^a Standard deviations are $\times 10^4$ for coordinates and $\times 10^3$ for B 's. ^b The position of the origin along the c axis is arbitrary and was chosen for convenience in computing a suitable unit in the electron-density maps. ^c See Table IV for the anisotropic thermal parameters for silver.

Table III. Distances and Angles for $C_6H_{12}(AgNO_3)_3$

Bonded Distances (Å) and Angles			
C ₁ -C ₂	1.532 ± 0.020	C ₁ -C ₃ -C ₄	107.6 ± 1.1°
C ₁ -C ₄	1.542 ± 0.019	C ₁ -C ₃ -C ₅	126.4 ± 1.2°
C ₁ -C ₅	1.384 ± 0.020	C ₁ -C ₄ -C ₃	122.9 ± 1.4°
Ag ₁ -C ₁	2.379 ± 0.015	Ag ₁ -C ₁ -C ₂	74.5 ± 0.9°
Ag ₁ -C ₂	2.411 ± 0.014	Ag ₁ -C ₂ -C ₁	71.9 ± 0.9°
N-O ₁	1.259 ± 0.015	O ₁ -N-O ₂	117.7 ± 1.1°
N-O ₂	1.259 ± 0.014	O ₁ -N-O ₃	121.9 ± 1.3°
N-O ₃	1.225 ± 0.013	O ₂ -N-O ₃	120.4 ± 1.2°
Midpoint of C ₁ -C ₂ to Ag ₁ 2.300 ± 0.014			
Nonbonded Distances (Å)			
C ₁ -C ₄	2.480 ± 0.020	O ₁ -O ₂	2.155 ± 0.016
C ₁ -C ₅	3.133 ± 0.027	O ₁ -O ₃	2.156 ± 0.015
Ag ₁ -C ₂	3.357 ± 0.016	O ₂ -O ₃	2.172 ± 0.016
Ag ₁ -C ₃	3.281 ± 0.017		
Distances (Å) and Angles in Silver Environment			
Ag ₁ -O ₂	2.438 ± 0.012	Ag ₁ -O ₃	3.190 ± 0.011
Ag ₁ -O ₃	2.927 ± 0.011	Ag ₁ -O ₁₁	3.240 ± 0.011
Ag ₁ -O ₄	2.484 ± 0.010	O ₁ -Ag ₁ -O ₄	97.7 ± 0.4°
Ag ₁ -O ₅	2.771 ± 0.012	O ₁ -Ag ₁ -O ₇	111.5 ± 0.3°
Ag ₁ -O ₇	2.474 ± 0.010	O ₄ -Ag ₁ -O ₇	86.3 ± 0.2°
(Midpoint of C ₁ -C ₂)-Ag ₁ -O ₇ 109.9 ± 0.2°			
(Midpoint of C ₁ -C ₂)-Ag ₁ -O ₃ 108.8 ± 0.2°			
(Midpoint of C ₁ -C ₂)-Ag ₁ -O ₄ 140.1 ± 0.2°			
Distances (Å) in Nitrate Environment			
Ag ₁ -O ₂	2.430 ± 0.012	Ag ₁ -O ₁	2.474 ± 0.010
Ag ₁ -O ₃	2.927 ± 0.011	Ag ₁ -O ₅	3.190 ± 0.011
Ag ₁ -O ₅	3.240 ± 0.011	Ag ₁ -O ₁	2.484 ± 0.009
Ag ₁ -O ₁	4.711 ± 0.010	Ag ₁ -O ₃	2.771 ± 0.012
Dihedral Angles between Planes Each Defined by Three Atoms			
C ₁ -C ₂ -C ₃ and C ₁ -C ₄ -C ₅	73.0 ± 1.7°		
Ag ₁ -C ₁ -C ₂ and C ₁ -C ₃ -C ₄	107.8 ± 1.5°		
Ag ₁ -C ₁ -C ₂ and C ₁ -C ₄ -C ₅	106.4 ± 1.5°		
C ₁ -C ₂ -C ₃ and a, b plane	49.3 ± 0.4°		
O ₁ -O ₂ -O ₃ and a, b plane	42.4 ± 0.8°		
Ag ₁ -Ag ₂ -Ag ₃ and O ₁ -O ₂ -O ₃	8.3 ± 1.0°		

As proposed,¹⁴ the cyclononatriene ring retains the crown configuration on complex formation with silver nitrate. The rings are stacked along the threefold axes

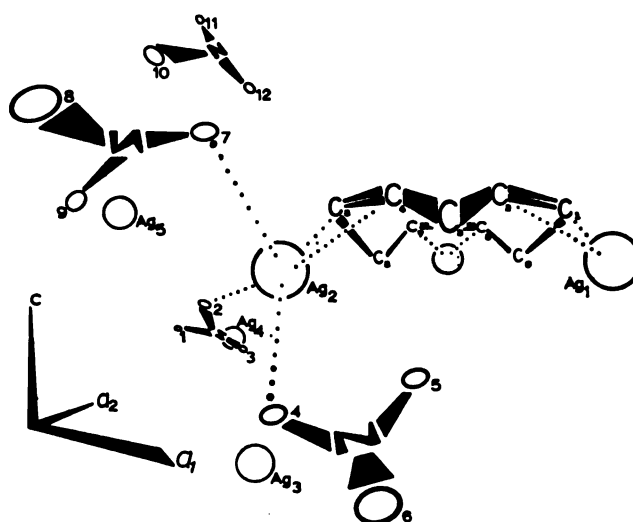


Figure 1. The environment of a silver ion (Ag_1) showing all neighboring oxygen atoms. Ag_1 and Ag_2 are related by a threefold axis; Ag_1 , Ag_4 , and Ag_5 are related by a 3_1 screw axis. A 3_2 screw axis relates the NO_3 groups 4-5-6, 7-8-9, and 10-11-12. Oxygens O_2 , O_3 , O_4 , O_5 , O_7 , O_8 , and O_{12} are within 4.0 Å of the silver ion. Ag_1 - O_2 , Ag_1 - O_4 , Ag_1 - O_7 , and Ag_1 -(midpoint of C₁-C₂) are the shortest distances and are in a roughly tetrahedral configuration (dotted lines).

of the crystal at intervals of $c/2$, each ring being rotated 35.7° from its nearest neighbors above and below. Each silver ion interacts with only one double bond, all other double bonds directionally feasible being greater than 5 Å distant. The closest approach of any two silver ions is 4.5 Å. Several nitrate groups surround the silver ions (Figure 1); five oxygen atoms approach within 3 Å, and three of these are close enough to 2.46, the sum of the atomic radii, to suggest some degree of covalency.⁸ These three oxygens together with the midpoint of the interacting double bond form a roughly tetrahedral arrangement around silver.

The average N-O bond length of 1.25 Å compares well with values determined in other silver nitrate complexes^{9,10} and in $AgNO_3$ itself.²⁰ It is slightly greater than the value of 1.218 ± 0.004 Å reported²¹ for $NaNO_3$. The average O-N-O bond angle is 120° , and the group is planar within experimental error.

The local environment of the nitrate group consists of three silver ions (Ag_2 , Ag_4 , and Ag_5) within 3.25 Å of the nitrogen atom which describe a plane somewhat above and parallel to the NO_3 plane. Ag_3 lies below and at a distance of 4.25 Å from the nitrogen atom. As is indicated by the Ag-O bond lengths in Table III, the silver-oxygen coordination is not simple. It appears as if each silver ion above the NO_3 group interacts with two oxygens and that Ag_3 is coordinated only to O_1 .

Silver anisotropic temperature parameters, U_{ij} 's, are given in Table IV. Also tabulated are the direction cosines (ϕ , ψ , and ω corresponding to the cell edges a_1 , a_2 , and c , respectively) and root-mean-square displacements of the principal axes of the ellipsoid of vibration. The errors in the directions of the principal axes are large. The only general conclusion drawn is that the most extensive thermal vibration is approximately along the c axis but is tilted slightly so that principal axis P

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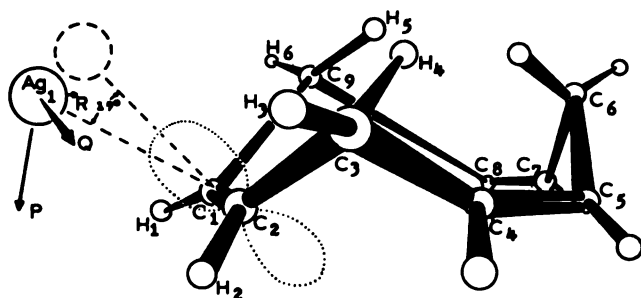


Figure 2. The cyclononatriene ring with assumed hydrogen positions. The silver ion is shown interacting with carbons C_1 and C_2 and distorted 17° from the normal position (dotted lines) along the perpendicular bisector of the ethylene group. P , Q , and R are the principal axes of thermal motion for the silver ion. One π -bonded p orbital is shown in its normal position. The lower lobe is convergent with five other lobes below the ring.

(Figure 2) lies almost parallel to the plane $C_5-C_1-C_3-C_3$. Therefore the silver motion is perpendicular to the direction of the p orbitals and allows the silver to remain approximately equidistant from the double bond throughout the vibration.

Table IV. Anisotropic Thermal Motion Parameters^a

U_{11}	U_{22}	Values of U_{ij} for Silver			
		U_{11}	U_{22}	U_{33}	U_{12}
0.01898 (0.00075)	0.01829 (0.00073)	0.03493 (0.00046)	0.00968 (0.00072)	0.00066 (0.00051)	0.00299 (0.00051)
Direction Cosines and Root-Mean-Square Values of Principal Axes					
Axis	ϕ	ψ	ω	$\sqrt{\mu^2}$ (Å)	
P	-0.84	0.87	0.17	0.1283 (31)	
Q	-0.50	-0.49	0.17	0.1365 (29)	
R	0.24	-0.07	0.97	0.1904 (14)	

^a Anisotropic temperature factors were calculated and refined in the form $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$ and were converted [D. W. J. Cruickshank, *Acta Cryst.*, **19**, 153 (1965)] to U_{ij} 's according to $U_{11} = \beta_{11}/a^{*2}2\pi^2$, etc.

Discussion

The carbon ring geometry is almost identical with that of the uncomplexed *cis,cis,cis*-1,4,7-cyclononatriene.⁶ The only possibly significant change is a stretching of the C_1-C_2 bond from 1.34 to 1.38 Å which would indicate a weakening due to the silver interaction as is also indicated by infrared studies of other silver π complexes.²² The increase in the normal trigonal angles to an average of 124° has the effect of separating the intraannular hydrogen atoms as discussed previously.⁶ It would appear, therefore, that the structure of the cyclic olefin is changed little, if at all, with silver complex formation.

At the request of a referee, an attempt was made to observe the effect of the hydrogen atoms on the ring geometry. The hydrogen positions (Table V) were not apparent in the difference Fourier maps and were therefore estimated using standard criteria. Two cycles of least-squares refinement resulted in a shortening of the C_1-C_2 , C_2-C_3 , and C_3-C_4 bond lengths to 1.372, 1.514, and 1.536 Å, respectively. The angle $C_2-C_3-C_4$ is

(22) H. Hosoya and S. Nagakura, *Bull. Chem. Soc. Japan*, **37**, 249 (1964).

increased to 109.4° , $C_1-C_2-C_3$ to 126.9° , and $C_3-C_4-C_5$ to 123.8° . These values generally show poorer agreement with normal bond lengths and angles than those previously obtained (Table III). Also, with the exception of the angle $C_2-C_3-C_4$, all shifts were within one standard deviation. Therefore the shifts were considered meaningless and Tables II-IV, which are based on the final refinement without the hydrogen atoms, were retained.

Table V. Estimated Hydrogen Coordinates

Atom	x/a_1	y/a_1	z/c
H ₁	0.859	0.383	0.434
H ₂	0.741	0.210	0.427
H ₃	0.625	0.141	0.242
H ₄	0.648	0.254	0.182

The Ag-C distances of 2.379 and 2.411 Å are within error of those obtained for the humulene-silver nitrate adduct,^{10,11} $C_{18}H_{24}(AgNO_3)_2$, and the silver nitrate adduct of norbornadiene,¹² $C_7H_8(AgNO_3)_2$. Corresponding values for the silver nitrate adduct of cyclooctatetraene,⁸ $C_8H_8AgNO_3$, and its dimer,⁹ $C_{16}H_{16}AgNO_3$, are approximately 0.1 Å longer due to the interaction of two or more ethylenic bonds with each silver ion.

The slight difference in the two Ag-C distances has been observed in all the silver π complexes thus far studied in detail. Turner and Amma²³ have explained the discrepancy for silver aromatic complexes in terms of molecular orbital theory. The 5s orbital of silver is expected to accept electrons from the bonding π orbital (e_1) and the filled d orbitals to donate electrons to the antibonding π orbital (e_2). The silver ion seeks a position allowing maximum overlap, which is directly above one of the carbon p lobes for the 5s, but is above and symmetrically between two carbon atoms for the d orbital. It is postulated that the equilibrium is a compromise somewhat off center, hence the difference in bond lengths. The same argument can be applied to Ag-olefin complexes although the observed discrepancy is considerably less than in Ag-aromatic complexes.

Several considerations enter a rationale for the fact that in $C_9H_{12}(AgNO_3)_2$ the plane $Ag-C_1-C_2$ is not perpendicular to the $C_1-C_2-C_3-C_4$ plane but rather forms an angle of 107° with it (Figure 2). This distortion of 17° from the normal silver position which would assure maximum overlap with the π orbital can be explained by (a) steric repulsions between the silver ion and the intraannular hydrogens or carbon atoms C_5 and C_6 ; (b) a twisting of the π -bonded p orbitals themselves so that silver is, in fact, in the optimum position for overlap; or (c) homoconjugation.

That steric effects play an important role in forcing the silver ion away from the ring is unlikely since in the normal position silver is encircled by a nearly symmetrical ring of hydrogen atoms (Table VI). Carbon atoms C_5 and C_6 would be too far away (3.3 Å) and in unfavorable directions to exert much steric influence. Also there is no evidence of twisting of the

(23) R. W. Turner and E. L. Amma, *J. Am. Chem. Soc.*, **88**, 1877 (1966).

Table VI. Estimated Hydrogen to Silver Distances (Å)

Ag-H ₁	2.53	Ag-H ₁ ^a	2.78
Ag-H ₂	2.54	Ag-H ₂	2.78
Ag-H ₃	3.49	Ag-H ₃	3.26
Ag-H ₄	3.49	Ag-H ₄	3.04
Ag-H ₅	3.40	Ag-H ₅	2.94
Ag-H ₆	3.40	Ag-H ₆	3.15

^a Ag_n refers to silver in the normal position estimated at $x/a_1 = 0.850$, $y/a_2 = 0.289$, $z/c = 0.187$.

C₃ and C₉ atoms about the C₁-C₂ bond. The dihedral angle between C₁-C₂-C₃ and C₂-C₁-C₉ is $1.8 \pm 2.3^\circ$.

That the divergent lobes of the p orbitals are twisted outward from their normal positions (assuming sp² hybridization) is consistent with the argument²⁴ that in *cis*-ethylenic systems the π -bonded carbon p orbitals are distorted in order to relieve strain due to bond oppositions. (It is noteworthy that for the *trans* double bond in the humulene-silver nitrate adduct the silver ion is distorted only 5° from the normal position, whereas for the *cis* double bonds in the norbornadiene adduct, the distortion is approximately 24°.)

Finally, a distortion of the p orbitals could be attributed to a rotation of the p orbitals about the C₁-C₂

(24) P. D. Gardner, R. L. Brandon, and N. J. Nix, *Chem. Ind. (London)*, 1363 (1958).

axis affecting a further spreading of the divergent lobes and a congestion of those which are convergent. The driving force for such a distortion would be a stabilization due to increased overlap of the convergent lobes and resulting homoconjugation. It is unlikely that homoconjugation is a very important factor in the bonding of the complex. Homoaromaticity in cyclononatriene itself is expected to be small according to simple LCAO-MO calculations,^{3,4} and it would seem reasonable that the silver ion would tend to withdraw electrons during complex formation, thus further decreasing any existing p-orbital overlap. Also, increases in the trigonal carbon angles and a decrease in the tetrahedral angles of the ring, which would be expected to accompany significant homoconjugation, are small and can be explained by the intraannular hydrogen interactions.

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Proton and Phosphorus-31 Nuclear Magnetic Resonance Studies of Tetraalkoxyphosphonium Hexachloroantimonates and Related Compounds^{1a}

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Contribution from the Department of Isotope Research, Weizmann Institute of Science, Rehovoth, Israel. Received November 15, 1966

Abstract: Tetramethoxyphosphonium hexachloroantimonate (Ia) was obtained in moderate yield from the reaction between trimethyl phosphite and methyl hypochlorite in the presence of antimony pentachloride (reaction ii, X = O). Proton and phosphorus-31 nuclear magnetic resonance (nmr) and infrared and conductivity studies support this formulation. Evidence was also obtained for the formation of the triethoxymethoxy- and triphenoxy-methoxyphosphonium cations. These results confirm that such salts are intermediates in the reaction between phosphite triesters and alkyl hypochlorites. The control reaction (iii) between trimethyl phosphite and antimony pentachloride gave a minor product which was shown to be trimethoxymethylphosphonium hexachloroantimonate (II), the intermediate from intermolecular transmethylation.

Current advances in the understanding of the mechanisms of phosphorus reactions owe much to the detection and characterization of four- and five-covalent intermediates resulting from valency expansion of phosphorus(III) compounds.²⁻¹¹ While stable pentaalkoxy-

phosphoranes² and trialkoxyalkylphosphonium salts^{3,4} have been isolated, the tetraalkoxyphosphonium salts have only been tentatively identified as transient intermediates. Denney and Relles¹² observed their formation using proton nmr in the reactions between trialkyl phosphites and neopentyl hypochlorite (reaction i).

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(7) B. Miller, ref 6, Vol. 2, 1965, p 133.

(8) G. M. Blackburn and J. S. Cohen, ref 6, Vol. 6, in press.

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(2) (a) F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.*, 85, 3252 (1963); (b) F. Ramirez, *Pure Appl. Chem.*, 9, 337 (1966).

(3) K. Dimroth and A. Nurrenbach, *Angew. Chem.*, 70, 26 (1958); *Chem. Ber.*, 93, 1649 (1960).

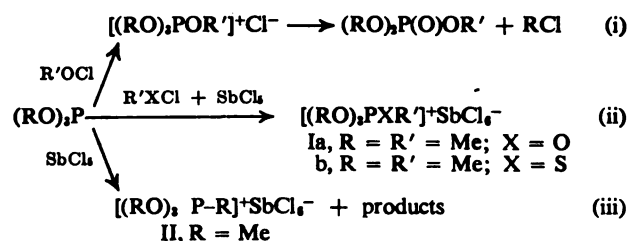
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(5) D. B. Denney and H. M. Relles, *J. Am. Chem. Soc.*, 86, 3897 (1964); 87, 138 (1965); 88, 1839 (1966).

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Antimony pentafluoride and related compounds have been used extensively in the now classical work of Olah and co-workers¹³ for the isolation of salts of relatively unstable carbonium ions. Hilgetag and Teichmann¹⁴ applied this technique to the reaction between trialkyl phosphites and alkyl sulfonyl chlorides (reaction ii, X = S) to give isolable tetraalkoxythiolphosphonium salts (I, X = S). The present work describes a similar application of the technique to the trialkyl phosphite-alkyl hypochlorite reaction (ii, X = O) leading to the first isolation and characterization of a tetraalkoxyphosphonium salt (Ia).

Investigation of the control reaction (iii) between trimethyl phosphite and antimony pentachloride led to the isolation of the minor product trimethoxymethylphosphonium hexachloroantimonate (II),¹⁵ which was shown to be the intermediate for intermolecular transmethylation.



Experimental Section

All phosphites were distilled and stored in a desiccator (sodium drying is not recommended). Antimony pentachloride (90%) was obtained from the Baker and Adamson Co., Morristown, N. J. The methylene dichloride used was analytical grade and was dried over calcium chloride. All melting points are corrected.

Nuclear Magnetic Resonance Spectroscopy. Proton nmr data were obtained using a Varian Associates A-60 spectrometer. Chemical shifts are quoted in τ values relative to tetramethylsilane (τ 10) as external reference.

Phosphorus-31 nmr data were obtained using a Varian Associates 4300B spectrometer operating at 24.3 Mcps with 5- or 15-mm non-spinning sample tubes. Chemical shifts are quoted in δ ppm relative to 85% H_3PO_4 as external reference. Unstable materials were stored and manipulated in nmr tubes at liquid nitrogen temperature.

Trimethoxymethylphosphonium Hexachloroantimonate (Ia). A methylene dichloride solution of methyl hypochlorite was prepared by carefully controlled (to pH 8.0) addition of 1 *N* acetic acid to sodium hypochlorite solution (4–6%, 90 ml) and methanol (2.8 ml).¹⁶ The methyl hypochlorite was extracted with methylene dichloride (five 5-ml portions) until no more yellow coloration was obtained. The extracts were dried (calcium chloride) and filtered into a four-necked flask, fitted with a reflux condenser and a calcium chloride tube, and cooled to -70° in an acetone-Dry Ice bath. Methylene dichloride solutions (15 ml) of trimethyl phosphite (3.5 ml, 1 mole) and antimony pentachloride (3.8 ml, 1 mole) were added dropwise under dry nitrogen with stirring. After the addition was completed (15–30 min), the flask was allowed to warm slowly up to 10° . Ether or petroleum ether (sodium dried) was added, and a white solid precipitated. This was separated by filtration using a sintered glass disk, washed with ether, and dried in a desiccator. Tetramethoxyphosphonium hexachloroantimonate (Ia) was recrystallized three times from methylene dichloride-ether and had mp 139° dec; 5.6 g (38%).

Anal. Calcd for $C_4H_{12}O_4Cl_6PSb$: P, 6.3; Cl, 43.5. Found: P, 6.5; Cl, 43.6.

(13) G. A. Olah, E. B. Baker, J. C. Evans, W. S. Tolgyesi, J. S. McIntyre, and I. J. Bastien, *J. Am. Chem. Soc.*, **86**, 1360 (1964), and others in the series.

(14) G. Hilgetag and H. Teichmann, *Chem. Ber.*, **96**, 1465 (1963).

(15) Cf. D. H. Brown, G. W. Fraser, A. McAuley, and D. W. A. Sharp, *Chem. Ind. (London)*, 2098 (1965).

(16) M. Anbar and I. Dostrovsky, *J. Chem. Soc.*, 1094, 1105 (1954).

The solid slowly decomposed during several weeks in an evacuated desiccator.

Proton Nmr Studies on Ia. (i) The solutions of methyl hypochlorite extracted into methylene dichloride and deuteriochloroform solvents showed only one product peak, τ 6.02, in the proton nmr spectrum.

(ii) The spectrum of the crude product Ia in methylene dichloride solution contained only a doublet centered at τ 5.70 ($J_{PH} = 11.2$ cps). Impurities were less than 5%. To a solution of a recrystallized sample of Ia at -50° a solution of trimethyl phosphite (10%) in methylene dichloride was added dropwise. An exothermic reaction ensued, and the nmr spectrum of the solution now contained ten major peaks including a doublet at τ 8.5 ($J_{PH} = 17$ cps).

(iii) There was no change in the spectrum of a solution of Ia in methylene dichloride after standing at 23° for 24 hr. On heating at 50° for 2 hr, the following doublets were observed: τ 5.80, 5.85, and 7.82 (the latter two in a ratio of 3–3.5:1) with coupling constants J_{PH} of 11.5, 11.5, and 17.2 cps, respectively. Ia was almost insoluble in $CHCl_3$ and $CDCl_3$.

Infrared Studies on Ia. An infrared absorption spectrum was recorded using a Beckman IR-7 spectrophotometer on a 4% methylene dichloride solution of Ia in a 0.5-mm cell. The bands shown in Table I were observed.

Table I

Band, cm^{-1}	Assignment
874 (m)	Sym P—(OC) ₃ stretching
1088 (s)	Asym P—(OC) ₃ stretching
1189 (m)	C—OP stretching
1270 (m)	P=O stretching
1454 (w)	CH ₃ asym bending
2310 (w)	$2 \times 1189\text{ cm}^{-1}$
2990 (s)	CH ₃ sym C—H stretching
3055 (vs)	CH ₃ asym C—H stretching

A spectrum was also recorded using a Perkin-Elmer Infracord spectrophotometer on a KBr disk of Ia. This showed no band corresponding to P=O stretching. All other bands were as given in Table I.

Conductivity Studies. Measurements were taken on a Barnstead PM3A conductivity meter operating at 60 cycles and 23° . The following values were recorded for the specific conductivities of 10^{-4} *M* solutions in methylene dichloride of compounds Ia and II; 1.08×10^{-6} and 1.22×10^{-6} ohm⁻¹ cm⁻¹, respectively. Pure methanol gave a value of 7.4×10^{-7} ohm⁻¹ cm⁻¹, methylene dichloride was nonconducting, and a number of tetraalkylammonium salts gave values in the range $2.0\text{--}2.3 \times 10^{-6}$ ohm⁻¹ cm⁻¹.

Trimethoxymethylphosphonium Hexachloroantimonate (II). (i) Using the same conditions as described above, methylene dichloride solutions of trimethyl phosphite (1.75 ml, 1 mole) and antimony pentachloride (1.9 ml, 1 mole) were dripped into a flask containing methylene dichloride (20 ml). Addition of ether gave a white precipitate of trimethoxymethylphosphonium hexachloroantimonate, 0.8 g (12%), which on recrystallization from methylene dichloride-ether had mp 153° dec.

Anal. Calcd for $C_4H_{12}O_4Cl_6PSb$: Cl, 44.9. Found: Cl, 44.7.

The proton nmr spectrum in methylene dichloride solution showed two doublets centered at τ 5.87 ($J_{PH} = 11.5$ cps) and 7.85 ($J_{PH} = 17.2$).

(ii) 1,1-Dichloroethane (distilled) was used as solvent for a reaction carried out as in part i. The product (3.0 g, 21% yield) was the same as in part i; the ratio of the doublets in the nmr spectrum in methylene dichloride solution was 3:1 (1,1-dichloroethane was not a useful solvent for the product since the low-field doublet was partially covered).

Phosphorus-31 Nmr Studies. (i) Reactions were carried out on a small scale, using proportionately one-quarter of the amounts of the reactants given above, but with smaller volumes of methylene dichloride (2–5 ml). The reaction solutions were quickly transferred from the cooled flask into a 5-mm nmr tube and scanned in the spectrometer. Chemical shifts for the major and consistent peaks are given in Table II. The minor component at -56 ppm in the control reaction (iii) could not always be observed.

(ii) A saturated methylene dichloride solution of Ia was prepared. The mean value for the chemical shift obtained, using a 15-mm

Table II. P^{31} Chemical Shifts (ppm) Relative to 85% H_3PO_4 [$(MeO)_3P^+SbCl_6^-$ in CH_2Cl_2 , -51.5]

Phosphite	+SbCl ₅		+SbCl ₅ + MeOCl		Formulation	Ref
	Chem shifts	Peak areas, %	Chem shifts	Peak areas, %		
$(MeO)_3P$	+1	25	+1	40	$(MeO)_3PO$	
	-8	30	-8	40	$(MeO)_3P(O)Cl$	
	-28	15	-27	7	$(MeO)_3P(O)CH_2Cl$	<i>b</i>
	-36	25	-34	3	$(MeO)_3P(O)Me$	<i>c</i>
	-53	10	$(MeO)_3P^+$	
$(EtO)_3P$	-56 ^d	3	$(MeO)_3P^+Me$	
	+16	5	$[(EtO)_3PO]_2O$	<i>e</i>
	+10	5	+8	5		
	+5	5		
	+1.5	45	+1	35	$(EtO)_3PO$	
$(CH_2O)_3POEt$	-4	30	-3	35	$(EtO)_3P(O)Cl$	<i>c</i>
	-16	5	-14	3		
	-22	5	-23	5	$(EtO)_3P(O)CH_2Cl$	<i>b</i>
	-50	5	$(MeO)_3P^+(OEt)_3$	
	+18	10	+14	25	$[RO]_3PO]_2O$	
$(CH_2O)_3P(O)R$	+4	25	+3	25	Acyclic phosphate	
	-3	30	-3	5	Acyclic $P(O)Cl$	
	-17	15	-18	10	$(CH_2O)_3P(O)OR$	17
	-25	15	-27	25	Acyclic $P(O)CH_2Cl$	<i>b</i>
	-39	5		
	-53	3	$(CH_2O)_3P(O)R$ (R = Me, Et)	<i>f</i>

* Spectra recorded on a Varian 4300B spectrometer at 24.3 Mcps using nonspinning 5-mm sample tubes. Only major and consistent peaks are recorded. Relative peak areas were variable, values are approximate (± 1). ^b This work. ^c K. Moedritzer, L. Maier, and L. C. D. Groeneweghe, *J. Chem. Eng. Data*, 7, 307 (1962). ^d This component not always observed. ^e R. A. Y. Jones and A. R. Katritzky, *Angew. Chem. Intern. Ed. Engl.*, 1, 32 (1962). ^f G. M. Blackburn, personal communication.

nonspinning sample tube, was -51.5 ppm. Attempts to observe the splitting pattern were unsuccessful.

(iii) Trimethyl phosphite was refluxed in methylene dichloride solution. Evolution of gas was observed. After 4 hr the solution was concentrated under vacuum, and the product showed the following chemical shifts: $+3$ (phosphate), -25 , and -32 [$(MeO)_3P(O)Me$] ppm in a ratio of 8:10:1 (also some residual phosphite, -140 ppm).

Triethoxymethoxyphosphonium Hexachloroantimonate. Methylene dichloride solutions of triethyl phosphite (5.0 ml, 1 mole) and antimony pentachloride (3.8 ml, 1 mole) were added dropwise to a solution of methyl hypochlorite. After completion of the reaction, petroleum ether (bp $30-40^\circ$) was added, and a yellow oil separated, which could not be crystallized. Some of this was pipetted into a cooled proton nmr tube and diluted with methylene dichloride. The spectrum obtained (see Figure 1) showed the following characteristics (apart from solvent peaks): multiplet centered at τ 5.32, 5.75 doublet ($J_{PH} = 11.5$ cps), and 8.37 distorted triplet ($J_{HH} = 7$ cps). An estimate of the areas under the multiplet and doublet (by weighing peaks) gave a ratio of 4:1, respectively. Heating the sample to 50 and then to 80° produced no systematic diminution in the splitting pattern of the multiplet.

Triphenyl Phosphite-Methyl Hypochlorite Reaction. Triphenyl phosphite (7.7 ml, 1 mole) and antimony pentachloride (3.8 ml, 1 mole) solutions were added dropwise to a solution of methyl hypochlorite in methylene dichloride. An unstable red precipitate was formed. A sample of the solution was quickly transferred to a cooled nmr tube. The spectrum showed a doublet centered at τ 5.38 ($J_{PH} = 12.2$ cps); an approximate ratio relative to the total broad phenyl proton multiplet was 1:10.

Addition of ether to half of the reaction mixture while still cold produced a copious brown precipitate (6 g, mp 137° dec after recrystallization of methylene dichloride-ether). The proton nmr spectrum showed a triplet at τ 8.16 ($J_{HH} = 7$ cps), a singlet at 5.46 (ratio 1:1.8, respectively), and a quartet at 4.98 (7 cps.). Addition of ether resulted in the reprecipitation of the solid. On redissolving in methylene dichloride the nmr spectrum now showed two sets of triplets (τ 8.80, 8.20) and quartets (6.47, 5.00), as well as the singlet (4.50).

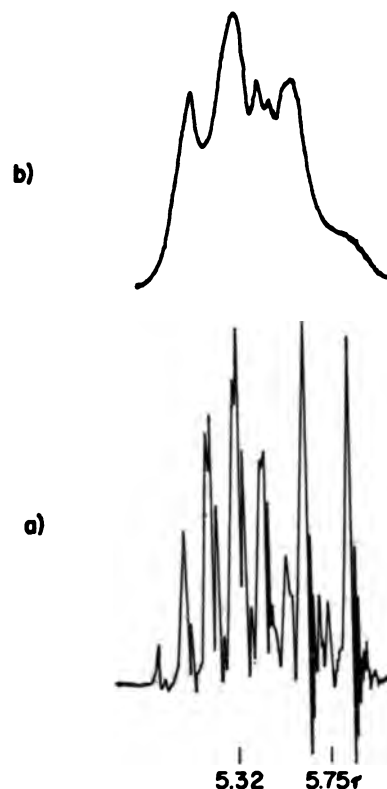


Figure 1. Section of proton nmr spectrum of triethoxymethoxyphosphonium hexachloroantimonate showing (a) multiplet of ethyl methylene protons and doublet of methoxy protons and (b) central peak of multiplet at higher resolution.

Ethyl Ethylene Phosphite Reactions. Ethyl ethylene phosphite was prepared by transesterification between triethyl phosphite and ethylene glycol.¹⁷ A reaction was carried out as described for Ia using this phosphite but gave no useful result.

Phosphorus-31 nmr studies were carried out as described above, and the results are detailed in Table II.

Perkow Reaction with Antimony Pentachloride. Trimethyl phosphite (3.6 ml, 1 mole) and antimony pentachloride (3.8 ml, 1 mole) were added simultaneously to a solution of α -chloroacetone (2.4 ml, 1 mole) in dichloromethane (15 ml). Addition of ether or petroleum ether to the reaction solution gave a yellow oil, the nmr spectra of which gave no consistent result.

The control reaction between α -chloroacetone and antimony pentachloride in methylene dichloride solution gave a precipitate while still cold, which was filtered onto a sintered-glass disk. The proton nmr spectrum in methylene dichloride solution showed two singlets at τ 6.97 and 5.34 (ratio 3:2). On addition of aliquots of a solution of α -chloroacetone in methylene dichloride, these peaks were observed to shift upfield in a stepwise manner. The solid was very unstable.

Results and Discussion

(a) Trimethyl Phosphite Reactions. The simultaneous addition of trimethyl phosphite and antimony pentachloride to a solution of methyl hypochlorite¹⁸ in methylene dichloride at -70° resulted in the formation of tetramethoxyphosphonium hexachloroantimonate (Ia) (38% yield). The proton nmr spectrum of this compound in methylene dichloride solution consisted of a doublet centered at τ 5.70 ($J_{PH} = 11.2$ cps). The value quoted by Denney and Relles¹² for the chemical shift of the α protons of tetraacetoxyphosphonium chloride, with half-life at room temperature of 3 min, was τ 5.69. By comparison with trimethyl phosphite (τ 7.0), trimethyl phosphate (τ 6.5), and penta-

(17) G. M. Blackburn, J. S. Cohen, and A. R. Todd, *Tetrahedron Letters*, 2873 (1964).

methoxyphosphorus⁸ (τ 6.3) such a value for the tetramethoxyphosphonium cation is consistent with less electron shielding at the α -hydrogen atoms. The product was shown not to be a molecular complex between trimethyl phosphite and antimony pentachloride since addition of a methylene dichloride solution of trimethyl phosphate resulted in an exothermic reaction.

Comparative phosphorus-31 nmr studies were carried out on a number of reaction mixtures. Results (Table I) when trimethyl phosphite was treated with antimony pentachloride and methyl hypochlorite (reaction ii, X = O) or with antimony pentachloride alone (reaction iii) indicated the formation in the former case of an additional product with a chemical shift (relative to 85% phosphoric acid) of about -50 ppm. That this peak corresponded to the tetramethoxyphosphonium cation was confirmed by the fact that pure Ia had a mean P³¹ chemical shift of -51.5 (\pm 1) ppm in methylene dichloride solution. This value confirms the recent qualitative prediction of Ramirez and Desai^{2a} that a tetraalkoxyphosphonium cation would have a chemical shift of the order of -60 ppm, with shielding at phosphorus intermediate between that of phosphites and phosphates.

The formation of a minor component with a chemical shift of -56 ppm in the control reaction of trimethyl phosphite with antimony pentachloride was investigated. Addition of ether to the reaction mixture resulted in the precipitation of a small amount of material. The proton nmr spectrum contained two doublets at τ 5.87 (J_{PH} = 11.5 cps) and 7.85 (J_{PH} = 17.2 cps) in a ratio of 3:1. The latter doublet corresponds reasonably well in chemical shift and coupling constant to those recorded for tetraalkylphosphonium salts.^{18,19} Together with the chlorine analysis, this evidence indicated a formulation [(MeO)₄P⁺Me]SbCl₆⁻ (II) for the product (12% yield). While this work was in progress, the isolation of the corresponding hexafluoroantimonate was reported by Brown, *et al.*,¹⁵ from the reaction between trimethyl phosphite and antimony pentafluoride. A chemical shift of -56 ppm has been assigned to a transient trialkoxyalkylphosphonium salt.^{2b}

The trimethoxymethylphosphonium ion is the intermediate for the Arbuzov-Michaelis reaction⁶



Previous preparations of trialkoxyalkylphosphonium salts (as opposed to triphenoxyalkylphosphonium derivatives²⁰) have been carried out by alkylation of phosphites with oxonium or carbonium salts.^{3,4}

A reaction carried out in 1,1-dichloroethane solution gave the same product II in roughly the same yield, confirming that II was not in fact an Arbuzov-Michaelis intermediate derived by reaction with the solvent. This minor component is presumably an intermediate in the formation of dimethyl methylphosphonate as one of the major products of the reaction. The intermolecular reaction would account for the moderate yields of the desired tetraalkoxyphosphonium salt Ia obtained in reaction ii (*cf.* ref 14). As expected, the

peak of dimethyl methylphosphonate shows a marked relative decrease when comparing reaction ii with iii (see Table II).

Although interaction with the solvent might have been anticipated, the absence of a peak in the phosphorus-31 nmr spectrum at -18.5 ppm, the value assigned for (MeO)₃P(O)CH₂Cl,²¹ appeared to show otherwise. A methylene dichloride solution of trimethyl phosphite was refluxed and then showed two major peaks at +3 (trimethyl phosphate) and -25 ppm. The latter value could only correspond to (MeO)₃P(O)CH₂Cl and is the same as the only hitherto unassigned value^{1a} obtained for the reactions between trimethyl phosphite and antimony pentachloride.

The proton nmr spectrum of Ia was unchanged after standing in methylene dichloride solution for 24 hr. On heating at 50° for 2 hr doublets at the following τ values were observed: 5.80, 5.85, and 7.82, with coupling constants J_{PH} = 11.5, 11.5, and 17.2, respectively. The latter two doublets were found to be consistently in a ratio of 3:1. It appears that the product is the same as that (II) obtained from the reaction (iii) between trimethyl phosphite and antimony pentachloride. The anticipated formation of dimethyl methylphosphonate is ruled out by the ratio of areas of the POCH₃ and PCH₃ doublets.

The infrared spectrum of Ia in solution in methylene dichloride (4%) showed some absorption at 1270 cm⁻¹, due to P=O stretching. However, the spectrum obtained on a potassium bromide pellet of Ia had no such absorption. The infrared spectrum quoted by Hilgetag and Teichmann¹⁴ for compound Ib shows a band at 583 cm⁻¹ corresponding to P-SC stretching but the apparent absence of strong absorption for P-OC stretching (at about 1000 cm⁻¹) is surprising.

That the symmetrical P-(OCH₃)₄ stretching of Ia absorbs as low as 874 cm⁻¹, compared with about 970 cm⁻¹ for triethyl phosphate,²² is analogous to the situation in trimethyl phosphate which shows this band at 850 cm⁻¹.²³ The corresponding antisymmetrical P-(OCH₃)₄ bands for Ia and trimethyl phosphate are at 1088 and 1042 cm⁻¹, respectively. The C-OP stretching band at 1189 cm⁻¹ is also analogous to that of trimethyl phosphate at 1171 cm⁻¹.

It is interesting to note that both for compound Ia and trimethyl phosphate only the antisymmetrical CH₃ bending gives rise to appreciable bands (at 1454 and 1447 cm⁻¹, respectively), while the symmetrical CH₃ bending (which usually shows a significant band at 1380 cm⁻¹) seems to be practically inactive. This may possibly result from the high symmetry in these cases.

The very high C-H stretching frequencies of Ia (2990 and 3055 cm⁻¹) are not, however, shared by trimethyl phosphate, which absorbs almost normally (at 2833 and 2933 cm⁻¹). The increase in the stretching frequency of the hydrogen atoms is unusual and might be connected with some kind of interaction between these atoms and the anionic chlorine atoms, which increases the energy needed for this stretching.

Conductivity measurements confirmed that Ia and II were salts.

(18) J. B. Hendrickson, M. L. Maddox, J. J. Sims, and H. D. Kaesz, *Tetrahedron*, **40**, 449 (1964).

(19) See also C. E. Griffin and M. Gordon, *J. Organometal. Chem.*, **3**, 414 (1965).

(20) R. F. Hudson and P. A. Chopard, *Helv. Chim. Acta*, **45**, 1137 (1962); **48**, 1983 (1965).

(21) See footnote c, Table II.

(22) E. D. Gergman, U. Z. Littauer, and S. Pinchas, *J. Chem. Soc.*, 847 (1952).

(23) Documentation of Molecular Spectroscopy Catalogue, Compound Card No. 5176.

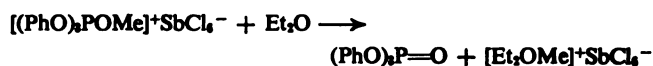
(b) **Reactions with Other Phosphites.** Evidence for the formation of a new P-O bond was obtained when methyl hypochlorite was treated with triethyl phosphite and antimony pentachloride (reaction ii, X = O, R = Et, R' = Me). Although no solid could be isolated in this case, addition of petroleum ether to the reaction mixture in methylene dichloride resulted in the separation of an oil. The proton nmr spectrum of this showed a doublet (Figure 1) with characteristic splitting ($J_{PH} = 11.5$ cps) for the P-OCH₃ group, and with a chemical shift (τ 5.75) expected for the presence of a positive charge at phosphorus. An additional peak was also observed at -50 ppm in the phosphorus-31 nmr spectrum compared to the control reaction iii (Table I).

For the presumed product [(EtO)₃P⁺OMe]SbCl₆⁻ it was not possible to accurately integrate the area of the doublet relative to that of the multiplet of the ethyl methylene protons (Figure 1) partly due to the fine splitting. However, an estimate of the ratio was obtained and was smaller than that required for the pure compound. Such a value would tend to indicate that no transesterification had occurred to produce, say, diethyl methyl phosphite.

The multiplet of the ethyl methylene group (Figure 1) and the distorted triplet of the ethyl methyl protons were both noted to contain a large degree of fine splitting. Some splitting in the latter case must result from the γ -phosphorus atom. Fine splitting has also previously been described for the methylene proton multiplet of triethyl phosphite and phosphate.²⁴ The splitting in these cases has now been found to persist in methylene dichloride solution. The observation of doubled resonances in a series of phosphate and other esters, in which the ester groupings were bulky, has been interpreted in terms of rotational isomerism.²⁵ It is possible to assign peaks in the multiplet (Figure 1) in such a way as to distinguish at least four quartets, with separations of 2 and 6 cps, as well as the splitting due to phosphorus of 8.5 cps. However, the splittings were not found to decrease on heating the sample up to 80°.

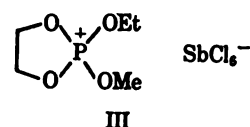
On treating methyl hypochlorite with triphenyl phosphite and antimony pentachloride (reaction ii, X = O, R = Ph, R' = Me), a doublet was again observed in the proton nmr spectrum of the reaction solution. This corresponded in splitting ($J_{PH} = 12.2$ cps) and chemical shift (τ 5.38) to the values expected for the presence of the ⁺P-OCH₃ group. However, it was not found possible to isolate the unstable red solid formed. Addition of ether to the reaction mixture while still cold

resulted in the formation of a stable precipitate with an nmr spectrum corresponding to the oxonium salt [Et₂O⁺Me]SbCl₆⁻.²⁶



Addition of ether to the solution of this product resulted in the presence of two sets of triplets and quartets in the spectrum. This clearly indicated that the solid was not the well-known complex Et₂O·SbCl₅,²⁷ which was often formed as a side product in these reactions.

A number of reactions were repeatedly attempted using a variety of other reagents, e.g., *t*-butyl hypochlorite, but without success. The reaction of ethyl ethylene phosphite with methyl hypochlorite and antimony pentachloride and the control reaction without hypochlorite were scanned for their P³¹ nmr spectra (Table II). A peak at low field (-53) was attributed to ethylene methylphosphonate.²⁸ The value for the intermediate cyclic tetraalkoxyphosphonium cation III would have been of interest for comparative purposes since it is a close analog of cyclic phosphate, but without d π -p π bonding.¹⁷ That complete ring opening had not occurred was evidenced by the presence of a major peak (-18 ppm) corresponding to the cyclic phosphate, which must be formed *via* III.



A number of unsuccessful attempts were also made to trap the phosphonium intermediate in the Perkow reaction between α -chloroacetone and trimethyl phosphite using antimony pentachloride.

It is concluded that while this work represents the first isolation of a stable tetraalkoxyphosphonium salt and confirms that these compounds are intermediates in the trialkyl phosphite-alkyl hypochlorite reaction (i), the use of antimony pentachloride does not appear to provide a general technique for the scavenging of such intermediates.

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(26) G. Hilgetag and H. Teichmann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 914 (1965).

(27) M. Webster, *Chem. Rev.*, **66**, 87 (1966).

(28) See footnote f, Table II.

(24) W. E. Shuler and R. C. Axtman, Atomic Energy Commission Research and Development Report No. DP 474, 1960; see also J. R. Ferraro and D. F. Peppard, *J. Phys. Chem.*, **67**, 2689 (1963).

(25) T. H. Siddall and C. A. Prohaska, *J. Am. Chem. Soc.*, **84**, 2502 (1962).

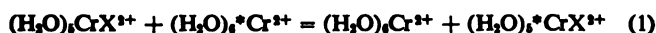
Kinetics and Mechanism of the Inner-Sphere Electron-Exchange Reaction of Hypophosphitochromium(III) and Chromium(II) Ions in Acidic Solution^{1a}

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Contribution from the Institute for Atomic Research and the Department of Chemistry, Iowa State University, Ames, Iowa 50010. Received November 12, 1966

Abstract: The kinetics of electron exchange between $\text{Cr}(\text{OH})_2(\text{H}_2\text{PO}_2)^{2+}$ and Cr^{2+} has been studied in aqueous acid solution. Over the range of acid concentration studied, 0.03–1.0 M, the rate equation has the form $k[\text{CrH}_2\text{PO}_2^{2+}][\text{Cr}^{2+}]/[\text{H}^+]$, with $k = 6.11 \times 10^{-4} \text{ sec}^{-1}$ at 25.0° and unit ionic strength. Values of the activation parameters associated with this rate constant are $\Delta H^\ddagger = 19.7 \pm 1.0 \text{ kcal mole}^{-1}$, and $\Delta S^\ddagger = -7.2 \pm 3.3 \text{ eu}$. Ion-exchange equilibration experiments were used to confirm the net charge on the complex as +2. The reaction mechanism involves a hypophosphite bridged transition state. The probable structure of the transition state, suggested by the inverse dependence of exchange rate upon $[\text{H}^+]$, involves double bridging by hypophosphite and hydroxide ions. Alternative formulations are also presented.

In an acidic solution electron exchange occurs between chromium(II) and a monosubstituted chromium(III) complex $(\text{H}_2\text{O})_5\text{CrX}^{2+}$ (eq 1). This process establishes Cr(II)–Cr(III) isotopic equilibrium, although net chem-



ical change does not occur (at least until much longer times have elapsed). Each reaction transfers X^- from Cr(III) to Cr(II) during electron exchange and the mechanism is most simply formulated as involving a transition state in which ligand X has penetrated the inner coordination sphere of both metal ions.²

The rates and mechanisms of a number of such inner-sphere Cr(II)–Cr(III) exchange reactions have been studied, including Cr(III) complexes containing fluoride,³ chloride,⁴ bromide,⁴ thiocyanate,⁴ and azide^{4,5} ions. Cr(II)–Cr(III) electron exchange has been studied also in the case of two tripositive Cr(III) species, $(\text{H}_2\text{O})_5\text{Cr}^{3+}$ ⁶ and $(\text{H}_2\text{O})_5\text{CrNH}_3^{3+}$.⁷ These reactions likewise have been interpreted⁷ in terms of an inner-sphere mechanism involving the ligand OH^- , although here only indirect evidence is available. The exchange rate law obeyed by each of these reactions takes the

form $k[(\text{H}_2\text{O})_5\text{CrX}^{n+2}][(\text{H}_2\text{O})_5\text{Cr}^{n+3}]/[\text{H}^+]^n$, with $n = 0$ and 1. The transition states for electron exchange have a 4+ ionic charge in each case.

We report here on a study of electron exchange between chromium(II) and monohypophosphitochromium(III) ions. In earlier work,¹⁰ we reported the preparation and characterization of the complex $(\text{H}_2\text{O})_5\text{CrH}_2\text{PO}_2^{2+}$ and studied the kinetics and thermodynamics of its formation and decomposition (eq 2).



This study of electron-exchange rates was undertaken with the expectation that the exchange-rate law and mechanism would parallel the previous studies on related complexes. In addition, since phosphorus oxyanions had not been studied previously as bridging groups for Cr(II)–Cr(III) electron transfer, the hypophosphite complex appeared interesting in this respect. The role of phosphorus oxyacids in biological oxidation–reduction reactions added interest to this subject. Although we confirmed that Cr(II)–Cr(III) exchange occurs with transfer of the ligand and without observable net reaction, it soon becomes apparent to us that the reaction mechanism differed appreciably from earlier exchange systems. The observed dependence of exchange rate on $[\text{H}^+]^{-1}$, corresponding to a transition state of 3+ charge, constitutes a novel situation for exchange, and one that provides some information on the structure of the transition state that can be interpreted in terms of an isomeric $\text{HP}(\text{O})(\text{OH})^-$ ligand, or in terms of a double-bridged electron-transfer mechanism.

Experimental Section

Reagents. Solutions of the monohypophosphitochromium(III) complex were prepared from chromium(III) perchlorate and hypophosphorous acid as described previously.¹⁰ The complex was isolated from the starting materials and from other chromium species by ion exchange. The resin column was first rinsed with 0.3 F perchloric acid to remove the free acid and any complexes of charge lower than 2+. The complex of interest was eluted with 1 F lithium perchlorate or perchloric acid. The visible and ultraviolet spectra of the complex have been reported earlier,¹⁰ and spectra of all samples obtained here were in quantitative agreement with the published values. Solutions of the separated complex generally

(1) (a) This work was performed in the Ames Laboratory of the U. S. Atomic Energy Commission. Contribution No. 1992. (b) Visiting summer faculty research participant; Department of Chemistry, State University College, Brockport, N. Y.

(2) (a) H. Taube, *Advan. Inorg. Chem. Radiochem.*, **1**, 1 (1959); (b) J. Halpern and L. E. Orgel, *Discussions Faraday Soc.*, **29**, 7 (1960); (c) N. Sutin, *Ann. Rev. Nucl. Sci.*, **12**, 285 (1962).

(3) Y. T. Chia and E. L. King, *Discussions Faraday Soc.*, **29**, 109 (1960).

(4) D. L. Ball and E. L. King, *J. Am. Chem. Soc.*, **80**, 1091 (1958).

(5) E. L. King and R. Snellgrove, *Inorg. Chem.*, **3**, 288 (1964).

(6) M. Anderson and N. A. Bonner, *J. Am. Chem. Soc.*, **76**, 3826 (1954).

(7) J. H. Espenson and D. W. Carlyle, *Inorg. Chem.*, **5**, 586 (1966). The reaction of $\text{Cr}(\text{OH})_2\text{NH}_3^{2+}$ and $\text{Cr}(\text{OH})_2^{3+}$ is not strictly an exchange reaction, since NH_3 is released as an accompanying feature of the electron transfer. It is closely related to the other reactions, however, in which all but one of the ligands originally on Cr(III) are labilized upon its reduction to Cr(II). In the other instances these ligands are H_2O , however, and this change is not reflected in observable net chemical reaction. Recent experiments^{8,9} have shown that halide complexes of chromium(III) undergo a chromium(II)-catalyzed aquation with a rate equation of the form $k[\text{Cr}^{2+}][(\text{H}_2\text{O})_5\text{CrX}^{3+}]/[\text{H}^+]$. This path presumably is a hydroxo-bridged process that releases the nonbridging X^- and is quite analogous to the reaction of $(\text{H}_2\text{O})_5\text{CrNH}_3^{3+}$.

(8) D. E. Pennington and A. Haim, *J. Am. Chem. Soc.*, **88**, 3450 (1966).

(9) A. Adin and A. G. Sykes, *J. Chem. Soc., Sect. A*, 518 (1966).

(10) J. H. Espenson and D. E. Binau, *Inorg. Chem.*, **5**, 1365 (1966).

tored 12–24 hr at -78° , which apparently preserved the composition since the spectrum remained unaltered.

In all experiments chromium(II) was labeled with chromium-51 tracer, obtained as a solution of chromium(III) chloride in 0.5 M hydrochloric acid. Labeled chromium(III) perchlorate stock solutions were prepared from ca. 0.1 F chromium(III) perchlorate solution to which had been added ca. 0.5 mcurie of ^{51}Cr per 100 ml of solution. Chromium(III) was reduced electrolytically at a mercury electrode under purified nitrogen. The concentration of chloride introduced from the tracer solution by this technique was relatively low (ca. 0.005 M).

Lithium perchlorate, used to adjust ionic strength, was prepared from lithium carbonate and perchloric acid and recrystallized three times.

Reagent grade perchloric acid was used without purification. Conductivity water, a double redistillation of laboratory distilled water from alkaline permanganate in a Barnstead still, was used in all solutions.

A Rex 50 W-X8 (50–100 mesh, Baker reagent grade) cation-exchange resin was washed with 4 F hydrochloric acid until free of iron(II) (negative test with thiocyanate) and then allowed to stand overnight in the presence of excess sodium hydroxide and hydrogen peroxide. The resin was reconverted to the hydrogen ion form by repeated washing with 4 F hydrochloric acid. A finer particle size (200–400 mesh) was employed in the experiments used to determine the net charge on the chromium complex.

Large Kinetics. The procedures employed in the kinetic studies and separations are as follows. All reagents except chromium(II) were added to a 150-ml milk dilution bottle equipped with a sealing rubber cap which served as the reaction vessel. The solution was flushed with oxygen-free nitrogen for at least 30 min; chromium(II) was introduced by syringe. Samples were withdrawn by syringe at appropriate intervals and quenched in a stream of nitrogen which oxidized chromium(II) to $\text{Cr}_2(\text{OH})_2^{4+}$, a dimeric form of chromium(III).¹¹ (Sample volumes generally were 1–3 ml but were not measured or controlled accurately since the specific activity was the quantity being measured.)

Ion-exchange separation of $\text{CrH}_2\text{PO}_3^{2+}$ from $\text{Cr}_2(\text{OH})_2^{4+}$. In 16 experiments only Cr^{2+} activity was followed, and in 10 experiments only $\text{CrH}_2\text{PO}_3^{2+}$. In an additional five experiments both activities were followed. Thus a total of 30 rate constants were measured. The air-quenched sample was transferred to a 2 mm \times 8 cm column of resin in the hydrogen ion form, contained in a short length of Tygon tubing, and eluted with 2 F perchloric acid. The first 7–8 ml of solution contained most of the phosphite complex, the specific activity of which was determined by counting a standard volume of the sample in a well-scintillation counter and spectrophotometrically analyzing chromium as chromate ion in alkaline solution after oxidation with hydrogen peroxide. In experiments where the chromium(II) activity was followed with time, the column was first rinsed with 5 ml of 2 F perchloric acid to remove all chromium species but $\text{H}_2\text{PO}_3^{2+}$, which then was removed from the resin by treatment with sodium hydroxide and hydrogen peroxide. The specific activity of chromium in the resulting solution was determined as follows.

Chromium(II) in each reaction solution was analyzed directly by spectrophotometric determination of the cobalt(II) produced by reaction with a small excess of pentaamminechlorocobalt(III) ion.¹² In two to four samples were withdrawn for analysis during the course of a run.

Results

Net Ionic Charge. The unexpected results found for the effect of hydrogen ion on the electron-exchange rate (see below) led us to reconsider the composition of the phosphite complex, previously formulated as PO_3^{2+} . Earlier work¹⁰ had established a 1:1 ratio of phosphorus and chromium in the complex, and the qualitative behavior of this species on separation from cation-exchange resin indicated the species had a net charge 2+ in 1 F solutions of either perchloric acid or lithium perchlorate.

M. Ardon and R. A. Plane, *J. Am. Chem. Soc.*, **81**, 3197 (1959). This reduction technique for chromium(II) analysis was employed by B. Zabin and H. Taube, *Inorg. Chem.*, **3**, 968 (1964). The spectrophotometric analysis of cobalt(II) has been described previously: J. Espenson, *ibid.*, **4**, 1025 (1965).

Ion-exchange equilibration experiments of the type developed by Cady and Connick¹³ were carried out to determine unambiguously the ionic charge on the hypophosphite complex. A low concentration of the species of interest was equilibrated with cation-exchange resin at two known hydrogen ion concentrations, 1 and 0.5 M. The presumed constancy of the equilibrium quotient for reaction 3 (overline = resin phase) on changing from 1 to 0.5 M H^+ allows computation of b from equilibrations with the same resin at two $[\text{H}^+]$



values. Precision of the method is limited by variation of the charge b from integral values, which may be caused by a change in the value of the equilibrium quotient for reaction 3 in 1 F compared to 0.5 F perchloric acid solution. A changing degree of protonation of the complex over this range of $[\text{H}^+]$ also would give nonintegral values. Hexaquo-chromium(III) was carried through some experiments as a check on the procedure. The results for this ion and for hypophosphitochromium(III) are presented in Table I. The

Table I. Net Ionic Charge on Chromium(III) Species

Total Cr(III), mmole ^{a,b}	$[\text{H}^+]$, M	Vol., ml	$[\text{Cr(III)}]$, $M \times 10^3$	Charge
A. Hexaquo-chromium(III) Ion				
0.432	0.980	120	0.935	2.94
0.413	0.490	200	0.1528	
0.432	1.012	60	1.271	2.95
0.419	0.506	100	0.1920	
B. Hypophosphitochromium(III) Ion				
0.437	1.017	120	2.43	2.08
0.388	0.508	200	0.868	
0.437	1.017	120	2.42	2.08
0.389	0.508	200	0.862	
0.437	1.050	60	4.054	2.14
0.396	0.525	100	1.300	
0.437	1.050	60	4.046	2.15
0.397	0.525	100	1.294	

^a The difference in the amount of total chromium between the first and second parts of an experiment reflects the amount removed for analysis of the first concentration. This removal of solution also accounts for the relation of $[\text{H}^+]$ and volume. ^b In the various experiments, between 3.45 and 3.57 g of resin, with a capacity of 3.55 mmole of H^+ per gram, was used.

charge value found (2.94) for hexaquo-chromium(III) is close to the value found by Cady and Connick (2.89).¹³ The value (average 2.11) determined for hypophosphitochromium(III) is slightly larger than the integral +2 value presumed for $\text{CrH}_2\text{PO}_3^{2+}$. Although the value is not an integer, this does not seem to constitute compelling evidence that the true charge on the hypophosphite complex is not +2. Since the kinetic evidence presented later indicates that almost certainly only a single species predominates over the range 0.026–1 M H^+ , the conclusion seems justified that this species is the dipositive ion $\text{CrH}_2\text{PO}_3^{2+}$, as in the original formulation.¹⁰

Exchange Rate Law. Where chromium(II) specific activity was followed with time, the McKay equation

(13) H. H. Cady and R. E. Connick, *J. Am. Chem. Soc.*, **80**, 2646 (1958).

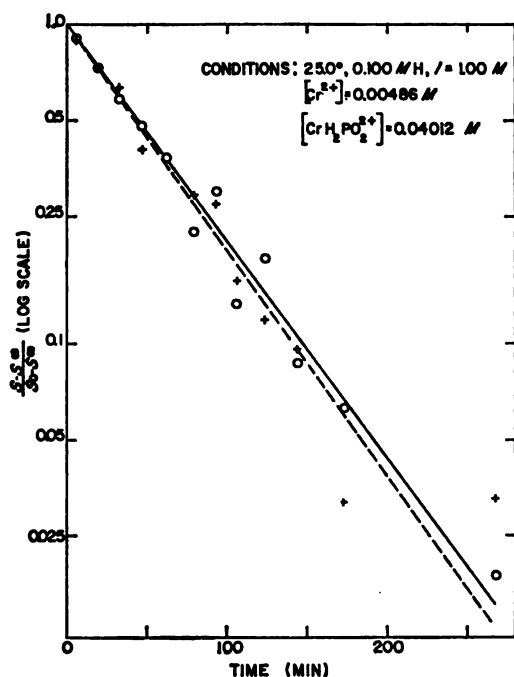


Figure 1. Illustrating McKay plots (eq 4) in a typical exchange experiment with the concentrations shown. The points represent Cr^{3+} sampling (+) and $\text{CrH}_2\text{PO}_3^{2+}$ sampling (O). The straight lines have slopes given by the computer calculated rate constants and correspond to half-times of 42.5 (+) and 44.3 min (O). The rate constants are $10^3 k_2 = 5.80 \pm 0.59 \text{ M}^{-1} \text{ sec}^{-1}$ (+) and $6.04 \pm 0.60 \text{ M}^{-1} \text{ sec}^{-1}$ (O), where the uncertainties represent the standard deviation of k_2 .

tion¹⁴ takes the form given in eq 4 in which S stands

$$d \ln \frac{S_t - S_\infty}{S_0 - S_\infty} = -R \frac{[\text{Cr}^{2+}] + [\text{CrH}_2\text{PO}_3^{2+}]}{[\text{Cr}^{2+}][\text{CrH}_2\text{PO}_3^{2+}]} dt \quad (4)$$

for specific activity of chromium(II), counts per minute per millimole, and R represents the rate law for exchange. An analogous equation with $S_0 = 0$ holds for runs where the activity of $\text{CrH}_2\text{PO}_3^{2+}$ was measured. As a working hypothesis we assumed that, at constant $[\text{H}^+]$, the rate of electron exchange is first order in each chromium species according to

$$R = k_2 [\text{Cr}^{2+}][\text{CrH}_2\text{PO}_3^{2+}] \quad (5)$$

A nonlinear, least-squares computer program¹⁵ was used to fit the exchange data in each run to eq 4 and 5. This program calculated R or k_2 , and also the "best" values of S_0 and S_∞ . This fit for S_∞ is preferable to the experimental value, since secondary reactions set in at long times.^{16,17} Data from a typical run in which

(14) H. A. C. McKay, *Nature*, 142, 997 (1938).

(15) This program is based on a report from Los Alamos Scientific Laboratory, LA2367 + Addenda. We are grateful to Drs. T. W. Newton and R. H. Moore for supplying us with the computer programs and to Mr. J. P. Birk for adapting them to the IBM 360 computing facilities.

(16) Spontaneous aquation of the metastable hypophosphite complex must be considered. This reaction becomes an important factor in exchange runs only at high $[\text{H}^+]$, however, since its rate varies as $[\text{H}^+]$, whereas the exchange rate varies as $[\text{H}^+]^{-1}$. Any interference from appreciable spontaneous aquation during an exchange run would result in a higher value of the calculated exchange rate constant. Of course, aquation, after exchange is substantially complete, has no effect. The Cr^{2+} that is the product of aquation would be collected with neither of the separated exchanging species. In one experiment with relatively low $[\text{Cr}^{2+}]$, $1.8 \times 10^{-3} \text{ M}$, and 0.95 M H^+ , the rates of aquation and exchange were comparable, and in another run exchange was only twice as fast as aquation. In all other experiments the effect of aquation was smaller, generally a good deal smaller.

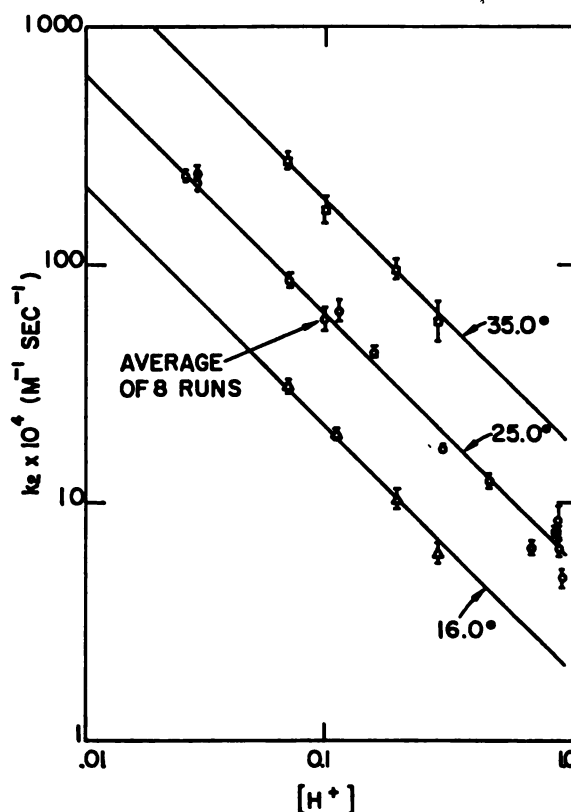


Figure 2. Illustrating the relation of k_2 and $[\text{H}^+]$ in a log-log plot. The lines drawn through the points have a slope of -1 .

both chromium(II) and the hypophosphitochromium(III) complex were followed are shown in Figure 1. For the run shown here, the two sampling techniques gave rate constants that agreed to within an average deviation of 2%. In the four other such pairs of determinations, average deviations were 0.1, 0.3, 4.3, and 12%, and no systematic bias of the direction of the deviation and the oxidation state sampled was noted.

Exchange experiments at 25.0° covered these concentrations: Cr^{2+} , $0.18\text{--}2.5 \times 10^{-2} \text{ M}$; $\text{CrH}_2\text{PO}_3^{2+}$, $0.37\text{--}4.0 \times 10^{-2} \text{ M}$. Every experiment fit the McKay equation, and constancy of the calculated k_2 at a particular $[\text{H}^+]$ confirmed the second-order exchange rate law shown in eq 5. The average of the standard deviations in 22 runs at 25.0° was 8.5%. When eight additional values at other temperatures were included as well, it was 8.9%.

Effect of Hydrogen Ion. Exchange experiments were carried out at several hydrogen ion concentrations in the range $0.026\text{--}1.0 \text{ M}$. Hydrogen ion exerted a strong inverse effect on the reaction rate. Figure 2 shows the variation of k_2 , the pseudo-second-order rate constant, plotted vs. $[\text{H}^+]$ on a log-log scale.

(17) In eight runs at low $[\text{H}^+]$, $<0.16 \text{ M}$, samples were taken at sufficiently long times to enable comparison of observed values of S_∞ with those calculated by the computer fit of the data. The average deviation of observed and fitted S_∞ values was 1.9% in these eight runs, justifying the procedure used. In principle S_0 and S_∞ are given by the solution composition. Loss of small amounts of chromium(II) by air oxidation prior to exchange, however, causes this to be a distinctly less attractive procedure. The extent of such loss of ^5Cr to exchange could be estimated roughly from the chromium(II) analyses. These corrections were extremely imprecise; they did show, however, that the observed S_0 and S_∞ values were in reasonable agreement with those calculated from the composition and the amount of chromium(II) converted to the non-exchanging dimer.

data are consistent with a rate equation containing a single term¹⁸ inversely proportional to $[H^+]$. The unweighted average value of 10^4k (sec^{-1})

$$\text{exchange rate} = k[\text{Cr}^{3+}][\text{CrH}_2\text{PO}_4^{2+}]/[H^+] \quad (6)$$

is $6.26 (\pm 0.87 \text{ std dev})$. A weighted average instantly expresses the results more meaningfully; each value is weighted by the computer-calculated standard deviation of k between observed and calculated values of specific activities fit to the McKay plot. With this weighting, the average value of 10^4k (sec^{-1}) is $6.11 (\pm 0.84 \text{ std dev})$. The effect of this weighting procedure is to count most heavily those runs with the least scatter in the data was lowest, and where the precision was obtained.

Temperature Dependence. The exchange rate was studied at two other temperatures, 16.0 and 35.0°C. Values¹⁹ of 10^4k (eq 6) are as follows: 35.0°C, 18.3 sec^{-1} ($\pm 1.1 \text{ std dev}$, 2 samples, 18.3 sec only), 16.0°C, 2.08 sec^{-1} ($\pm 1.1 \text{ std dev}$, 4 samples, 2.08 sec only). When these values are plotted as at 25.0°C, 10^4k (sec^{-1}) = 18.5 ± 1.0 and 2.10

of the enthalpy and entropy of activation were calculated from the 30 individual rate constants according to the absolute rate theory expression with $\kappa = 1$. The primary weighting procedure in the least-squares method of rate constants would be a weight of $1/k^2$, but a 1 per cent accuracy is presumed to be the same at all temperatures. We have chosen a weighting where the precision of each run is taken into account; here each value is weighted as $1/k\sigma_k$ where σ_k is the standard deviation in k , as generated by the data in that particular run. On this basis the activation parameters and their standard deviations are $E^\ddagger = 19.7 \pm 1.0 \text{ kcal mole}^{-1}$ and $\Delta S^\ddagger = -7.2 \text{ eu}$. Rate constants (10^4k , sec^{-1}) recalculated as parameters at 16.0, 25.0, and 35.0°C are 2.073, 6.11, and 18.29, compared to the individual averages at temperatures of 2.10, 6.11, and 18.5.

Discussion

Structure of Hypophosphitochromium(III) Ion. The structure of $(\text{H}_2\text{O})_5\text{CrH}_2\text{PO}_4^{2+}$ was determined by X-ray crystallography. The question remains of the structure of the coordinated anion in this complex. Consider the formulas $(\text{H}_2\text{O})_5\text{Cr}(\text{OPH}_2\text{O})^{2+}$ and $(\text{H}_2\text{O})_5\text{Cr}(\text{H}_2\text{PO}_4)^{2+}$. Hypophosphorous acid is a monobasic acid which coordination number four for phosphorus is reserved; its formula is HOPH_2O . Considerable evidence has been noted for a second and

alternative dependences on $[H^+]$ were considered including proportional to $[H^+]^0$ and/or $[H^+]^{-1}$. The fit of the data was improved by such terms, and the values of the rate constants were generally within a standard deviation of zero. In 25.0°C, the rate law $k[H^+]^{-1} + k'$ had values $10^4k = 6.04 \pm 1.1$ and $10^4k' = -1.1 \pm 5.2 \text{ M}^{-1} \text{ sec}^{-1}$. The same data in the form $[H^+]^{-1} + k''[H^+]^{-2}$ gave values $10^4k = 5.8 \pm 0.23 \text{ sec}^{-1}$ and $10^4k'' = 0.6 \pm 1.5 \text{ M sec}^{-1}$. For these three equations, the weighted fit was as follows: k only, 0.32; k and k' , 0.32; k and k'' , 0.32. These results led us to conclude that a single term in $[H^+]^{-1}$ is consistent with these data.

Tabulation of the individual exchange experiments listing concentration and time, fraction exchange has been deposited as Document 9357 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington, D. C. 20540. It may be secured by citing the document number and remitting the fee of \$1.25 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Document Service, Library of Congress.

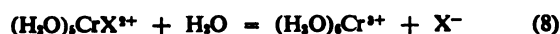
more reactive form of the acid which plays an important role in a number of oxidation reactions²⁰ of hypophosphorous acid and also in the exchange reaction²¹ of the nonacidic protons. The rate-limiting step in these reactions involves only hypophosphorous acid (and an acid catalyst), in which a structural rearrangement is presumed (eq 7). The latter structure is by far the less



stable; various estimates^{20,21} give the equilibrium quotient of this structural change reaction as 10^{-9} – 10^{-12} .

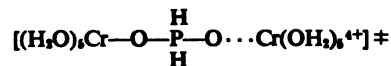
A postulated isomeric structure $\text{Cr}(\text{OPHOH})^{2+}$ for the complex raises questions both of its rate of formation and of its stability. The rate of reaction of Cr^{2+} and H_2PO_4 is sufficiently low to be consistent²² with estimates of the rate of reaction 7, but the intrinsic stability required to enable the species $(\text{H}_2\text{O})_5\text{Cr}(\text{OPHOH})^{2+}$ to form in preference to $(\text{H}_2\text{O})_5\text{Cr}(\text{OPH}_2\text{O})^{2+}$ in spite of the $\sim 15 \text{ kcal}$ by which HOPH_2O is favored over $(\text{HO})_2\text{PH}$ seems larger than the free energies available for most $\text{Cr}(\text{III})$ complexes. It is difficult to rule out the form $(\text{H}_2\text{O})_5(\text{OPHOH})^{2+}$ on this basis, however, since stability constants for species of known structure are not available. The noncommittal representation $\text{CrH}_2\text{PO}_4^{2+}$ will be used in the discussion that follows except when points of detailed structure must be raised.

Exchange Mechanism. Electron exchange of chromium(II) and hypophosphitochromium(III) ions proceeds without release of hypophosphite ion from the primary coordination sphere of chromium(III). The reaction necessarily involves bridging by this anionic ligand similar to other exchange reactions of $(\text{H}_2\text{O})_5\text{CrX}^{2+}$.^{2,7} Replacement of X^- by a water molecule (eq 8) is in most instances (including $X^- = \text{H}_2\text{PO}_4^-$)



a thermodynamically favored process, but its spontaneous rate is so low that it is not a major reaction during the time in which $\text{Cr}(\text{II})$ – $\text{Cr}(\text{III})$ exchange occurs.¹⁶ The feature that electron transfer and X^- transfer proceed at identical rates constitutes an interesting and significant aspect of the mechanism of these reactions.

The energy of the two exchange sites must first become equivalent before electron exchange occurs.²³ A mechanism for this energy equalization is the formation of a symmetrical transition state. The exchange reaction of $(\text{H}_2\text{O})_5\text{CrH}_2\text{PO}_4^{2+}$ and $\text{Cr}(\text{H}_2\text{O})_6^{3+}$ would appear to have available an inner-sphere transition state that maintains symmetry at each chromium atom



(20) (a) R. O. Griffith and A. McKeown, *Trans. Faraday Soc.*, **30**, 530 (1934); (b) R. O. Griffith, A. McKeown, and R. P. Taylor, *ibid.*, **36**, 752 (1940); (c) P. Hayward and D. M. Yost, *J. Am. Chem. Soc.*, **71**, 915 (1949).

(21) W. A. Jenkins and D. M. Yost, *J. Inorg. Nucl. Chem.*, **11**, 297 (1959). This article contains a review of H_2PO_4 reaction mechanisms and demonstrates the interrelation of H exchange and oxidation-reduction reactions.

(22) The rate of the transformation in eq 7 is of the form $k_{\text{HA}}[\text{H}_2\text{PO}_4] \cdot [\text{HA}]$ in which HA is an acid catalyst.²¹ If the complex formation rate constant¹⁹ $k_f[\text{H}_2\text{PO}_4][\text{Cr}^{2+}]$ is regarded as a rate constant of this type, its value ($0.2 \text{ M}^{-1} \text{ hr}^{-1}$) does not appear unreasonable for $\text{Cr}^{2+} + \text{HA}$ in view of the acid strength of Cr^{2+} relative to other HA catalysts studied previously.²¹

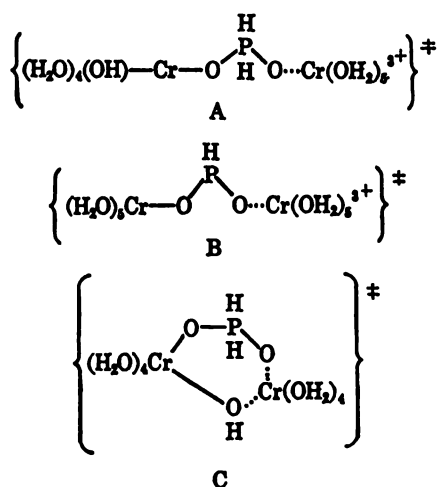
(23) W. F. Libby, *J. Phys. Chem.*, **56**, 863 (1952).

This transition state could be formed from the reactants with an apparent minimum of structural reorganization. Over the entire range of $[H^+]$ studied here, even at 1 M H^+ , this symmetrical transition state remains quite an unimportant pathway,¹⁶ relative to a configuration containing one proton less. The net activation process, written to ignore the role of solvent molecules, is given by eq 9.



Three reasonable formulations for this transition state that we wish to consider are shown in Scheme I. Since during exchange hypophosphite ion is transferred, and not replaced by water, only transition states with a bridging hypophosphite ion are considered. The three formulations are a nonsymmetrical transition state (A) containing a nonbridging hydroxide ion ligand, a symmetrical configuration (B) involving (formally,

Scheme I



at least) proton loss from phosphorus, and a symmetrical double-bridged structure (C). The kinetic results we have obtained do not alone allow us to eliminate any of the kinetically equivalent alternatives; the discussion that follows is based largely on analogy with other exchange reactions and on the properties of hypophosphite ion.

The nonsymmetrical transition state (A) has no known counterpart in other Cr(II)–Cr(III) exchanges. Rate laws of this form were noted^{7–9} for some reactions of $(H_2O)_5CrX^{2+}$ and Cr^{3+} . These reactions result in aquation of X and not its transfer, however; presumably hydroxide ion is a bridging ligand in these cases, and the nonbridging X^- group aquates upon electron transfer. Formulation A suffers from the further disadvantage that it is not symmetrical. Symmetry is not a criterion for a suitable exchange transition state, but it generally does provide the best mechanism for bringing about energy equivalence of the two electron exchange sites.²³ On the basis of these arguments we are inclined to regard A as a relatively improbable configuration for the transition state.

Formulation B involves a significant structural change in the reactant hypophosphite complex. The phosphorus protons in the free acid are nonlabile, and it seems unlikely those on the coordinated anion are substantially more so. Thus this mechanism cannot be a rapid acid dissociation equilibrium of a P–H proton in the complex $(H_2O)_5Cr(OPH_2O)^{2+}$. Were the pre-

viously considered isomeric complex $Cr(OPHOH)^{2+}$ the predominant form, the symmetric formulation B would be easily understood. Since this structure for the hypophosphite complex was deemed the less likely, B seems relatively improbable unless further studies on the complex reveal its structure.

Formulation C, a double-bridged transition state involving the anion $H_2PO_3^-$ and one *cis* hydroxide ion, is also consistent with all evidence now at hand. This formulation preserves symmetry in the transition state, accounts for the observed rate dependence on $[H^+]^{-1}$, and would involve a rapid preequilibrium loss of a labile proton from coordinated water.

Direct evidence for double-bridged transition states has been found only for *cis*-diazido complexes.^{24,25} They have been shown to be unimportant in some other instances, including difluoro³ and diaquo complexes.²⁶ Doubly bridged transition states employing hydroxide ion analogous to C have also been suggested for the rate terms varying as $[H^+]^{-1}$ in the reaction of $CrSCN^{3+}$ and Cr^{3+} ,²⁷ and in the reaction of *cis*- $Co(NH_3)_4(OH_2)(O_2CCH_3)^{2+}$ and Cr^{3+} .²⁸ Preliminary work on *cis*- $Cr(H_2PO_3)_2 + Cr^{3+}$ indicates important contributions of a double-bridged transition state.²⁹

Related Reactions. Since the form of the rate law for this reaction differs from that in previously studied Cr(II)–Cr(III) exchange reactions involving Cr^{III} –X–complexes, a comparison of the kinetic parameters cannot be made. The exchange reactions Cr^{2+} – Cr^{3+} and $CrNH_3^{2+}$ – Cr^{3+} each have a rate law of the form $[Cr^{III}][Cr^{2+}]/[H^+]$, analogous to the present results.^{7–9} In those instances, however, presumably the transition states involve hydroxide ion bridging, which is certainly not the case in the present reaction.

Further information on the mechanism of the exchange reaction will be obtained from studies on the kinetics and equilibrium of iron(III)–hypophosphite ion complex formation. Since complex formation would be rapid relative to isomerization of hypophosphorous acid, the kinetics and equilibrium of this reaction may point up some important differences related to the structural features. In addition, alternate syntheses of chromium(III) hypophosphite complex using relatively rapid reactions (*e.g.*, oxidation–reduction techniques) may clarify the question of the possibility of two forms of the monohypophosphite complex.

More directly, the use of labeled hypophosphorous acid (*i.e.*, tritium labeling of H_2PO_3 as in the studies of Jenkins and Yost³¹) may clarify many points. An answer to the question of whether one of the two “non-exchangeable” hydrogens is exchanged on complex formation or on electron exchange or not at all can provide valuable information both on the structure of the complex and on the exchange mechanism not available at present. The preferred formulation (C) causes transfer of one water oxygen as well, but oxygen-18 labeling will not be a useful technique since repeated exchange will cause all *cis* and *trans* oxygens in the complex to exchange.

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The Oxidation of Water by Cobaltic Aquo Ions

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Abstract: The oxidation of water to oxygen by $\text{Co(III)}_{\text{aq}}$ has been investigated using O^{18} as tracer. It has been shown that the oxidation reaction, which proceeds by inner-sphere ligand to metal electron transfer, involves the oxidation of a $\text{Co(III)}_{\text{aq}}$ dimer by a $\text{Co}_{\text{aq}}^{2+}$ ion. The HO_2 radical, which is being formed in the rate-determining step, is therefore the immediate precursor of molecular oxygen. $\text{Co(III)}_{\text{aq}}$ was shown to contain substantial amounts of dimers even in strongly acid solutions.

Cobaltic aquo ions in aqueous solution are known to oxidize water to oxygen. The kinetics of this reaction have been studied by several investigators;¹⁻³ however, the mechanism of this reaction has not been to unequivocally elucidated.⁴ Mechanisms proposed for this reaction have been based solely on kinetic evidence, on which conflicting information is available.⁴ On thermodynamic grounds it may be inferred that the primary step of oxidation of water to oxygen by $\text{Co(III)}_{\text{aq}}$ does not involve a single electron transfer, since the reaction $\text{Co(III)}_{\text{aq}} + \text{H}_2\text{O} \rightarrow \text{Co(II)}_{\text{aq}} + \text{OH}$ has a positive free energy of about 24 kcal/mole.^{5,6} An alternative primary product is hydrogen peroxide, formed by the concerted reduction of two $\text{Co(III)}_{\text{aq}}$ ions. Kinetics of reduction of $\text{Co(III)}_{\text{aq}}$ by water as interpreted by Bawn and White² support a bimolecular pathway; however, no experimental evidence for the formation of H_2O_2 as a primary product of oxidation of water is available. A third possibility suggested by Baxendale in his interpretation of the kinetic data³ is the formation of a primary product by the oxidation of a $\text{Co(III)}_{\text{aq}}$ dimer by $\text{Co}_{\text{aq}}^{2+}$. This mechanism is thermodynamically more favorable than the former one by a ΔF of about 3 kcal/mole.^{5,6}

Another open question is whether hydrogen peroxide, if formed, is produced by an inner-sphere electron transfer from the ligand⁷⁻⁹ or by an outer-sphere oxidation of the solvent molecules. By the use of O^{18} as tracer, we were able to show that HO_2 is formed as primary product in the oxidation of water by $\text{Co(III)}_{\text{aq}}$ and that this reaction proceeds by an inner-sphere oxidation of water bound to the metal.

Experimental Section

Materials. Oxygen-18 enriched water was supplied by the separation plant of the Weizmann Institute of Science. It was distilled several times over alkaline permanganate in an all-glass still. $\text{Co(ClO}_4)_3$ (reagent grade, G. F. Smith Chemical Co., Columbus, Ohio) and hydrogen peroxide 50% (Analar grade,

B.D.H.) were used. Triply distilled water was used throughout this study.

$\text{Co(III)}_{\text{aq}}$ solutions were prepared by electrolytic oxidation of 0.6 M $\text{Co(ClO}_4)_3$ in 6 M HClO_4 at 0°. The electrolysis (current density of 300 ma/cm²) was carried out in a cell consisting of a platinum anode inside a nonglazed ceramic vessel surrounded by a copper foil cathode. The solution was electrolyzed for 2 hr, i.e., considerable time after the oxidation of Co(II) was complete. As soon as the electrolytic oxidation was stopped, the $\text{Co(III)}_{\text{aq}}$ solution was frozen in liquid nitrogen and kept as such until used. The Co(II) content of the Co(III) solutions prepared by this method is negligible.

$\text{Co(III)}_{\text{aq}}$ labeled with ^{18}O was prepared by the same method using H_2^{18}O (~70 atom % ^{18}O) as solvent.

Methods. One milliliter of the concentrated stock solution of $\text{Co(III)}_{\text{aq}}$ (0.6 M) enriched in ^{18}O was mixed under vacuum at room temperature (22–24°) with 20 ml of degassed, triply distilled water of natural ^{18}O content. Any oxygen dissolved, or formed in the $\text{Co(III)}_{\text{aq}}$ solution, was quantitatively removed before mixing by continuous pumping from the two solutions until the moment of mixing. The oxygen formed after mixing was completely pumped off by a Toepler pump at predetermined time intervals (3, 6, 10, 30, 120, and 360 min following time of mixing), and its isotopic composition was mass-spectrometrically analyzed. Masses 28 and 40 were also measured to check on air contamination. The experiments were repeated using $\text{Co(III)}_{\text{aq}}$ of natural ^{18}O content mixed with water enriched in ^{18}O .

The experiments designed for detection of the intermediary formation of hydrogen peroxide were carried out as follows: 50 μl of 0.6 M $\text{Co(III)}_{\text{aq}}$ stock solution were injected through a aseptological cap into 250 ml of 10^{-4} M H_2O_2 solution, thoroughly degassed, and vigorously stirred. The isotopic composition of the solvent water was different from that of the coordination sphere of $\text{Co(III)}_{\text{aq}}$; the H_2O_2 was of natural isotopic composition. The acidity of the reaction mixture was preadjusted by NaOH to give a final pH of ~4. After the reaction was complete the molecular oxygen formed was pumped off for isotopic analysis. The solution was then thoroughly degassed, and the residual hydrogen peroxide was decomposed by injecting either a suspension of platinum black in water or a solution of ceric ions. The O_2 produced from the residual H_2O_2 was then analyzed for its isotopic composition.

Results and Discussion

The working hypothesis of this study was that the oxidation of water by $\text{Co(III)}_{\text{aq}}$ proceeds by an inner-sphere electron transfer from the coordinated ligand water to the central ion. This hypothesis could be proven by demonstrating that the molecular oxygen formed originates from water molecules bound to the metal ion in the inner coordination sphere. Cobaltic ions are known to form substitution inert complexes.¹⁰ The $\text{Co(III)}_{\text{aq}}-\text{H}_2\text{O}$ isotopic exchange has been estimated to be a relatively slow process¹⁰ unless $\text{Co(II)}_{\text{aq}}$ ions are present; these may catalyze the water exchange by $\text{Co(III)}_{\text{aq}}-\text{Co(II)}_{\text{aq}}$ electron exchange.¹¹ It seemed plausible therefore that when the aquo complex of Co(III) labeled with ^{18}O reacts with H_2^{18}O , the rate of

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Table I. Calculated and Experimental Values of the Isotopic Distribution of Oxygen in O₂ Evolved from Co(III)_{aq} and Water

% of Co(III) decom- posed	Atom % ¹⁸ O			% mole fraction										
	A	B	C	P	x	y	z	k	l	m	α	f	β	g
0-100	65	2.6	6.65	0.0677	0.829	3.08	2.86	88.81	4.37	0.053	12.03	11.27	0.39	0.34
0-20	63	2.6	16.5	0.229	3.14	10.69	9.10	73.10	3.90	0.051	5.22	5.14	0.63	0.60
20-39	63	2.6	6.49	0.0640	0.88	3.00	2.56	88.76	4.74	0.062	11.60	10.96	0.33	0.29
39-59	63	2.6	3.26	0.0109	0.149	0.508	0.433	93.83	5.01	0.066	17.03	16.32	0.091	0.065
59-89	63	2.6	2.77	0.0027	0.033	0.123	0.114	94.61	5.05	0.067	18.30	18.00	0.035	0.015
0-9	63	2.6	32.0	0.487	6.66	22.69	19.3	48.70	2.60	0.034	2.19	1.95	0.76	0.61
9-31	63	2.6	5.50	0.048	0.657	2.24	1.90	90.30	4.82	0.063	12.88	11.98	0.25	0.23
31-79	63	2.6	2.70	0.001	0.013	0.045	0.039	94.77	5.06	0.066	18.56	18.60	0.021	0.022
0-16	63	2.6	22.8	0.336	4.60	15.68	13.35	62.96	3.10	0.037	3.59	3.37	0.71	0.54
16-40	63	2.6	3.85	0.0239	0.327	1.11	0.95	92.60	4.56	0.055	16.39	16.04	0.18	0.16
40-72	63	2.6	2.47	0.0012	0.015	0.053	0.045	94.76	4.54	0.056	20.60	20.22	0.022	0.024
0-10	65	2.6	31.4	0.463	5.67	21.08	19.57	51.13	2.51	0.030	2.40	1.98	0.83	0.53
10-22	65	2.6	5.51	0.0497	0.608	2.26	2.098	90.52	4.45	0.054	13.58	19.41	0.32	0.053
22-78	65	2.6	2.52	0.0019	0.023	0.086	0.080	95.08	4.68	0.057	19.95	19.55	0.0003	0.018
0-8	33	2.0	17.8	0.509	22.83	22.49	5.54	47.18	1.93	0.019	2.87	2.72	0.22	0.20
8-13	33	2.0	11.0	0.291	13.08	12.88	3.17	68.10	2.78	0.028	5.18	5.00	0.20	0.18
13-63	33	2.0	2.20	0.0071	0.318	0.312	0.077	95.36	3.89	0.039	22.77	24.65	0.028	0.072
0-17	33	1.4	11.54	0.321	14.40	14.19	3.49	66.02	1.87	0.013	5.01	5.12	0.21	0.16
17-29	33	1.4	5.80	0.139	6.28	6.18	1.52	83.62	2.37	0.016	10.51	9.86	0.18	0.13
29-42	33	1.4	3.12	0.0535	2.40	2.36	0.582	92.00	2.61	0.017	18.90	18.20	0.12	0.092
42-77	33	1.4	1.51	0.0035	0.156	0.153	0.037	96.88	2.75	0.019	22.67	22.67	0.10	0.075
0-8	33	1.4	16.2	0.469	21.07	20.75	5.11	51.59	1.46	0.011	3.27	2.95	0.23	0.050
8-14	33	1.4	11.5	0.321	14.40	14.19	3.49	66.02	1.87	0.013	5.00	8.11	0.21	0.14

ligand oxidation might compete with that of ligand exchange resulting in the formation of molecular oxygen partly labeled with ¹⁸O. To check on these assumptions we have treated ¹⁸O labeled Co(III)_{aq} with H₂¹⁸O and determined the ¹⁸O content of the oxygen formed. As there are no reliable data available on the rate of the Co(III)_{aq}-H₂O isotopic exchange, it was impossible to predict the relative rates of isotopic exchange *vs.* oxidation of water *a priori*.

It has been found that $(6.65 - 2.6)/65 = 6.2\%$ of the oxygen evolved originates from the inner coordination sphere of Co(III)_{aq}. This result could be interpreted in two ways: either that 6.2% of the reaction proceeds by an inner-sphere oxidation mechanism and the rest by an outer-sphere process, or that all the oxygen formed originates from the ligand water but that an over-all average of 93.8% of the ligand H₂¹⁸O has exchanged with the solvent before oxidation. The second interpretation seems to be much more plausible in view of the ¹⁸O content of O₂ collected in successive fractions during the reaction of Co(III)_{aq} with water (Table I). It may be seen that, whereas the first fraction collected contains up to half of the oxygen originating from the inner sphere, the last fractions collected have an isotopic composition identical with that of the solvent. These findings show that the relatively low yield of ¹⁸O in the molecular oxygen formed is due to H₂O_{solvent}-H₂O_{ligand} isotopic exchange, and that it is very likely that all the oxygen evolved originates from the inner sphere of hydration. It is experimentally hard to sample oxygen at the very early stages of Co(III)_{aq} decomposition, which could allow the isotopic composition of the evolved oxygen at time zero to be obtained. Thus a small contribution (<5%) of an outer-sphere mechanism cannot be completely excluded.

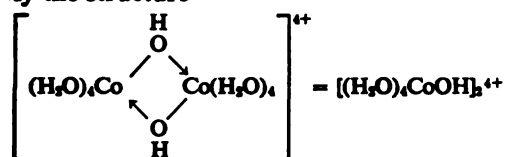
In view of the competition between the ligand exchange and ligand oxidation it was of interest to examine the exact isotopic distribution of ¹⁸O in the oxygen molecules produced. We have examined therefore the isotopic distribution of ¹⁸O between ¹⁸,¹⁶O₂

and ¹⁶,¹⁶O₂ and found it to be far from the statistical: $[^{16,18}\text{O}_2]/[^{18,18}\text{O}_2][^{16,16}\text{O}_2] = 4.12$. If the O₂ formed originated from two Co(III)_{aq} ions labeled with ¹⁸O, the oxygen should contain ¹⁸,¹⁸O₂. However, in view of the extensive isotopic exchange, it seemed improbable that ¹⁸,¹⁸O₂ would be formed in any appreciable amount if the oxygen originated from the reaction between two separate Co(H₂O)₆²⁺ ions. On the other hand, if the ¹⁸,¹⁸O₂ would originate from H₂¹⁸O labeled Co(III)_{aq} in a chemical form which does not readily undergo isotopic exchange with the solvent, one could calculate the isotopic distribution of ¹⁶,¹⁶O₂, ¹⁶,¹⁸O₂, and ¹⁸,¹⁸O₂ assuming that the evolved O₂ originates from two sources: O₂ labeled with ¹⁸O formed from the labeled Co(III)_{aq} exclusively and the rest of the O₂ from the water exclusively. Following this assumption the mole fractions of ¹⁶,¹⁶O₂ (x), ¹⁶,¹⁸O₂ (y), and ¹⁸,¹⁸O₂ (z) originating from the Co(III)_{aq} containing an atom fraction A = $(0.5y + z)/(x + y + z)$ of ¹⁸O are in isotopic equilibrium, i.e., $y^2/xz = 4$. Analogously the molar fractions ¹⁶,¹⁶O₂ (k), ¹⁶,¹⁸O₂ (l), and ¹⁸,¹⁸O₂ (m) of oxygen originating from solvent contain an atom fraction B of ¹⁸O ($B = (0.5l + m)/(k + l + m)$ and $l^2/mk = 4$). The oxygen formed is a mixture of molecules originating from the two sources and contains an atom fraction C of ¹⁸O: $C = (0.5y + 0.5l + z + m)/(x + y + z + k + l + m)$, and, as $x + y + z + k + l + m = 1$, $C = 0.5(y + l) + z + m$. If one defines the mole fraction of O₂ originating from the Co(III)_{aq} as P = $x + y + z$, then $C = AP + B(1 - P)$ or $P = (C - B)/(A - B)$. From these equations one may derive that $x = P(1 - A)^2$; $y = 2AP(1 - A)$; $z = PA^2$; $k = (1 - P)(1 - B)^2$; $l = 2B(1 - P)(1 - B)$; $m = (1 - P)B^2$. Thus the values of the ratios $\alpha = ^{16,16}\text{O}_2/^{16,18}\text{O}_2 = (x + k)/(y + l)$ and $\beta = ^{18,18}\text{O}_2/^{16,18}\text{O}_2 = (z + m)/(y + l)$ could be calculated on basis of the measured values of A, B, and C and

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red with the ratios between the masses $^{16,18}\text{O}_2$, $^{16,18}\text{O}_3$ (34), and $^{18,18}\text{O}_2$ (36) experimentally determined by the mass spectrometric analysis of the evolved $r = (32)/(34)$ and $g = (36)/(34)$. The results presented in Table I show a satisfactory agreement between calculated values of α and β and the experimental of f and g , respectively. Thus the assumption the oxygen formed is a mixture of two types of molecules with practically no isotopic equilibrium between them has been verified. As the value was much smaller than 32 and 34, the accuracy of α is better than that of f . Consequently the agreement between α and f is evidently better than between β and

only explanation of these results we are able to give is the following. Oxygen is formed from binuclear complexes of $\text{Co(III)}_{\text{aq}}$ and these oxygen molecules arise exclusively from their inner hydration sphere. $\text{Co(III)}_{\text{aq}}$ solution (0.6 M in 6 M HClO_4) contains 6.2% in percentage (<3.1%) of dimers having mostly the structure



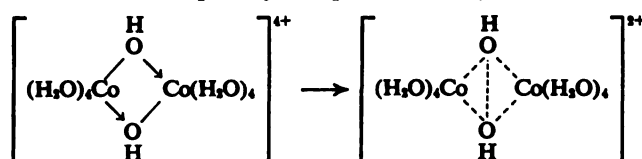
in addition to monomeric $\text{Co}(\text{H}_2\text{O})_6^{3+}$ ions. The formation of O_2 from $\text{Co(III)}_{\text{aq}}$ requires 4 equiv of Co(III) , which have to be in a dimeric form. Thus the presence of 6.2% of nonequilibrated oxygen implies the existence of $\geq 3.1\%$ nonequilibrated dimers introduced into the dilute solution. If one assumes that the equilibrium $\text{Co}(\text{H}_2\text{O})_6\text{OH}^{3+} \rightleftharpoons \text{dimer}$ is strongly shifted right, then the concentration of the dimer will be approximately equal to that of $\text{Co}(\text{H}_2\text{O})_6\text{OH}^{3+}$. The equilibrium constant for $\text{Co}(\text{H}_2\text{O})_6^{3+} \rightleftharpoons \text{Co}(\text{H}_2\text{O})_5\text{OH}^{2+} + \text{H}^+$ has been found to be 0.22 ± 0.05 .¹³ At this value one may derive the concentration of dimers in 6 M HClO_4 to be $\leq 3.5\%$, in good agreement with our findings. These dimers yield oxygen before undergoing isotopic exchange with the solvent. The monomeric $\text{Co}(\text{H}_2\text{O})_6^{3+}$ has to undergo dimerization to yield O_2 . However, the rate of water exchange of $\text{Co}(\text{H}_2\text{O})_6^{3+}$ is faster than the rate of dimerization; thus the coordination sphere of the newly formed dimers, and consequently the O_2 formed from them, will be in isotopic equilibrium with the solvent. The exchange of the dimers present in the concentrated solution of $\text{Co(III)}_{\text{aq}}$ undergo cleavage to give monomers, which will undergo complete isotopic exchange with the solvent before reacting to give a dimer again. The rapid exchange of the monomers is most probably induced by the $\text{Co(II)}-\text{Co(III)}$ electron exchange.¹¹

The existence of polynuclear species higher than dimers in our solution cannot be excluded. It is, however, unlikely that these exist in 6 M HClO_4 , and their rate of formation is a rather slow process (cf. processes in Fe(III) or Al(III) solutions), their contribution to the over-all oxidation of water by $\text{Co(III)}_{\text{aq}}$ under our experimental conditions may be neglected.

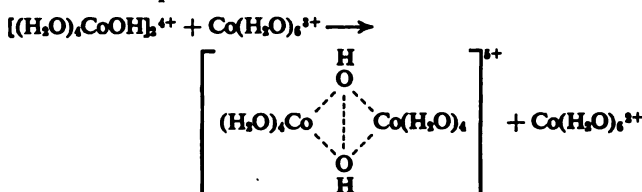
The mechanism of oxidation of the ligand in the dimeric $\text{Co(III)}_{\text{aq}}$ remained an open question. Two alternative

J. Conoccioli, G. N. Nancollas, and N. Sutin, *Inorg. Chem.*, **9**.

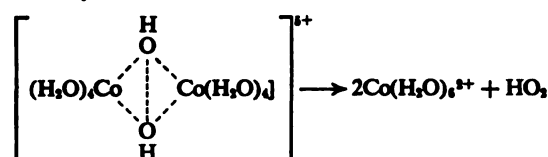
mechanisms are possible. (a) One is the intramolecular conversion of the dimeric complex of Co(III) into a binuclear peroxy complex of Co(II)



followed by hydrolysis of the cobalto peroxide to $\text{H}_2\text{O}_2 + 2\text{Co(II)}$. The following steps would then be $\text{H}_2\text{O}_2 + \text{Co}(\text{H}_2\text{O})_6^{3+} \rightarrow \text{Co}(\text{H}_2\text{O})_5\text{OH}^{2+} + \text{H}^+ + \text{HO}_2$ and $\text{HO}_2 + \text{Co}(\text{H}_2\text{O})_6^{3+} \rightarrow \text{Co}(\text{H}_2\text{O})_5\text{OH}^{2+} + \text{O}_2 + \text{H}^+$. (b) The other is an attack of $\text{Co}(\text{H}_2\text{O})_6^{3+}$ on the dimeric aquo cobaltic complex



followed by the formation of HO_2 radical



followed by either $\text{HO}_2 + \text{Co}(\text{H}_2\text{O})_6^{3+} \rightarrow \text{O}_2 + \text{Co}(\text{H}_2\text{O})_6^{3+} + \text{H}^+$ or $2\text{HO}_2 \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$.

As we know from the kinetic behavior of the $\text{Co(III)}_{\text{aq}}$ oxidation of water, the rate of this reaction is proportional to $[\text{H}_2\text{O}_2]^{1/2}$ which is implied in the pre-equilibrium: $2\text{Co}(\text{H}_2\text{O})_6^{3+} \rightleftharpoons [(\text{H}_2\text{O})_4\text{CoOH}]_2^{4+} + 2\text{H}^+$.¹⁴ As we have shown, $\text{Co(III)}_{\text{aq}}$ dimers exist even in 6 M HClO_4 solution; consequently, in less acid solution, e.g., $<0.01 \text{ N H}^+$, practically all $\text{Co(III)}_{\text{aq}}$ will be in the dimeric form.

In order to decide between the two mechanisms, we have carried out a series of experiments in which $\text{Co(III)}_{\text{aq}}$ reacted with water in the presence of H_2O_2 . We had to choose conditions where the rate of the $\text{Co(III)}_{\text{aq}}-\text{H}_2\text{O}$ reaction competes with the $\text{Co(III)}-\text{H}_2\text{O}_2$ oxidation reaction. The kinetic information available for both reactions³ indicates that only at low acidities and high dilutions of $\text{Co(III)}_{\text{aq}}$ has the ligand oxidation a chance to compete with the H_2O_2 reaction. Accordingly we chose pH 4 and $[\text{Co(III)}_{\text{aq}}] = 10^{-4} \text{ M}$ as the appropriate experimental conditions. Using $\text{Co(III)}_{\text{aq}}$ and H_2O of different isotopic composition from that of H_2O_2 , it was possible to examine by isotope dilution the amount of hydrogen peroxide formed as intermediate in the oxidation of water. The results presented in Table II show that under the experimental conditions some oxidation of water by $\text{Co(III)}_{\text{aq}}$ took place in spite of the efficient competitive reaction of $\text{Co(III)}_{\text{aq}}$ with H_2O_2 ; moreover, some hydrogen peroxide produced from the $\text{Co(III)}_{\text{aq}}$ and from water could be detected in the residual H_2O_2 . From a quantitative evaluation of the results, one could determine

(14) An OH^- -induced $\text{S}_\text{N}2$ hydrolysis of the cobalto peroxide formed according to the first mechanism or of the complex formed by the second mechanism may be excluded in view of the measured rates and the steady-state concentration of OH^- ions in the range of acidities investigated.

Table II. The Isotopic Composition of Oxygen and Hydrogen Peroxide Formed from $\text{Co(III)}_{\text{aq}}$ in the Presence of Hydrogen Peroxide*

H_2O	$\text{Co(III)}_{\text{aq}}$	Atom % ^{18}O in—	
		Evolved O_2	Residual H_2O_2
0.213	63.0	1.71 ± 0.30	0.402 ± 0.03
25.2	0.200	0.54 ± 0.06	0.311 ± 0.04
25.2	63.0	2.48 ± 0.42	0.432 ± 0.04

* $[\text{Co(III)}_{\text{aq}}] = 1.10^{-4} \text{ M}$; $[\text{H}_2\text{O}_2] = 2.10^{-4} \text{ M}$; ^{18}O content of $\text{H}_2\text{O}_2 = 0.2 \text{ atom } \%$.

the mole fractions of O_2 and H_2O_2 which originate from the $\text{Co(III)}_{\text{aq}}$ and from water, respectively.

As we have carried out these experiments with $\text{Co(III)}_{\text{aq}}$ and H_2O of different isotopic composition (Table II), the contribution of each pathway could be determined by solving three simultaneous linear equations with three unknowns. From the composition of the evolved oxygen, it was calculated that under the experimental conditions $2.3 \pm 0.4\%$ of the oxygen is formed from the $\text{Co(III)}_{\text{aq}}$ (i.e., from the dimers present in the original $\text{Co(III)}_{\text{aq}}$ solution; see above), and $1.4 \pm 0.3\%$ originates from the water. This means that in the presence of H_2O_2 , about 60% of the oxygen originates from the isotopically (nonequilibrated) dimers and only 40% from secondary dimers, compared with 16.2 vs. 93.2% in pure water. This result is not surprising if one assumes that the rate of reaction of $\text{Co(H}_2\text{O)}_6^{3+}$ with H_2O_2 is considerably faster than that of the $\text{Co(III)}_{\text{aq}}$ dimer, which may undergo ligand oxidation before being reduced by H_2O_2 in solution.

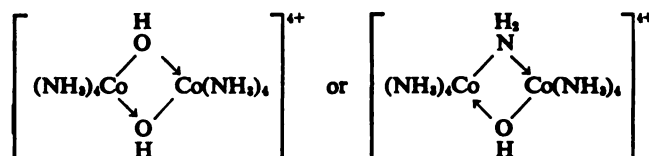
The analysis of the residual H_2O_2 data shows that $0.3 \pm 0.1\%$ of the H_2O_2 originates from the $\text{Co(III)}_{\text{aq}}$ and $0.2 \pm 0.1\%$ from the water. The latter results indicate that H_2O_2 is *not* the precursor of the oxygen evolved. If H_2O_2 would be the only intermediate in the formation of O_2 as required by mechanism a, one would expect to find much more H_2O_2 originating from the $\text{Co(III)}_{\text{aq}}-\text{H}_2\text{O}$ reaction in the residual H_2O_2 than in the evolved oxygen. The small amounts of labeled H_2O_2 detected are most probably due to the secondary reaction $\text{HO}_2 + \text{HO}_2 \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$, which is unfavored in the presence of H_2O_2 and of $\text{Co(H}_2\text{O)}_6^{3+}$.

Our results exclude the formation of an O—O bond in the dimer prior to its being attacked by $\text{Co(H}_2\text{O)}_6^{3+}$. If the cobaltic dimer would undergo spontaneous intramolecular conversion to a cobalto peroxide complex, the latter would undergo rapid hydrolysis, owing to the substitution lability of Co(II) , and release H_2O_2 .

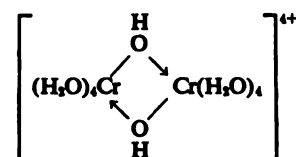
From the tracer experiment described here one may reach the following conclusions. (1) O_2 is formed

from $\text{Co(III)}_{\text{aq}}$ and water only *via* dimers. (2) The formation of oxygen involves the reaction of these dimers with $\text{Co(H}_2\text{O)}_6^{3+}$ resulting in the formation of HO_2 as intermediate. If the latter process is the rate-determining step, one would expect the rate at low acidity to be proportional to $[\text{Co(III)}_{\text{aq}}]^{1/2}$. Such a kinetic behavior has been actually observed,⁸ and the results were interpreted by the same mechanism. We have thus corroborated the mechanism suggested by Baxendale and Wells which has been challenged⁴ for lack of supporting evidence. (3) $\text{Co(III)}_{\text{aq}}$ contains substantial amounts of dimers even in concentrated acid solutions. In less acid solution $\text{Co(III)}_{\text{aq}}$ is predominantly in the dimeric form.

The formation of dimeric aquo or hydroxo complexes of Co(III) should not be surprising in view of the existence of other binuclear Co(III) complexes such as^{15,16}



or of analogous Cr(III) binuclear complexes¹⁷



It is interesting to note that the oxidation of substituted Co(II) complexes, e.g., $[\text{Co}(\text{NH}_3)_5\text{H}_2\text{O}]^{2+}$ ¹⁸ or $[\text{Co}(\text{CN})_5\text{H}_2\text{O}]^{2-}$,¹⁹ by molecular oxygen produces binuclear peroxy complexes of the type $[(\text{NC})_5\text{Co}(\text{O}_2)\text{Co}(\text{CN})_5]^{6-}$ or $[(\text{NH}_3)_5\text{Co}(\text{O}_2)\text{Co}(\text{NH}_3)_5]^{4+}$, which may be further oxidized to $[(\text{NC})_5\text{Co}(\text{O}_2)\text{Co}(\text{CN})_5]^{5-}$ and $[(\text{NH}_3)_5\text{Co}(\text{O}_2)\text{Co}(\text{NH}_3)_5]^{5+}$, respectively.²⁰ These complexes are most probably closely related with the intermediate postulated in this study.

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Formation of Open-Cage and Closed-Cage Carboranes from Tetraborane(10) and Acetylene

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Contribution from the Cobb Chemical Laboratory, University of Virginia, Charlottesville, Virginia. Received December 22, 1966

Abstract: The vapor-phase reaction of tetraborane(10) and acetylene has been examined at 25, 50, and 100°, and the volatile products were isolated and structurally characterized. At 25 and 50°, methyl derivatives of tricarbaheptaborane(7) and monocarbaheptaborane(9) are formed. At 100° a flash reaction takes place in which nine volatile products are obtained, all of which are closed-cage carboranes having three to eight boron atoms. Pyrolysis of the 2-methyl and 2,4-dimethyl derivatives of 2,3,4-tricarbaheptaborane(7) yields no carboranes, but the 2,3-dimethyl derivative produces new dimethyl derivatives of 2,4-dicarbapentaborane(7) and tricarbaheptaborane(7) in small yields. Comparison of these results with earlier work from several laboratories permits some tentative conclusions concerning carborane formation in vapor-phase alkyne-borane reactions.

In recent years a number of carborane cage compounds have been synthesized by direct reactions of saturated hydrocarbons with boranes in the vapor phase.

Several observations concerning these reactions now seem to have general significance: (1) simple alkynes often lead to carborane formation, but alkenes do not; (2) formation of closed-cage species (B_nH_{n+2} series) is favored in high-energy situations such as electric discharges¹⁻³ or flash reactions;^{4,5} (3) synthesis of open-cage carboranes containing hydrocarbon bridges, e.g., CB₅H₅,⁶ C₂B₄H₆,⁷ C₃B₃H₇,⁸ or derivatives of these, occurs under comparatively mild conditions (thermally induced reactions at 25 to 100°); (4) formation of methyl-substituted carboranes from acetylene is common in both high-energy and low-energy reactions;^{1-7,9} (5) methyl substitution occurs primarily in boron cage positions in the high-energy syntheses, but C-methylation is frequently observed in low-energy reactions.

Previous reports of carborane formation from reactions in the vapor phase have involved B₂H₆,^{5,6} B₄H₁₀,^{4,7,8} or B₆H₁₀¹⁰ as reactants. The action of acetylene on ethylene has been studied,^{11,12} but no carboranes are produced and the principal product is 2,4-dimethyltetrahydroborane. In this paper we describe an investigation of the vapor-phase interaction between tetraborane and acetylene in which both open- and closed-cage carboranes were obtained under varying conditions.

The results of this study lend further support

to the above generalizations and offer some insight into the nature of the carborane-forming processes in these systems.

Results and Discussion

Reactions at 25 and 50°. The gas-phase reaction between chromatographically pure B₄H₁₀ and C₂H₂ in a 1:1 mole ratio takes place slowly at room temperature, and more rapidly at 50°, to give a white, non-volatile organoboron polymer and several volatile carboranes, all having open-cage structures (Table I). In addition to B₄H₁₀ and an unstable material which may be the parent 2,3,4-tricarbaheptaborane(7), the products are the 2-methyl, 2,3-dimethyl, and 2,4-dimethyl derivatives of 2,3,4-tricarbaheptaborane(7), the infrared spectra of which are presented in Table II, plus 4-methyl-2-carbaheptaborane(9). (The last-mentioned compound has been previously reported⁷ as a product of the reaction of B₄H₁₀ with C₂H₂ at 215°.) No other volatile materials have been detected in significant amounts despite the use of sensitive chromatographic methods, and the same products were obtained at 50° as at 25°.

The white solid is highly reactive toward both dry air, in which it inflames, and moisture, which rapidly degrades it to boric acid. Infrared analysis indicates the presence of both CH and BH₂ groups and strongly suggests a polymeric structure. The formation of this material is not wall catalyzed, since it is produced homogeneously throughout the reactor and settles to the bottom, and it appears to be the major product of a gas-phase hydroboration attack of acetylene on B₄H₁₀ in which the volatile carboranes are side products.

These results for the B₄H₁₀-C₂H₂ system are in sharp contrast to those recently reported for the B₂H₆-C₂H₂ gas-phase reaction,¹⁴ in which ethyldiborane and 1,1-diethyldiborane were the major volatile products at 85° and no carboranes were found. Thus it is clear that none of the carborane products obtained in the present work could have resulted from direct interactions between C₂H₂ and B₂H₆ (some of which is always present as a decomposition product in B₄H₁₀ vapor). Moreover, since other experiments¹⁵ have established that neither B₂H₆ nor B₅H₁₁ combines with C₂H₂ at room

Philip Francis du Pont Predoctoral Fellow, 1965-1967.

Although both open- and closed-cage carboranes have been prepared by other methods, we wish to restrict this discussion to direct gas-phase reactions between hydrocarbons and boranes.

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Table I. Reactions of B_4H_{10} with C_2H_2 ^a

Reactants, mmoles (500-ml flask) B ₄ H ₁₀ C ₂ H ₂		Temp, °C	Reaction time, hr	Reactants recovered, mmoles B ₄ H ₁₀ C ₂ H ₂		Mole % of volatile products ^{b,c}																Total vola- tile products, mmoles
						2,3,4-C ₂ B ₃ H ₇ deriv				1,5-C ₂ B ₃ H ₅ deriv		1,6-C ₂ B ₃ H ₅ deriv		2,4-C ₂ B ₃ H ₇ deriv				Other				
B ₄ H ₁₀	C ₂ H ₂			B ₄ H ₁₀	C ₂ H ₂	1a	1b	1c	1d	2a	3a	4a	4b	4c	4d	4e	5a	6a	7a	7b		
3.33	3.37	25	140	1.68	0.0	3	15	21	18	0	0	0	0	0	0	0	2	41	0	0	0.097	
3.60	7.20	25	192	0.88	0.0	...	15	26	18	0	0	0	0	0	0	0	4	37	0	0	0.114	
0.89 ^a	0.82 ^a	50	3.8	0.48	0.0	...	7	14	6	0	0	0	0	0	0	0	...	70	0	0	0.034	
3.58	3.58	100	...	0.0	0.10	0	0	0	0	4	4	35	9	17	9	4	0	0	11	7	0.116	
0.98	1.92	100	...																			

^a Typical experiments; gas phase. ^b Exclusive of H_2 . ^c Key: 1a = $C_2B_3H_7$ (?), 1b = 2- $CH_3C_2B_3H_5$, 1c = 2,3-(CH_3) $_2C_2B_3H_5$, 1d = 2,4-(CH_3) $_2C_2B_3H_5$, 2a = 2- CH_3 -1,5- $C_2B_3H_4$, 3a = 1,6- $C_2B_3H_4$, 4a = 2,4- $C_2B_3H_7$, 4b = 1- CH_3 -2,4- $C_2B_3H_5$, 4c = 2- CH_3 -2,4- $C_2B_3H_5$, 4d = 3- CH_3 -2,4- $C_2B_3H_5$, 4e = 5- CH_3 -2,4- $C_2B_3H_5$, 5a = 4- CH_3 -2- $C_2B_3H_5$, 6a = B_4H_{10} , 7a = $C_2B_3H_7$, 7b = B- $CH_3C_2B_3H_5$. ^d Trace. ^e 125-ml flask. / Flashed after 6 min at 100°. ^f Exploded violently after 5 min at 100°.

Table II. Gas Infrared Spectra of Tricarbahexaborane(7) Derivatives^a

2- CH_3 - $C_2B_3H_5$	2,3-(CH_3) $_2$ - $C_2B_3H_5$	2,4-(CH_3) $_2$ - $C_2B_3H_5$
3070 sh	3010 sh	3030 m
3030 m	3000 sh	2950 vs
2960 s	2950 vs	2910 m
2920 s	2920 vs	2880 m
2870 s	2870 m	2590 vs
2590 vs	2830 sh	1980 w
1900 m, b	2590 vs	1950 m, b
1840 sh	1975 w	1500 m
1530 s	1920 m	1455 s
1440 s	1870 m	1360 m
1328 m	1585 w	1290 w
1225 m	1470 vs	1140 sh
1065 m	1450 sh	1110 m
1020 w	1390 m	1060 m
990 sh	1320 m	1000 w, b
950 m	1210 m	945 w
905 w	1160 w	815 s
825 m	1125 m	790 m
765 m	1065 w	735 w
690 m	990 sh	
615 m	940 s	
	880 w	
	835 m	
	755 m	
	725 m	

^a In cm^{-1} at 25 mm pressure.

temperature to give more than traces of the tricarbahexaborane(7) products in Table I, it is apparent that the two pentaboranes, as such, are not significant intermediates in the formation of the $C_2B_3H_7$ derivatives from B_4H_{10} . We conclude, then, that formation of the $C_2B_3H_7$ products is initiated by a direct attack of C_2H_2 on B_4H_{10} itself or on a fragment formed therefrom (B_3H_7 is a reasonable possibility).

Reaction at 100°. The interaction between B_4H_{10} and C_2H_2 at 100° is of an entirely different nature from that occurring at 25 or 50°. Within a few minutes an equimolar mixture flashes, yielding dark gray solids and a series of nine volatile closed-cage carboranes having no hydrogen bridges (Table I). With the exception of 2- $CH_3C_2B_3H_5$, $C_2B_3H_{10}$, and B- $CH_3C_2B_3H_5$, the same species have also been produced in electric discharges of B_2H_6 - C_2H_2 mixtures,⁶ which implies somewhat similar mechanisms. It is notable, however, that among the products obtained in the present study there is no indication of the 1,2- $C_2B_3H_5$ methyl derivatives^{5,6,16}

(16) R. N. Grimes, *J. Organometal. Chem.* (Amsterdam), in press.

which were significant products of the B_2H_6 - C_2H_2 discharge reaction.

Pyrolysis of Tricarbahexaborane(7) Derivatives. In order to examine the possibility that the alkylated $C_2B_3H_7$ species which form at low temperatures might be intermediates in the synthesis of closed-cage carboranes at 100°, vapor-phase pyrolysis experiments have been carried out on the three $C_2B_3H_7$ methyl derivatives obtained in the B_4H_{10} - C_2H_2 reaction at 25°. All three compounds are completely stable at 100°, and neither 2- $CH_3C_2B_3H_5$ nor 2,4-(CH_3) $_2C_2B_3H_5$ is affected by heating at 250° for several days, although the latter substance decomposes at 350° to hydrogen and nonvolatile solids. The 2,3-dimethyl derivative, on the other hand, at 250° gives traces of a dimethyl-2,4-dicarbaheptaborane(7) plus a B,C-dimethyl derivative of $C_2B_3H_7$, and at 300° yields a small quantity of a second (CH_3) $_2C_2B_3H_5$ product which appears to be alkylated at the B(1) and B(7) positions.

Clearly the $C_2B_3H_7$ derivatives are not significant precursors of the closed-cage molecules which form in the 100° reaction.¹⁷ Indeed it is not surprising that the $C_2B_3H_7$ cage system appears to have far less tendency to form closed-cage carboranes on pyrolysis than does the structurally similar (and isoelectronic) $C_2B_4H_8$.^{8,18} This is to be expected from the accepted valence theory for the polyhedral carboranes, which requires two cage carbon atoms and therefore necessitates the formal "ejection" of one carbon from the $C_2B_3H_7$ framework before closure can be completed.

While a detailed clarification of the reaction mechanisms involved in acetylene-borane interactions is not yet available, a comparison of the results of this work with those from earlier investigations does permit some tentative observations. First, it is now evident that, in the low-energy reactions, the nature of the products obtained is strongly dependent on the specific borane starting material. As the data in Table III indicate, the four boranes whose gas-phase reactions with acetylene have been studied under moderate conditions give almost totally different sets of products.^{18a} This is certainly reasonable from the viewpoint that the experimental conditions in each case do not presage extensive

(17) The possibility of interaction between the $C_2B_3H_7$ derivatives and C_2H_2 was eliminated by appropriate control experiments in which no reaction was observed.

(18) T. P. Onak, F. J. Gerhart, and R. E. Williams, *J. Am. Chem. Soc.*, **85**, 3378 (1963).

(18a) NOTE ADDED IN PROOF. Results obtained in this laboratory on the B_4H_{10} - C_2H_2 system fit the pattern indicated in Tables III and IV. At 25° the major product is 2- $C_2H_5B_4H_8$ while the 100° flash reaction virtually duplicates the results of the 100° B_4H_{10} - C_2H_2 reaction.

integration of the borane framework, and the organoboron products evidently retain many of the B-H and/or B-B bonds present in the borane reactant.

Table III. Low-Energy Borane-Acetylene Reactions^a

Borane reactant	Temp, ^b °C	Volatile organoboron products	Ref
B ₂ H ₆	70	C ₂ H ₂ B ₂ H ₄ + 1,1-(C ₂ H ₅) ₂ B ₂ H ₄	14
B ₂ H ₁₀	25-50	Three methyl derivatives of 2,3,4-C ₃ B ₃ H ₇ + small amount of 4-CH ₃ -2-CB ₃ H ₅	This work
B ₂ H ₆	215	2,3-C ₂ B ₂ H ₄ + three methyl derivatives of 2-CB ₃ H ₅	7, 8
B ₂ H ₆ ^c	200	(CH ₃) ₂ C ₂ B ₂ H ₄	10

^a Vapor phase. ^b Temperatures cited are the lowest at which reaction was reported to occur. ^c Reaction with (CH₃)₂C₂.

In considering the rapid, high-energy interactions between acetylene and boranes, however, one is led to a different conclusion. Although some variation in product mixtures is evident in the three systems that have been studied (Table IV), all of the volatile organoboron products so far identified in these reactions are closed-cage carboranes. It should be noted further that in cage systems, 1,6-C₂B₄H₆ and 2,4-C₂B₄H₆, are predominant in each case. At least insofar as these three reaction systems are concerned, it is apparent that the specific cage structure of the borane reactant is not a major factor in determining final product structures, and that mechanisms involving severe disruption of the borane framework must be dominant. In this situation it may be assumed that the final product distribution is largely determined by the relative thermodynamic stabilities of the carborane cage systems.

Table IV. High-Energy Borane-Acetylene Reactions^a

Borane reactant	Reaction conditions	Volatile organoboron products	Ref
B ₂ H ₆	Flash or glow discharge	1,5-C ₂ B ₄ H ₆ , 1,6-C ₂ B ₄ H ₆ , 2,4-C ₂ B ₄ H ₆ , and methyl derivatives of these; + (CH ₃) ₂ -1,2-C ₂ B ₄ H ₆ (two isomers); + higher carboranes	5, 6, 16
B ₂ H ₁₀	Flash	1,5-C ₂ B ₄ H ₆ , 1,6-C ₂ B ₄ H ₆ , 2,4-C ₂ B ₄ H ₆ , and methyl derivatives of these; + C ₂ B ₄ H ₆ and B-CH ₃ C ₂ B ₄ H ₆	This work
B ₂ H ₆	Glow discharge	1,5-C ₂ B ₄ H ₆ , 1,6-C ₂ B ₄ H ₆ , 1,2-C ₂ B ₄ H ₆ , 2,4-C ₂ B ₄ H ₆ , plus unidentified products	3, 4

^a Vapor phase.

In summary, it is reasonable to expect that still unidentified high-energy vapor-phase interactions between boranes and acetylene will yield a series of closed-cage carboranes and derivatives similar to those in Table IV. As a consequence, the remaining undiscovered borane systems will most probably be synthesized under relatively mild, controlled reaction conditions which favor at least partial retention of the original

borane cage structure and which limit the extent of cage rearrangement in the products.

Experimental Section

Materials. B₂H₁₀ was prepared from B₂H₆ (Olin Mathieson) by the hot-cold reactor method of Klein, *et al.*,¹⁰ and was purified by repeated fractionation through traps at -95 and -135°; the purity was monitored by gas chromatography and infrared spectra. C₂H₂ (Matheson) was purified by passage through a -135° trap several times and was checked by infrared analysis.

Procedures. All reactions were carried out in sealed Pyrex bulbs equipped with break-off tips. Volatile products were separated by preparative-scale gas chromatography under air-free conditions using either a 9.5 ft × 0.25 in. column of tricresyl phosphate on Chromosorb W or a 9.5 ft × 0.25 in. column of Kel-F on Chromosorb W. Purification of individual products was effected by repeated passages through the column when necessary.

Spectroscopy. Infrared spectra were obtained on a Beckman IR-8 grating spectrophotometer. Gas infrared spectra were measured in a 3.5-ml, 9-cm Pyrex cell with NaCl windows. Mass spectra were recorded on a CEC 21-103C spectrometer with digital readout, proton nmr spectra were obtained on a Varian A-60 instrument, and ¹¹B nmr spectra were measured with a Varian HR-100 spectrometer at 32.2 Mc.

Reactions of Tetraborane(10) with Acetylene. Measured quantities of tetraborane(10) and acetylene were condensed into an evacuated 125- or 500-ml flask cooled in liquid nitrogen, after which the reactor was sealed and the reaction allowed to proceed to the desired temperature (Table I). At 25°, reaction was evidenced after 1 to 2 hr by the accumulation of a white solid at the bottom. At 50° the same effect was noted within 2 to 3 min. In the experiments at 100°, typically within 6 min a flash was observed with instantaneous formation of large quantities of dark solids, which were not investigated. No breakage of the reactor was observed when the C₂H₂:B₄H₁₀ ratio was 1.0 or less, but when a 2:1 ratio was used the result was a violent explosion (Table I).

Following each experiment most of the unreacted B₄H₁₀ and C₂H₂ was removed by passage through a trap at -95°, after which the volatile products were separated by chromatography as described above. 2-CH₃C₂B₄H₆, 2,3-(CH₃)₂C₂B₄H₆, and 2,4-(CH₃)₂C₂B₄H₆ were structurally characterized by means of their ¹H and ¹¹B nmr, infrared, and mass spectra as reported earlier.⁹ An additional product which has an infrared spectrum similar to the three C₂B₄H₆ derivatives, except for the bands attributable to methyl groups, is possibly the parent C₂B₄H₆, but further investigation of this material was hampered by its instability even at room temperature. 4-CH₃CB₃H₅ was identified from its mass spectrum, which is in precise agreement with the published spectrum⁷ and is clearly distinguishable from the other known carborane fragmentation patterns.

Several attempts to remove the white polymer from the reactor in order to obtain an infrared spectrum were unsuccessful, even in dry argon, due to reaction with traces of oxygen or moisture. This problem was finally circumvented by allowing the reaction between B₄H₁₀ and C₂H₂ to proceed in a gas infrared cell in such a manner that the solid collected on the NaCl windows. All volatile materials were then removed, and the spectrum of the solid was recorded. The only well-defined bands are at 2900 and 2500 cm⁻¹, but a series of broad absorptions appears between 700 and 1500 cm⁻¹. The spectrum was unchanged after the cell had stood 13 days at room temperature.

Of the products obtained in the 100° flash reaction, the following were identified by comparison of their infrared and mass spectra²⁻⁶ with those of authentic samples: 2-CH₃-1,5-C₂B₄H₆, 1,6-C₂B₄H₆, 2,4-C₂B₄H₆, 1-CH₃-2,4-C₂B₄H₆, 3-CH₃-2,4-C₂B₄H₆, and 5-CH₃-2,4-C₂B₄H₆. 2-CH₃-2,4-C₂B₄H₆, which is the only other possible monomethyl derivative²⁰ of 2,4-C₂B₄H₆, was characterized from its mass spectrum (high-mass cutoff = *m/e* 100, and the calculated boron-11 monoisotopic fragmentation pattern closely resembles the patterns of known C₂B₄H₆ derivatives) and its infrared absorption bands, which appear at 2925 (s), 2870 (m), 2590 (vs), 1440 (m, b), 1195 (s), 1110 (m), 1025 (m), 955 (w), 890 (w), 850 (w), 780 (w), and 710 (m) cm⁻¹. Absence of bridge hydrogens is indicated by the lack of absorptions between 1500 and 2500 cm⁻¹. The existence of a band at 1440 cm⁻¹, while none is found near 1320 cm⁻¹,

(19) M. J. Klein, B. C. Harrison, and I. Solomon, *J. Am. Chem. Soc.*, **80**, 4149 (1958).

(20) Excluding optical isomers.

is indicative of a C-methyl rather than a B-methyl group, and the spectrum in the cage vibrational region (700 to 1200 cm^{-1}) is similar to the spectra⁶ of 2,4- $\text{C}_2\text{B}_5\text{H}_7$ and its derivatives.

Identification of $\text{C}_2\text{B}_5\text{H}_{10}$ was accomplished from its mass spectrum (high-mass cutoff = m/e 122, and the fragmentation pattern is characteristic of a closed-cage carborane²¹) and the infrared spectrum, which discloses no alkyl substituents or bridge hydrogens. Bands are observed at 3090 (w), 2590 (vs), 1310 (w, b), 1125 (s), 1110 (sh), 1040 (w), 970 (m), 960 (m), 945 (m), 880 (m), 815 (m), 775 (s), and 660 (s) cm^{-1} . Since the spectrum of authentic $\text{C},\text{C}'\text{-(CH}_3)_2\text{-1,6-C}_2\text{B}_5\text{H}_8$ is similar in the cage vibrational region, while that of $\text{C},\text{C}'\text{-(CH}_3)_2\text{-1,10-C}_2\text{B}_5\text{H}_8$ is quite different,²² it seems likely that the $\text{C}_2\text{B}_5\text{H}_{10}$ product described here is the 1,6 isomer.

Characterization of the B-methyl derivative of $\text{C}_2\text{B}_5\text{H}_{10}$ was similarly based on infrared and mass spectra. The high-mass cutoff is at m/e 136, and the fragmentation pattern is very close to that of the $\text{C}_2\text{B}_5\text{H}_{10}$ described above. The infrared bands are at 2940 (w), 2585 (vs), 1315 (s), 1170 (m), 1130 (s), 1090 (w), 1030 (w, b), 970 (w, b), and 670 (m) cm^{-1} . B-Methyl deformation is indicated by the characteristic band at 1315 cm^{-1} and the absence of a significant absorption near 1450 cm^{-1} (C-CH₃ deformations).

Pyrolysis of Tricarbaborane(7) Derivatives. 2- $\text{CH}_3\text{C}_2\text{B}_5\text{H}_8$ (0.03 mmole) was sealed in a 7-ml reactor and heated 5 days at 250°, at the end of which all of the starting material was recovered unchanged. Similarly, 2,4- $(\text{CH}_3)_2\text{C}_2\text{B}_5\text{H}_8$ (0.01 mmole) in a 15-ml tube did not react in 16 hr at 250°. The same sample was replaced in the reactor and heated 19 hr at 350°, after which only nonvolatile solids and H_2 remained.

(21) A compact, stable framework which resists breakdown is indicated by the fact that the peaks in the parent group (fragments formed by loss of H only) are the most intense in the spectrum; see ref 3, 4, 7, and 16.

(22) The spectra of the dimethyl derivatives of $\text{C}_2\text{B}_5\text{H}_{10}$ were provided by Professor M. F. Hawthorne, University of California, Riverside, Calif.

2,3- $(\text{CH}_3)_2\text{C}_2\text{B}_5\text{H}_8$ (0.100 mmole) in a 10-ml tube failed to react at 100° over a 20-hr period. The same sample in 120 hr at 250° gave cleanly, with no solids, 0.016 mmole of a dimethyl derivative of 2,4- $\text{C}_2\text{B}_5\text{H}_7$. The mass spectrum of this compound has a high-mass cutoff at m/e 114, and the calculated boron-11 monoisotopic spectrum is characteristic of the 2,4- $\text{C}_2\text{B}_5\text{H}_7$ cage structure. The infrared spectrum has bands indicating C-H, B-H, C-CH₃, and B-CH₃ groups, and the cage vibrational bands are similar to those of known 2,4- $\text{C}_2\text{B}_5\text{H}_7$ derivatives.⁶ Also obtained in the same pyrolysis was 0.012 mmole of a product characterized as a B,C-dimethyl derivative of 2,3,4- $\text{C}_2\text{B}_5\text{H}_7$. The mass spectrum has a high-mass cutoff at m/e 104 and the fragmentation pattern closely matches those of the known derivatives of $\text{C}_2\text{B}_5\text{H}_7$.⁶ Moreover, calculated boron-11 monoisotopic spectra can be fitted to the observed data only when three borons or fewer are assumed. The infrared spectrum contains, in addition to C-H, B-H, and bridge proton bands, absorptions at 1450 and 1320 cm^{-1} which are characteristic of C-CH₃ and B-CH₃ deformations, respectively.

The same starting material (2,3- $(\text{CH}_3)_2\text{C}_2\text{B}_5\text{H}_8$, 0.045 mmole) was heated to 300° for 7 days, after which chromatographic and infrared analyses disclosed the same two products as were obtained at 250° (see above), plus an additional product which is probably 1,7- $(\text{CH}_3)_2\text{-2,4-C}_2\text{B}_5\text{H}_8$. Identification was by means of the mass spectrum (high-mass cutoff at m/e 114) and the infrared spectrum, which contains no C-CH₃ deformation bands but has a very strong absorption at 1320 cm^{-1} , the B-CH₃ deformation frequency. In addition, the cage vibrational region is remarkably similar to that in 1- $\text{CH}_3\text{-2,4-C}_2\text{B}_5\text{H}_8$ (the monoapically substituted derivative),⁶ which is taken as a strong indication that this product is the 1,7 (diapically substituted) derivative.

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Organic and Biological Chemistry

The Chemistry of Methylnorbornyl Cations. I. Introduction and General Survey¹

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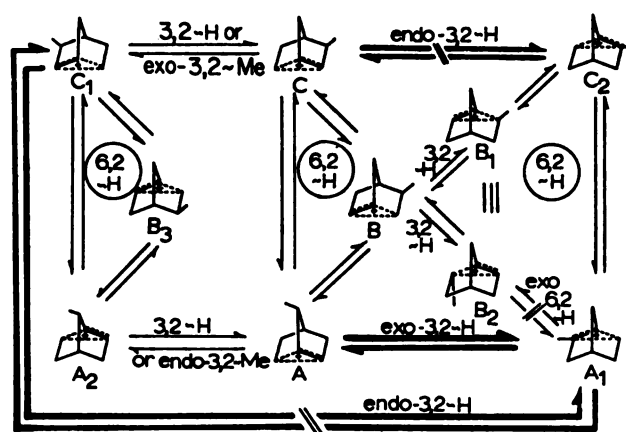
Abstract: A scheme is presented summarizing the structural and mechanistic relationships among the nine methylnorbornyl cations. References are given to the accompanying papers which detail experimental evidence supporting scheme.

In accompanying papers⁴⁻⁸ we report the results of several investigations of the behavior of carbocations of the norbornyl series labeled with methyl. These studies supplement extensive previous work on norbornyl cations⁹ and, in particular, permit discussion of several aspects of the chemistry of these cations not readily visible heretofore. These include: relative rates of vicinal *vs.* transannular hydride shifts, the relative rates of hydride shift and capture by solvent, the stereochemistry of vicinal hydride shifts, and the quantitative evaluation of transition-state effects in solvolysis and product formation. These results bear on the vexatious question of the precise nature (classical *vs.* nonclassical) of the structures of such intermediates and provide experimental evidence that the "windshield-wiper effect" cannot be of all of their special stereochemical behavior¹⁰).

Scheme I is intended as a guide to the complex maze of structural and mechanistic relationships embodied in the work. In the papers that follow, experimental evidence is presented in support of the various parts of the scheme.

Reversions of nine different Wagner-Meerwein rearrangements are involved in Scheme I. The pairs are listed below but for economy of space are shown in nonclassical notation without implication of the electronic structure. (Mechanistically,

Scheme I



ten cations should be considered, but the B₁-B₂ set is structurally and stereochemically degenerate.) At the core of the scheme are the parent cations A, B, and C, which are mutually interconvertible by transannular "6,2"-hydride shifts. On the periphery lies another set of 6,2-hydride shifts which in principle might interconvert six pairs of cations. Access from the core to the periphery (or *vice versa*) is by way of vicinal "3,2"-hydride and/or methyl shifts, which interconvert either a pair of secondary cations (light arrows) or a tertiary with a secondary cation (heavy arrows). The scheme is oversimplified in the sense that additional intermediates describing ion-pair return processes should be included. Although it seems entirely probable that such processes do occur, their influence on the product patterns does not seem to be significant (papers IV, V, and VI⁴⁻⁶).

The cyclic series of rearrangements can be entered *via* solvolyses of several methyl-substituted norbornyl derivatives. The location of the methyl group relative to the positive charge at C-2 in the resulting first intermediate is 3-*endo*:7-*anti* (cation A, paper V⁷), 3-*exo*:7-*syn* (cation C, paper VI⁶), 5-*exo*:5-*endo* (cation B, paper IV⁴), and 6-*exo*:6-*endo* (cation B₁ = B₂, paper IV⁴). Under kinetically controlled conditions, the six products from the inner core set of cations A, B, and C are observed regardless of which entry into the cycle

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National Institutes of Health Predoctoral Fellow, 1964-1966.

II: J. A. Berson, A. W. McRowe, R. G. Bergman, and D. Houston, *Am. Chem. Soc.*, **89**, 2563 (1967).

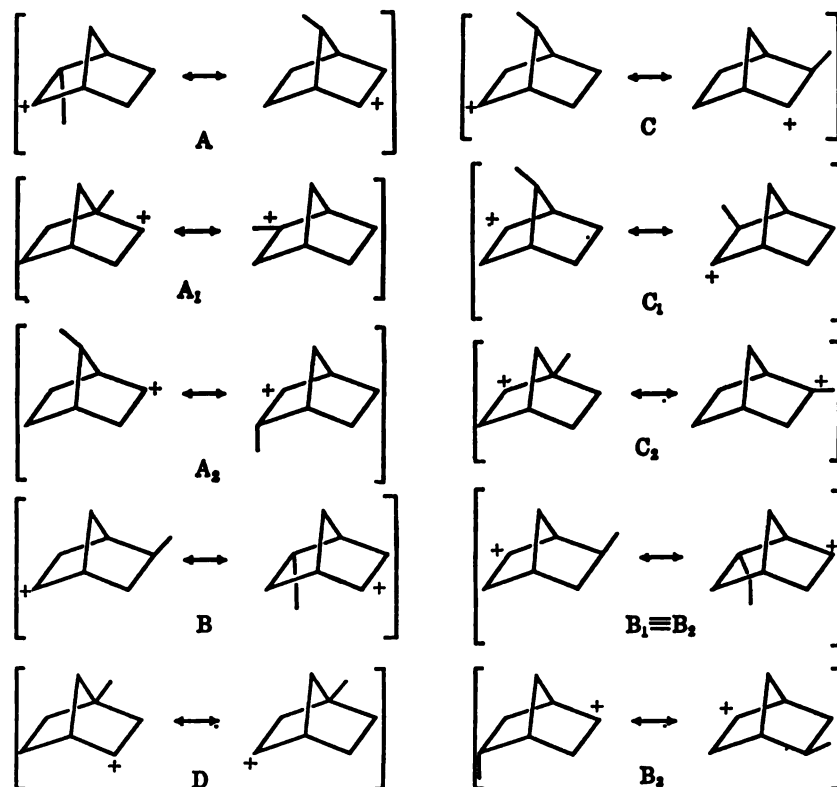
III: J. A. Berson and R. G. Bergman, *ibid.*, **89**, 2569 (1967).

IV: J. A. Berson, A. W. McRowe, and R. G. Bergman, *ibid.*, **89**, 2573 (1967).

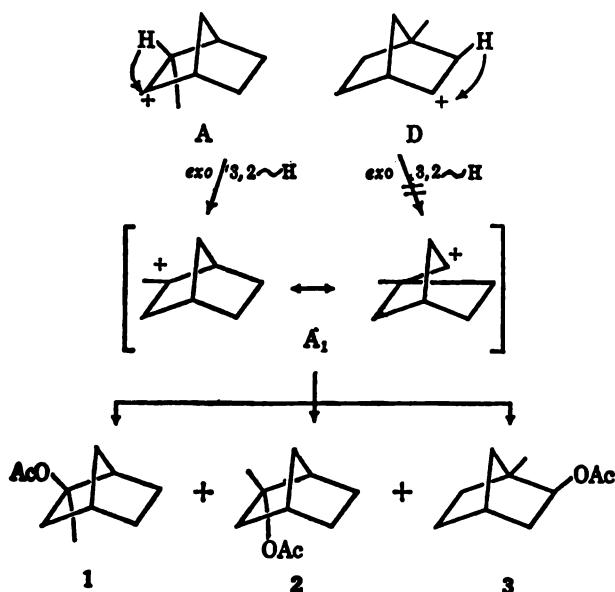
V: J. A. Berson, R. G. Bergman, J. H. Hammons, and A. W. McRowe, *ibid.*, **89**, 2581 (1967).

VI: J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, Allen Remanick, and D. Houston, *ibid.*, **89**, 2590 (1967).

review, see J. A. Berson in "Molecular Rearrangements," H. E. R. May, Ed., Interscience Publishers, Inc., New York, N. Y., 1966.

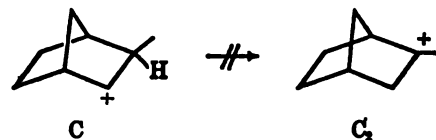


is used. The influence of solvent and point of entry on the distribution of these products gives some information on relative rates of hydride shift and nucleophilic capture. The steric effect of a methyl group in



various positions of the norbornyl system also is elucidated from the product distributions (paper IV⁶). Three additional products, 1, 2, and 3, are observed. These are derived from the vicinal *exo*-hydride shift which

converts secondary cation A to tertiary cation A₁. Vicinal hydride and/or methyl shift which interconverts two secondary ions (B → B₁, C → C₁, A → A₂) is slow. Even the stability associated with tertiary cation A₁ is insufficient to force vicinal hydride shift (D → A₁) when the migrating hydrogen departs from a secondary center (papers IV and V^{6,7}). Direct vicinal shift of an *endo*-hydride, even when tertiary-secondary (C → C₂), does not occur (blocked heavy arrow of Scheme I). Thus, entry into the core cycle at cation C eventually does give products 1, 2, and 3 derived from a tertiary cation, *but only by a circuitous route*. This involves conversion of C to A followed by exit *via* cation A₁, the enantiomer of C₂. The distinction is made on the basis of stereochemical correlations given in papers III,⁵ V,⁷ and VI.⁸



The preference for *exo*-3,2-hydride shift is not attributable to a large thermodynamic bias favoring cation A over cation C but rather to an intrinsically faster rate for *exo* than for *endo* migration (paper VI⁸). This behavior is consistent with the formulation of the cationic intermediates with nonclassical structures.

The Chemistry of Methylnorbornyl Cations. II. Sources and Identification of Sixteen of the Methylnorbornanols¹

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Contribution from the Departments of Chemistry, University of Wisconsin, Madison, Wisconsin, and the University of Southern California, Los Angeles, California. Received October 31, 1966

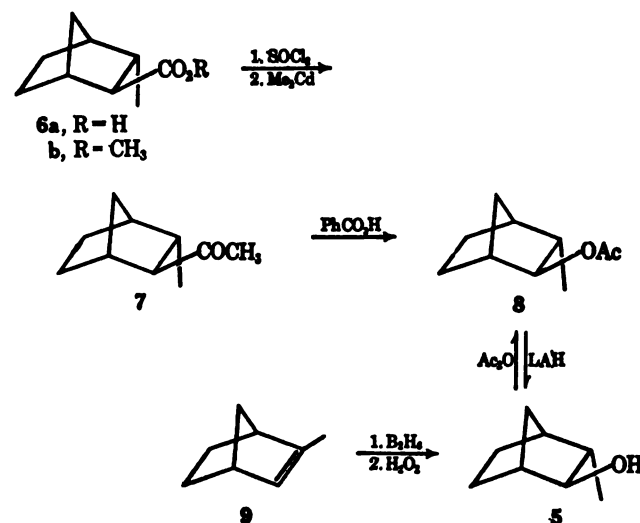
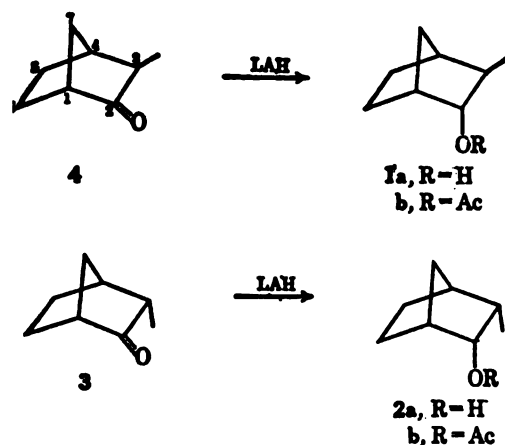
Abstract: Structures are assigned to 16 of the methylnorbornanols by a variety of methods including independent syntheses, structural interconversions, and proton magnetic resonance spectroscopy. The substances involved are the four 3-methyl-2-norbornanols, the four 5- and 6-methyl-2-*exo*-norbornanols, the two 7-methyl-2-*exo*-norbornanols, the two 1-methyl-2-norbornanols, the two 1-methyl-3-norbornanols, and the two 2-methyl-2-norbornanols.

In connection with studies of methyl-labeled norbornyl cations,⁴ it was necessary to be able to identify the methylnorbornanols. Since some of these compounds were unknown when this work was begun, the literature did not provide strong assignments for them, and therefore, we set out to acquire the needed information. This paper presents the results.

Four 3-Methyl-2-norbornanols. Both of the previously known stereoisomers of 3-methyl-2-norbornanol, **2a**, have an *endo* hydroxyl and differ only in the position of the methyl group. The configurations assigned^{5,6} on the following grounds. The *cis-endo* and **2a** and the 3-*exo*-methyl isomer **1a** were the products of the lithium aluminum hydride reduction of 3-*endo*- and 3-*exo*-methyl-2-norbornanone (**3** and **4**, respectively).⁶ We confirm this in the case of ketone **4** which gives 86.6% **1a** and 13.4% *cis-exo* isomer (**10**). Analogous results to other examples of such reactions with unsubstituted norbornanones⁷ suggested that

attack from the *exo* direction would be preferred. Further, of the two alcohols then known, the one derived from **4** showed the larger cryoscopic molecular weight exaltation and was thus the less hindered, as would be expected for the *trans* member of a *cis-trans-endo* pair.^{5,6}

Syntheses of the two remaining members of the series provide confirmation of the assignments. The other *trans* isomer **5** is obtained by two routes, first by the "acid → acetate" sequence from the known^{8,9} 3-*endo*-methyl-2-*exo*-norbornanecarboxylic acid (**6a**), and also by hydroboration-oxidation^{8b} of 2-methyl-2-norbornene (**9**).⁹ The second procedure is more easily



adapted to the preparation of substantial quantities of alcohol **5**, since the requisite olefin **9** is readily available, and the hydroboration-oxidation step, in accord with previous experience,^{8b} proceeds quite cleanly in an *exo-cis* anti-Markovnikov manner. The crude product is 94% **5** and is readily purified to the level of 99% or better by a single pass through an automatic preparative gas chromatograph.

The *cis-exo* acetate **10** is obtained as a side product in the Baeyer-Villiger oxidation of 3-*exo*-methyl-2-*endo*-acetylnorbornane (**11**), which in turn is preparable

(8) (a) Syntheses of several methyl esters and carboxylic acids needed as reference compounds in the 3-methyl-2-norbornane and 3-methyl-5-norbornene-2-carboxylic acid series are described in the Experimental Section. (b) Cf. H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(9) K. Alder and H. J. Ache, *Chem. Ber.*, **95**, 503, 511 (1962).

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To whom inquiries should be directed; (b) University of Wisconsin; (c) University of Southern California.

National Institutes of Health Predoctoral Fellow, 1964-1966. Part I of this series: J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Am. Chem. Soc.*, **89**, 2561 (1967), and following papers.

Beckmann, A. Dürkop, R. Bamberger, and R. Mezger, *Ann.*, **475**, 1 (1955).

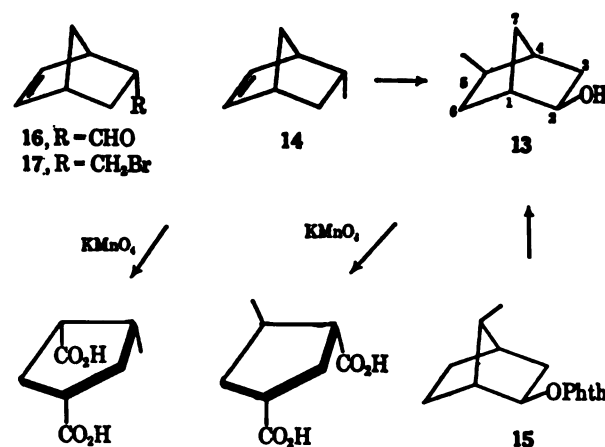
Beckmann and R. Mezger, *Chem. Ber.*, **90**, 1559, 1564 (1957).

For a review and summary of references, see J. A. Berson in *Allyl Rearrangements*, Part 3, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963.

from the known⁶ 3-*exo*-methyl-2-*endo*-carboxylic acid (12). Oxidation with perbenzoic acid is slow, but no epimerization occurs, and 3-*exo*-methyl-2-*endo*-norbornyl acetate (1b) is obtained free of 10. Although oxidation with peroxytrifluoroacetic acid is faster, epimerization now becomes noticeable, and isolable quantities of the *cis*-*exo* acetate 10 are formed. This substance is also the minor component of the mixture obtained by acetylation of the lithium aluminum hydride reduction product from 3-*exo*-methyl-2-norbornanone (4).

The configurational assignments are confirmed by the nuclear magnetic resonance (nmr) spectra. In the acetates, the C-2 proton resonance occurs in a readily identifiable region about 4.5 ppm downfield from tetramethylsilane. The spectrum of the *cis*-*endo* acetate 2a shows this resonance as a doublet of doublets with $J \cong 5$, 4 cps; that of the *cis*-*exo* acetate 10 shows a broadened doublet, $J = 7$ cps. The pattern in the 2a spectrum is consistent with moderately strong coupling between the C-2 proton and both the C-3 and C-1 protons, as has been observed with many other C-2 *exo* protons in analogous systems.¹⁰ In 10, however, the C-2 *endo* proton is strongly coupled only to the *cis*-*endo* proton at C-3 and weakly or not at all to the bridgehead C-1 proton, again in accord with experience.¹⁰ Although we have made no real attempt to identify it, the additional weak coupling that produces the slight broadening of the components of the C-2 multiplet (3.5 cps width at half-height) probably is attributable to long-range splitting, perhaps with the *anti*-7 proton.¹⁰ This interpretation is supported by the absence of such broadening in 7-*anti*-methyl-2-*exo*-norbornyl acetate, the C-2 spectrum of which shows a doublet of doublets with widths at half-height of <1 cps for each component. The spectrum of the *trans* compound 1a, with a C-2 *exo* proton, shows a doublet of doublets, $J \cong 3.5$, 3.5 cps. These splittings are about the same as those previously observed for C-1 to *exo* C-2 and *trans* C-2 to C-3 couplings,¹⁰ in agreement with the assigned stereochemistry. In the spectrum of *trans*-acetate 8, with a C-2 *endo* proton, one sees a poorly resolved doublet of doublets, in accord with the expected relatively weak long-range and *trans*-vicinal couplings.¹⁰

The 5- and 6-Methyl-2-*exo*-norbornanols. Esters of an alcohol assigned the structure 5-*exo*-methyl-2-*exo*-norbornanol (13) were isolated from formic acid or acetic-sulfuric acid treatment of a hydrocarbon assigned the structure 5-*endo*-methylnorbornene (14)¹¹ and from formolysis of *syn*-7-methyl-2-*exo*-norbornyl acid phthalate (15).¹² Oxidation of 13 and 14 gave two different 4-methylcyclopentane-*cis*-1,3-dicarboxylic acids.¹² The possibility that the alcohol was a 6-methyl derivative was excluded on the grounds that its formation from 15 would require a vicinal secondary-secondary hydride shift, which had been sought for and not found in the parent norbornyl system.¹³ The *exo* configuration for the hydroxyl group was assigned¹² on the basis of the observed facile further rearrangement of the alcohol in formic acid. These arguments,



while plausible, are not completely convincing. The exclusion of the 6-methyl possibility seems less than absolute, since it now is quite probable¹⁴ that vicinal secondary-secondary shift, although slow, does occur in formic acid, especially under equilibrating conditions. The assignment of the *exo* stereochemistry to the methyl group of 13 depends critically on the assignment of the *endo* stereochemistry to the hydrocarbon 14. Otherwise, the argument is circular, for internally, the oxidation-hydration scheme merely demonstrates that the alkene and the alcohol are Wagner-Meerwein related and would apply equally well to the *exo*-methyl-norbornene-*endo*-methyl alcohol pair. The assignment of stereochemistry to the hydrocarbon 14 rests entirely on the application of the Alder rule of *endo* addition to the precursors (the cyclopentadiene adducts 16 and 17) used for its preparation.¹¹ Since the rule is frequently violated,¹⁵ independent evidence for the assignments of stereochemistry seems desirable.

Stereochemically homogeneous *endo*- and *exo*-2-methyl-5-norbornenes (14 and 18) can be prepared from the corresponding known^{16,17a} carboxylic acids by a reduction-arenesulfonylation-reduction sequence.^{17b} Hydroboration of each leads to a pair of alcohols. Although the pair from 2-*exo*-methyl-5-norbornene (18) can be analyzed by capillary gas chromatography, preparative separation is difficult. However, the two alcohols from the *endo* olefin 14 are readily separable by preparative gas chromatography. In this way, 5-*endo*-methyl-2-*exo*-norbornanol (19) and 6-*endo*-methyl-2-*exo*-norbornanol (20) are obtained in pure form. Conversion of 19 and 20 to *p*-bromobenzenesulfonates (19-OBs and 20-OBs) and solvolyses of the latter¹⁸ under nonequilibrating conditions establish the identities of the entire series. Thus, 19-OBs gives 19, 21, and the characteristic products derived from the complex series of transannular hydride shifts and Wagner-Meerwein rearrangements summarized in the scheme given elsewhere,¹⁹ but does not give any 20 or

(14) C. C. Lee and L. K. M. Lam, *ibid.*, **88**, 5355 (1966), and references cited therein.

(15) J. A. Berson, Z. Hamlet, and W. A. Mueller, *ibid.*, **84**, 297 (1962).

(16) C. D. Ver Nooy and C. S. Rondestvedt, Jr., *ibid.*, **77**, 3583 (1955).

(17) (a) Cf. J. A. Berson and D. A. Ben-Efraim, *ibid.*, **81**, 4083 (1959); (b) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *ibid.*, **83**, 3986 (1961).

(18) Paper IV of this series: J. A. Berson, A. W. McRowe, and R. G. Bergman, *ibid.*, **89**, 2573 (1967).

(19) Paper I of this series.⁴

(10) J. C. Davis, Jr., and T. V. Van Auken, *J. Am. Chem. Soc.*, **87**, 3900 (1965), and references cited therein.

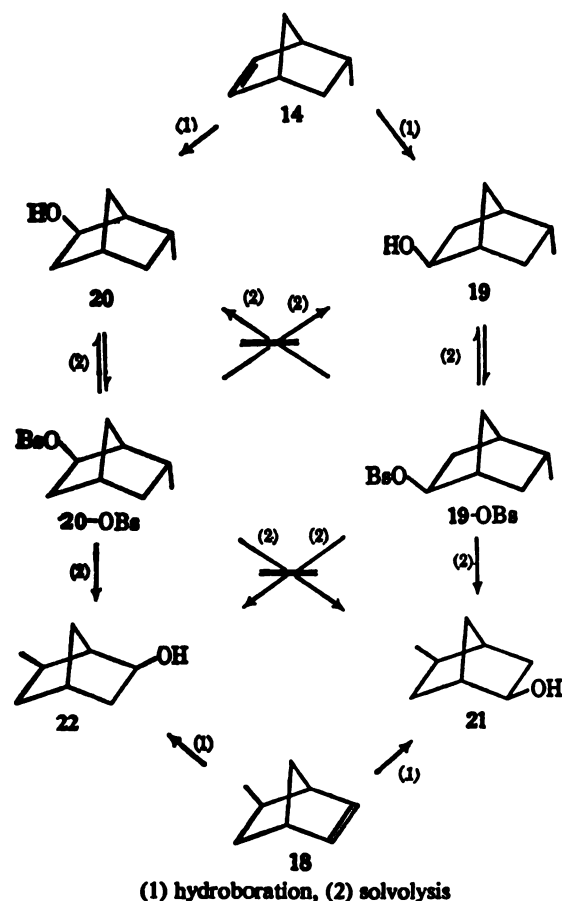
(11) S. Beckmann and R. Schaber, *Chem. Ber.*, **88**, 1703 (1955).

(12) S. Beckmann and G. Eder, *ibid.*, **91**, 2878 (1958).

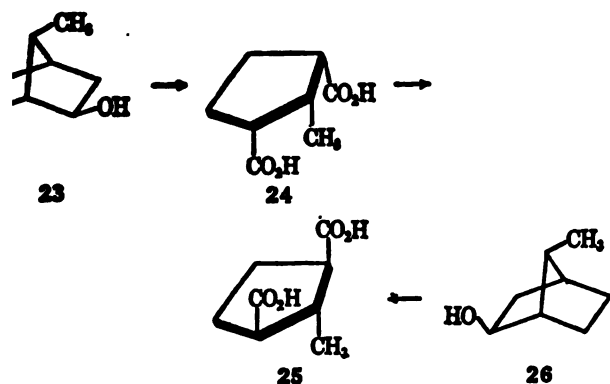
(13) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).

whereas 20-OBs, being blocked from that mechanism by the barrier to secondary-secondary vicinal hydride shift, merely regenerates 20 and the Wagner-Meerwein related 22 in addition to tertiary product in 6,2 shift.¹⁸ The data combined with the reasonable assumption that these kinetically controlled solvolyses give *exo* products⁷ are consistent with only one nulation, which is shown in Scheme I.

Scheme I



3-Methyl-2-*exo*-norbornanols. Deaminative nitration of 3-*exo*-methyl-2-*endo*-norbornylamine was expected to give a complex mixture of products. Fractional crystallization of the acid phthalate and saponification gave an alcohol "isoaposenol," which was assigned the structure *syn*-7-methyl-2-*exo*-norbornanol.²⁰ The location and stereochemistry of the methyl

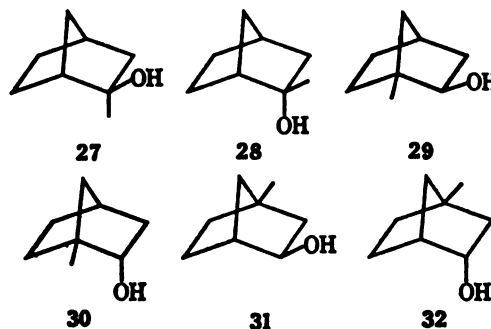


up at C-7 were established by oxidation to "isoaposenic acid" (24), which was not identical with but was

(19) G. Komppa and S. Beckmann, *Ann.*, 523, 68 (1936).

epimerizable to an acid "cis-aposenic acid," 25, prepared by structurally unquestionable synthesis and shown to have *cis*-carboxyl groups. If the less stable of the two acids is the "all-*cis*" form 24, then "isoaposenol" is 23. The *anti* isomer 26 was never isolated pure,²⁰ but its presence in the deamination mixture from 3-*endo*- and/or -*exo*-methyl-2-*endo*- and/or -*exo*-norbornylamine was inferred from the isolation of "cis-aposenic acid" (25) from the oxidation of a fraction of the mixed alcohols obtained by combining reaction products from both amines. Although a detailed reexamination of the deaminations is reported elsewhere,¹⁸ we note here merely that alcohol 26 is formed in substantial quantity from the 3-*endo*-methyl-2-*exo* amine and also (as the acetate) from acetolysis of the corresponding arenesulfonates. It can readily be isolated in pure form by preparative vapor chromatography.¹⁸ The structure assigned is supported on the circumstantial grounds that 26 formed by carbonium ion process is invariably accompanied by an approximately equal amount of its Wagner-Meerwein relative 3-*endo*-methyl-2-*exo*-norbornanol (5).¹⁸ Also, the nmr spectrum of the acetate of 26 shows a sharp doublet ($J = 7$ cps) at δ 0.9 (superimposed on diffuse absorption), attributable to the C-7 methyl group, and a clean doublet of doublets centered around δ 4.5, attributable to the *endo*-C-2 proton coupled with the appropriate¹⁰ coupling constants ($J_{2,3 \text{ trans}} = 3$ cps, $J_{2,3 \text{ cis}} = 7$ cps) to the C-3 *exo* and *endo* protons, respectively. The absence of further splitting ($J \cong 1$ cps)¹⁰ of this multiplet is consistent with the absence of a 7-*anti* proton. Further, chemical evidence for the structure is provided by a number of transformations.²¹

1- and 2-Methyl-2-norbornanols and 1-Methyl-3-norbornanols. The 2-methyl-2-norbornanols 27 and 28 and the 1-methyl-2-norbornanols 29 and 30 are well known,^{6,12,22} and require no further comment. 1-



Methyl-3-*exo*-norbornanol (31) is formed together with 1-methyl-2-*exo*-norbornanol (29) in the hydroboration of 1-methyl-2-bornornene. The epimer 1-methyl-3-*endo*-norbornanol (32) is obtained in a mixture with 31 by oxidation of 31 and hydride reduction of the derived ketone.

Experimental Section²³

Vapor chromatographic (vpc) analyses were performed with capillary columns on Barber-Colman gas chromatographs,

(21) Paper III: J. A. Berson and R. G. Bergman, *J. Am. Chem. Soc.*, 89, 2569 (1967).

(22) N. J. Toivonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fennicae, Ser. AII*, No. 64 (1955).

(23) Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Models 61-C and 5000, using argon carrier gas and radium or tritium ionization detectors. Column stationary phases were TCEP (tri- β -cyanoethoxypropane, 250 ft) (column L) and two polypropylene glycol columns (Ucon 50-HB-2000, 100 and 250 ft) (columns M and N). Preparative vpc separations were accomplished with Wilkens (now Varian) Aerograph Models A-90-P and A-700 Autoprep instruments equipped with thermal conductivity detectors and using helium carrier gas. Tricyanoethoxypropane (TCEP) stationary phase as obtained commercially always contained impurities which showed infrared absorption at 2.7–3.1 and 5.9–6.3 μ . Although good packed columns could be prepared with this material, it was unsuitable for capillary work, since columns prepared from it bled excessively and had short useful lifetimes. The TCEP was purified by percolation (as a solution in pure methylene chloride) through Woelm alumina, basic, activity grade III. The material so prepared gave relatively durable capillary columns. Table I lists the packed and capillary columns used in this work.

Table I. Vapor Chromatographic Columns

Column	Substrate	Dimensions, mm \times m	Substrate, %	Chromosorb/Type	Mesh
Packed columns					
A	TCEP ^a	9.5 \times 6	20	P	45–60
B	TCEP	6.5 \times 3	25	P	60–80
C	TCEP	22.5 \times 5	25	P	60–80
D	Ucon ^b	9.5 \times 6	30	W	60–80
D-1	Ucon	6.5 \times 4	20	P	60–80
E	Carbowax ^c	9.5 \times 6	20	P	60–80
F	Carbowax	9.5 \times 3.5	30	W	60–80
G	Carbowax	6.5 \times 2	20	P	45–60
G-1	Carbowax	9.5 \times 6	25	P	60–80
G-2	Carbowax	6.5 \times 9	20	P	60–80
H	DC-200 ^d	9.5 \times 6	25	P	60–80
H-1	SF-96 ^e	6.5 \times 0.8	20	P	60–80
J	FFAP ^f	9.5 \times 6	30	W	60–80
K	FFAP	6.5 \times 2	20	W	60–80
Capillary columns					
L	TCEP	0.25 \times 80
M	Ucon	0.25 \times 30
N	Ucon	0.25 \times 80
N-1	Ucon	0.25 \times 90
O	DC-200	0.25 \times 50

^a Tri- β -cyanoethoxypropane. ^b Union Carbide polypropylene glycol. ^c Union Carbide polyethylene glycol. ^d Dow-Corning silicone oil. ^e Wilkens Aerograph "free fatty acid phase." ^f Johns-Manville diatomaceous silica.

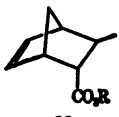
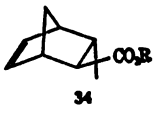
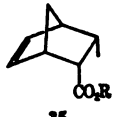
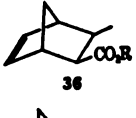
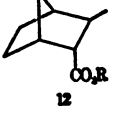
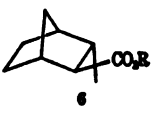
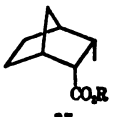
Proton magnetic resonance spectra (nmr) were obtained with a Varian Associates A-60 instrument. Samples of about 50 mg were dissolved in 250 μ l of carbon tetrachloride containing tetramethylsilane as internal standard, and resonance positions are reported in parts per million downfield from tetramethylsilane (δ units). The J values reported are approximate multiplet spacings which in some but not all cases are the same as true coupling constants.

Infrared spectra of neat films (unless otherwise indicated) were taken with the Perkin-Elmer Model 137 or Beckman Model IR-8 instruments.

A number of carboxylic acids and the corresponding methyl esters were prepared for use as reference compounds in this work. Some of the acids but none of the esters had been previously reported. Analytical data for the esters and a new acid 35 are given in Table II. The table also lists melting points for the previously known acids, which were prepared by literature procedures. The methyl esters were prepared by the action of ethereal diazomethane on the acids followed by bulb-to-bulb distillation. They were homogeneous by capillary vpc.

3-endo-Methyl-2-endo-carbomethoxy-5-norbornene (35, R = CH₃) was obtained in the following manner. A crude acidic fraction was derived from mother liquors from the preparation of 3-exo-methyl-5-norbornene-2-endo-carboxylic acid (33, R = H) by zinc reduction of the corresponding iodolactone.⁸ This material was treated with diazomethane to give a mixture of 33, 34, and 35 (R = CH₃) in proportions that varied with the purity of the iodolactone starting material and the amount of 33 (R = H) removed in

Table II. Properties of Some Acids and Esters

	— Mp, °C — Acid, R = H	Lit. ^a	Me ester, R = CH ₃ , Found, ^b % C	H
	91–93	95	72.05	8.57
	59–61	61–62	71.96	8.42
	120.5–121 ^d	...	72.26	8.44
	c	
	67.5–69	68–69	71.36	9.64
	44–45	40–41	71.59	9.77
	71.33	9.75

^a References 6 and 20. ^b Anal. Calcd for C₁₀H₁₆O₂: C, 72.26; H, 8.49. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. ^c Identified by retention time; not isolated. ^d Anal. Calcd for C₉H₁₄O₂: C, 71.03; H, 7.95. Found: C, 70.91; H, 7.96.

the crystallization. Preparative vpc on column H, afforded pure 35 (R = CH₃), homogeneous by capillary vpc under conditions where 33 and 34 were cleanly detectable. The retention times on both capillary columns were identical with those of the minor component of the 96:4 two-component mixture produced by epimerization of 34 (R = CH₃) in boiling methanol-sodium methoxide for 3 hr. The nmr spectrum showed a methyl doublet (J = 7 cps) at δ 0.75, a methoxyl singlet at 3.55, a complex series of multiplets between 1.3 and 2.9 (6-proton intensity), and a 2-proton signal in the olefinic region centered near 6.15 as a pair of four-line multiplets separated by 17 cps, J = 3 cps. The corresponding acid, 35 (R = H), was obtained in small yield by saponifying the ester with aqueous methanolic sodium hydroxide and recrystallizing the resulting product from acetonitrile. The corresponding saturated ester, 37 (R = CH₃), was isolated by preparative vpc on column H.

The *exo-cis* unsaturated ester 36 (R = CH₃) was obtained only in admixture with the *trans* form 33 by epimerization of the latter.

The TCEP capillary column separated the four unsaturated esters in the following order of elution: 34, 33, 35, 36.

3-*exo*-Methyl-2-*endo*-acetylnorbornane (11). Pure, racemic 3-*exo*-methyl-2-*endo*-norbornanecarboxylic acid (12), 27.0 g (0.24 mole), was treated with 35 ml of freshly distilled thionyl chloride for 10 hr at room temperature. The excess reagent was distilled off and the acid chloride distilled at 86–87° (20 mm) to yield 39.6 g of product (96%).

Dimethylcadmium reagent was prepared by adding 60 g (0.63 mole) of dry methyl bromide to 13.5 g (0.55 g-atom) of magnesium turnings in 400 ml of ether, letting the Grignard reagent stand 3 hr, and then adding with cooling 58 g (0.32 mole) of anhydrous cadmium chloride and allowing the mixture to stir for 2 hr at room temperature.

cadmium reagent was cooled to -5° , and the acid chloride ml of ether was slowly added dropwise with efficient stirring to maintain a temperature below $+5^{\circ}$. After 2 hr at room temperature, the mixture was poured onto dilute hydrochloric acid and the separated ether layer was washed successively with saturated sodium bicarbonate solution, and saturated brine, over sodium sulfate, and carefully concentrated through a fractionation column. The residue distilled at $92.0-92.5^{\circ}$ (n) to give 27.9 g (80%) of clear, colorless liquid. The products homogeneous on both capillary columns.

l. Calcd for $C_{10}H_{14}O$: C, 78.90; H, 10.59. Found: C, 78.90; H, 10.60.

Semicarbazone was recrystallized from 95% ethanol; it had $7-178^{\circ}$.

l. Calcd for $C_{11}H_{15}N_2O$: C, 63.13; H, 9.15. Found: C, 63.13; H, 9.11.

2,4-dinitrophenylhydrazones were recrystallized from aqueous alcohol to give orange-yellow plates, mp $114-115^{\circ}$.

l. Calcd for $C_{14}H_{15}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.95; H, 6.09; N, 16.87.

o-Methyl-2-endo-acetoxynorbornane (1b). Method A. A form solution of peroxybenzoic acid was prepared in the manner,²⁴ with the exception that the suggestion of Vilkas²⁴ was followed. This modification involved addition of the basic solution of the peracid to the aqueous acid prior to the chloroform extraction. In this manner, there was always excess acid present, and the decomposition of the half-neutralized solution was avoided. Titrimetric assay indicated yields greater than 95% were typical.

1.46 g (29.3 mmoles) of pure ketone 11 was added to 6.1 g (50%) of peroxybenzoic acid in 130 ml of chloroform. The mixture was stoppered and stored in darkness at room temperature for 3 days. Assay of an aliquot indicated that 10% of the original ketone activity remained. Enough 10% sodium bisulfite solution was added to give a negative starch-iodide test. The organic layer was washed with 50 ml of 1 *N* sodium hydroxide solution, with 50 ml of saturated sodium bicarbonate solution, and with saturated brine; it was dried twice over sodium sulfate. The solvent was fractionated off, and the pale yellow residue was distilled at $75.0-75.5^{\circ}$ (7 mm). Another fraction distilled over at $76.0-76.5^{\circ}$ (1 mm). Both were clear and colorless. The first fraction (7 g (74%)) of a mixture analyzing on the Ucon capillary column as 94% of the desired acetate (1b) and 6% of the starting ketone 11. The second component, 1.0 g, contained only 3% of the desired acetate, the remainder being condensation products. The fraction contaminated with 6% of the ketone was distilled on column C and distilled bulb to bulb at reduced pressure to give pure 1b homogeneous on the Ucon capillary column. The nmr spectrum showed $COCH_3$, δ 1.96, singlet; $CHCH_3$, δ 1.03, doublet, *cis*; C-2-*exo*-H, δ 4.31, doublet of doublets, *J* \approx 3 cps, *trans* at half-height.

l. Calcd for $C_{10}H_{14}O_2$: C, 71.39; H, 9.58. Found: C, 71.39; H, 9.59.

Methyl ester 12 ($R = OCH_3$) that would have resulted from migration instead of the observed ring migration was cleanly separated on columns L and N and was shown to be completely different from the reaction mixture. Likewise, the presence of the *cis-exo* acetate 10 could have been detected, but was not detected.

Method B. Methyl ketone 12, 38.0 g (0.25 mole), with less than 1% ionic contamination was dissolved in 780 ml of methylene chloride and 147 g (1.04 mole) of sodium monohydrogen phosphate added. Peroxytrifluoroacetic acid prepared²⁴ from 10.9 g (0.25 mole) of 90% hydrogen peroxide, 99 ml (0.46 mole) of acetic anhydride, and 130 ml of methylene chloride was added to the ketone mixture with stirring at a rate sufficient to maintain a modest reflux rate. There was considerable evolution of gas, and the odor of ozone was prominent. Stirring and reflux maintained for 6 hr after the stiff foam and gas evolution subsided a total of 24 hr. The mixture was then cooled, and 450 ml of water was added to completely dissolve the buffer salts.

The organic layer was drawn off and the aqueous phase was washed twice with more solvent. The combined organic layers were washed with saturated brine and dried over two successive portions of sodium sulfate. The solution was carefully con-

centrated and the residue distilled through a 300×7 mm tantalum wire spiral column at 16 mm. The main fraction distilled at $95-97^{\circ}$ and amounted to 34.8 g (82.8%). The second fraction, 10.4 g, boiled over a considerable temperature range. This material was not investigated further; it contained less than 5% of the desired product as determined by capillary vpc. The major fraction consisted mainly of the acetate 1b contaminated with several impurities; 1.5% starting ketone, ca. 0.5% of material presumed to be trifluoroacetate (infrared absorption 5.57μ), and smaller amounts of three other acetates. This material was not further purified but directly converted to the alcohol.

When a large-scale run of the oxidation of ketone 11 was carried out by method B in the optically active series,²⁷ the distilled acetate product contained 10% of a compound which was isolated by preparative vpc on column D. It emerged shortly after acetate 1b and was reprocessed to achieve purification to capillary vpc homogeneity. The new material was assigned the structure 3-*exo*-methyl-2-*exo*-norbornyl acetate (10) on the grounds given in the Discussion.

3-*exo*-Methyl-2-*endo*-norbornanol (1a). Acetate 1b, prepared by method A (after chromatographic purification), gave pure alcohol 1a in high yields on reduction with lithium aluminum hydride. No contamination was noted on either capillary column. Pure alcohol 1a from the acetate could be obtained more quickly by reduction of the product mixture and separation of the alcohol mixture, utilizing the greater separation of the alcohols for larger injections on columns C or A. Alcohol obtained similarly from acetate of method B contained about 2% of several impurities on column N and was most easily purified in the racemic series by conversion to the acid phthalate, mp $126.5-128.0^{\circ}$ (lit.⁴ mp $131-132^{\circ}$).

The *p*-toluenesulfonate of alcohol 1a, recrystallized from absolute methanol, yielded white needles, mp $43-44^{\circ}$.

Anal. Calcd for $C_{11}H_{17}O_2S$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.17.

The *p*-bromobenzenesulfonate, recrystallized from absolute methanol or hexane, melted at $101-102^{\circ}$.

Anal. Calcd for $C_{14}H_{17}O_2BrS$: C, 48.70; H, 4.96; Br, 23.14. Found: C, 48.71; H, 4.95; Br, 23.25.

The *p*-nitrobenzenesulfonate, prepared from alcohol 1a of low optical activity, gave light yellow crystals on recrystallization from absolute ethanol, mp $104-106^{\circ}$.

Anal. Calcd for $C_{14}H_{17}O_4NS$: C, 54.01; H, 5.50; N, 4.50. Found: C, 54.03; H, 5.66; N, 4.52.

3-*endo*-Methyl-2-*exo*-acetylnorbornane (7). Pure, racemic acid 6a was converted to its acid chloride and the acid chloride to the ketone 7 via the dimethylcadmium reagent as in the *endo* series. The distilled acid chloride, bp $95-96^{\circ}$ (17 mm), was prepared in 97% yield from thionyl chloride. The ketone 7 isolated in 75% yield from the acid chloride contained several small impurities as detected on capillary column L. The higher boiling residue, amounting to about 20% of the expected yield, distilled readily at 120° (3 mm) to give a mixture of material which, to judge by its infrared spectrum, contained aldol condensation products (ketol and α,β -unsaturated ketone).

The semicarbazone was recrystallized from 95% ethanol, mp $184-185^{\circ}$ dec.

Anal. Calcd for $C_{11}H_{17}ON_2$: C, 63.13; H, 9.15. Found: C, 63.27; H, 9.24.

Ketone 7 was obtained homogeneous on capillary vpc (columns L and N) from the semicarbazone by hydrolysis in warm 20% aqueous sulfuric acid, immediate steam distillation, pentane extraction, drying over calcium sulfate, and concentration. Distillation through a short Vigreux column yielded solvent-free material, bp $94.5-95.0^{\circ}$ (22 mm). This material was identical in every respect with a small sample of material purified by preparative vpc on column A.

Anal. Calcd for $C_{10}H_{14}O$: C, 78.90; H, 10.59. Found: C, 78.88; H, 10.57.

The 2,4-dinitrophenylhydrazone, mp $119.5-120.0^{\circ}$ from methanol, had mp $103-106^{\circ}$ when admixed with that of ketone 11.

Anal. Calcd for $C_{14}H_{15}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.88; H, 6.05; N, 16.95.

3-*endo*-Methyl-2-*exo*-norbornyl Acetate (8). Pure, racemic ketone 7, 6.0 g (39.4 mmoles), was oxidized with two portions of excess perbenzoic acid in chloroform over 5 days at room temperature.

G. Braun, "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1941, p 431.

M. Vilkas, *Bull. Soc. Chim. France*, 1401 (1959).

M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Am. Soc.*, **80**, 6393 (1958).

(27) Cf. paper VI: J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *ibid.*, **89**, 2590 (1967).

The oxidation also was achieved with *m*-chloroperbenzoic acid in methylene chloride. The material was worked up as in the *endo* series (method A). The crude residue contained no starting ketone. The acetate was distilled at 76–77° (7 mm) to give a colorless liquid, homogeneous by capillary vpc (column L), in 79% yield. Infrared spectrum and vpc retention times were identical with the material obtained by hydroboration of 2-methyl-2-norbornene, oxidation, and acetylation. The latter is the more convenient method for obtaining either racemic or optically active acetate 8. The nmr spectrum showed bands for COCH₃, δ 1.93, singlet; CHCH₃, δ 1.04, doublet, *J* = 7 cps; C-2-*endo*-H, δ 3.96, doublet of doublets, *J* ~ 2.5, 2.5 cps.

Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.17; H, 9.44.

From Hydroboration of 2-Methyl-2-norbornene (9). A three-necked round-bottomed flask equipped with a magnetic stirring apparatus was charged with 22.5 g of 2-methyl-2-norbornene,⁹ 3.70 g of sodium borohydride, and 150 ml of tetrahydrofuran (THF), distilled from LiAlH₄ before use. A solution of 16.7 ml of boron trifluoride etherate (freshly distilled) dissolved in 50 ml of THF was then added dropwise to the flask, with rapid stirring. A white precipitate formed during the addition. After the resulting mixture had been stirred overnight, it was cooled to –5° in an ice-salt bath, and 5 ml of water was slowly added, followed by 50 ml of a 10% aqueous solution of sodium hydroxide. The flask was then allowed to warm to room temperature while 55 ml of a 30% aqueous solution of hydrogen peroxide was added dropwise with stirring.

After the resulting two-phase mixture had been stirred for 3 hr, the phases were separated, and the aqueous layer extracted twice with pentane. The combined organic phases were washed three times with a 10% aqueous solution of sodium hydroxide and once with a solution of saturated NaCl, and dried overnight over solid sodium sulfate. The liquid was then decanted and the pentane carefully removed by distillation through a Vigreux column on a steam bath, leaving 25.1 g (96%) of alcohol as a slightly greenish oil which slowly solidified into a gummy mass. The alcohol was converted to 3-*endo*-methyl-2-*exo*-norbornyl acetate in the usual way and the acetate distilled bulb to bulb to give a water-white, sweet-smelling oil which had an infrared spectrum and vpc retention time identical with those of the acetate obtained as above from 3-*endo*-methyl-2-*exo*-acetylnorbornane. The acetate obtained from the hydroboration route was contaminated with about 6% of presumably isomeric materials. It could be purified by automatic chromatography (Wilkens A-700 "Autoprep" instrument) on column E; by this procedure it was obtained 99.0% pure after one pass, as determined by analysis on capillary columns L and N-1.

3-*endo*-Methyl-2-*exo*-norbornanol (5). The purified 3-*endo*-methyl-2-*exo*-norbornyl acetate (8) described above was reduced to the corresponding alcohol (5) with lithium aluminum hydride in the standard way. The alcohol was again obtained as a semisolid which was sublimed at 120° (15 mm) to give fine, white crystals, mp 95.5–97.0°.

Anal. Calcd for C₉H₁₄O: C, 76.14; H, 11.18. Found: C, 76.14; H, 11.25.

3-*endo*-Methyl-2-*exo*-norbornyl acid phthalate was obtained after two recrystallizations from heptane as a white powder, mp 89.5–90.0°.

Anal. Calcd for C₁₈H₁₈O₄: C, 70.06; H, 6.61. Found: C, 70.20; H, 6.57.

3-*endo*-Methyl-2-*exo*-norbornyl *p*-toluenesulfonate was formed when 0.79 g of the alcohol in 3 ml of pyridine was stirred at 0° and treated portionwise with 1.20 g of solid *p*-toluenesulfonyl chloride (freshly recrystallized from carbon tetrachloride). After 4 days at 5°, the mixture was poured onto cracked ice and extracted with ether. The ether solution, after thorough washing with water and brine, was dried over sodium sulfate, decanted, and evaporated. The residue was dried *in vacuo* (0.1 mm for 3 hr) to give 1.50 g (84%) of a solid which, after four recrystallizations from heptane, had mp 58.8–59.8°.

Anal. Calcd for C₁₇H₁₈O₃S: C, 64.26; H, 7.19; S, 11.44. Found: C, 63.98; H, 7.06; S, 11.31.

The corresponding *p*-bromobenzenesulfonate was obtained by a procedure which differed only in that the reaction mixture was stored in the cold for only 36 hr. The compound was obtained as white crystals, mp 71–72°, from heptane; it was moderately stable at –5° but decomposed to a black, intractable semisolid on standing overnight at room temperature.

Anal. Calcd for C₁₄H₁₆O₃SB: C, 48.68; H, 4.96; S, 9.29; Br, 23.15. Found: C, 48.56; H, 4.96; S, 9.34; Br, 23.21.

5- and 6-*endo*-Methyl-2-*exo*-norbornyl Acetates (Acetates of 19 and 20). Pure, racemic 5-norbornene-2-*endo*-carboxylic acid was converted to 5-*endo*-methyl-2-norbornene (14) via the methanol and its *p*-bromobenzenesulfonate according to the method previously reported.^{17b} To a slurry of 35 ml of purified tetrahydrofuran (distilled from lithium aluminum hydride after reflux over potassium hydroxide), 4.68 g (43.3 mmoles) of the pure hydrocarbon, and 0.85 g (22.4 mmoles) of sodium borohydride was slowly added 3.7 ml of boron trifluoride etherate in 10 ml of solvent with vigorous stirring. The hydroboration mixture was allowed to stir for 18 hr. With cautious dropwise addition of 10 ml of 10% sodium hydroxide solution and 10 ml of 30% hydrogen peroxide solution, the very exothermic oxidation was achieved within a 1-hr period. The addition of water and extraction with ether four times, back washing the combined organic layers three times with saturated brine, drying over sodium sulfate, and careful concentration yielded the crude alcohol mixture which was inseparable on capillary columns L or N. Acetylation gave a mixture of acetates, which showed on capillary vpc on column L two main peaks contaminated by less than 2% unidentified olefins and 1% isomeric acetates. The acetates of 20 and 19 were present in the ratio of 56.3:43.7 (average over two separate hydroborations and work-ups, standard deviation = ±0.3% absolute) in order of increasing retention time on column L.

The two major acetate components could be preparatively separated with relative ease on columns A or E.

6-*endo*-Methyl-2-*exo*-norbornyl acetate, the first main fraction of the preceding hydroboration mixture, was repressed once again on column E to give colorless liquid acetate, pure by capillary vpc. This compound was not present in the products resulting from the acetolysis of arenesulfonates of 3-*exo*-methyl-2-*endo*-norbornanol (1a) or 5-*endo*-methyl-2-*exo*-norbornanol (19).

Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.69.

6-*endo*-Methyl-2-*exo*-norbornanol (20) was obtained from its acetate by reduction with lithium aluminum hydride in the usual manner. Bulb-to-bulb distillation at reduced pressure produced a low melting solid, not completely liquified at room temperature.

Anal. Calcd for C₉H₁₄O: C, 76.14; H, 11.18. Found: C, 75.92; H, 11.06.

The *p*-nitrobenzoate, after two recrystallizations from absolute methanol, melted at 108.5–109.0°.

Anal. Calcd for C₁₁H₁₇NO₄: C, 65.44; H, 6.22. Found: C, 65.29; H, 6.34.

The *p*-toluenesulfonate 20-OTs was isolated as an oil which began to crystallize after 2 months standing at –20°. Recrystallization from pentane–ethyl acetate at about –50° gave white plates, mp 37.5–38.5°, which were not stable for more than 1 day at room temperature.

The *p*-bromobenzenesulfonate 20-OBs was isolated as white needles while wet with pyridine. Recrystallization from pentane or vacuum suction to remove the pyridine resulted in the spontaneous decomposition of the *p*-bromobenzenesulfonate within 5 min at 0°.

6-*endo*-Methyl-2-norbornanone. A small amount of the alcohol 20 was oxidized with Jones reagent in acetone to yield the ketone contaminated with about 5–8% alcohol. The ketone was purified by preparative vpc on column G to yield a low melting, waxy solid.

Anal. Calcd for C₉H₁₄O: C, 77.38; H, 9.74. Found: C, 77.51; H, 9.84.

The 2,4-dinitrophenylhydrazone was obtained as orange crystals, mp 129.4–130.0°.

Anal. Calcd for C₁₄H₁₆N₄O₄: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.12; H, 5.37; N, 18.35.

5-*endo*-Methyl-2-*exo*-norbornyl acetate, the component of longer retention time from the hydroboration of 5-*endo*-methylnorbornene, was repressed once again on column E to give a liquid acetate pure by capillary vpc. This material had a retention time (column L) identical with that of one of the products of the acetolysis of 3-*exo*-methyl-2-*endo*-norbornyl *p*-bromobenzenesulfonate.

Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.36; H, 9.50.

5-*endo*-Methyl-2-*exo*-norbornanol (19) was obtained from the acetate by reduction with lithium aluminum hydride. After bulb-to-bulb distillation it was a viscous mass.

Anal. Calcd for C₉H₁₄O: C, 76.14; H, 11.18. Found: C, 76.29; H, 11.12.

: *p*-nitrobenzoate had mp 56.5–57.0° (from absolute methanol). *ul*. Calcd for $C_{14}H_{17}NO_4$: C, 65.44; H, 6.22. Found: 22; H, 6.17.

: *p*-toluenesulfonate of this alcohol remained a liquid in our . The *p*-bromobenzenesulfonate, 19-OBs, decomposed in a r manner to that of 20.

endo-Methyl-2-norbornanone. A small sample of alcohol 19 onverted to the ketone with Jones reagent in acetone and the ct purified on column G to yield a clear liquid which crystal- ust below room temperature.

ul. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, ; H, 9.92.

: 2,4-dinitrophenylhydrazone of the ketone was obtained as e platelets, mp 151.0–151.5° (absolute methanol).

ul. Calcd for $C_{14}H_{15}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. f: C, 55.22; H, 5.36; N, 18.25.

nd 6-*exo*-Methyl-2-*exo*-norbornyl acetates (acetates of 21 and ere obtained from pure 5-norbornene-2-*exo*-carboxylic acid : same procedure used for the 5- and 6-*endo*-methyl com- ls. Analysis with capillary column L showed two main to be present in a ratio of 1:1 and two smaller peaks, each nsity about 3% of the total. Presumably the latter peaks ent a small amount of *endo*-hydroboration product. The merging of the two major peaks, the 6-*exo*-methyl-2-*exo* r (acetate of 22), was completely absent from the acetolysis cts of 19-OBs or the arenesulfonates of 1a. Its retention as identical with that of one of the two products from ace- of 20-OBs, the second product being the acetate of 20.¹⁸

other major peak (acetate of 21) had a retention time iden-

tical with that of one of the products from the acetolysis of 19- OBs and 1a.¹⁸

1-Methyl-3-*exo*-norbornanol (31) was formed by alkaline hydro- gen peroxide oxidation of the residues from partial asymmetric hydroboration¹⁸ of 1-methyl-2-norbornene,⁹ a reaction that had been carried out in another study.¹⁹ The resulting mixture of 1- methyl-2-*exo*- and 1-methyl-3-*exo*-norbornanols (29 and 31) was sep- arated by vpc on column D (31 emerged second) and then on column F. Alcohol 31 was obtained as a waxy solid.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.97; H, 11.29.

The *p*-nitrobenzoate was recrystallized from methanol and had mp 93–94°.

Anal. Calcd for $C_{14}H_{17}O_4N$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.35; H, 6.12; N, 5.06.

The acetate was a liquid.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.62.

The *p*-toluenesulfonate was a liquid that could not be induced to crystallize at –65° in pentane. It was homogeneous by thin layer chromatography.

Jones oxidation of 31 followed by lithium aluminum hydride re- duction of the resulting ketone gave a two-component mixture of 31 and a much larger amount of another alcohol, presumably 1-methyl-3-*endo*-norbornanol (32), which emerged just before 31 on column L.

(28) S. Fanega, unpublished work.

The Chemistry of Methylnorbornyl Cations. III. Configurational Correlation of 2,3- and 2,7-Substituted Norbornyl Derivatives by Way of 3-Substituted Nortricyclenes¹

Jerome A. Berson and Robert G. Bergman²

Contribution from the Department of Chemistry, University of Wisconsin,
Madison, Wisconsin. Received October 31, 1966

Abstract: The relative configurations and optical rotations of *anti*-7-methyl-2-*exo*- and -3-*endo*-methyl-2-*exo*- norbornyl acetates are established by two independent correlations. Both correlations involve 3-nortricyclene derivatives as relay compounds, and the transformations provide absolute configurations and rotations of these sub- stances also.

ough a network of absolute and relative con- figurational correlations among 1- and 2-substi- bridged bicycloheptane and bicyclooctane deriva- has been constructed,³ only a few correlations en 2- and 7-substituted norbornanes are avail-

In studying one aspect of the mechanism of car- m ion rearrangements of methyl-labeled nor- yl cations,⁴ we found the need to establish such lations. Since the methods adopted to achieve nvolve nortricyclic relay compounds, the present s also provide the first determinations of abso- onfiguration of nortricyclenes.

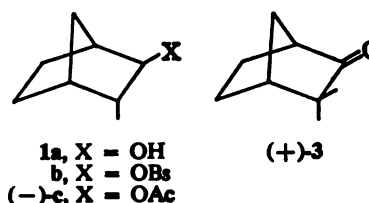
The support of part of this work by the National Institutes of is and Metabolic Diseases through Grant No. AM-07505 is ally acknowledged.

National Institutes of Health Predoctoral Fellow, 1964–1966.

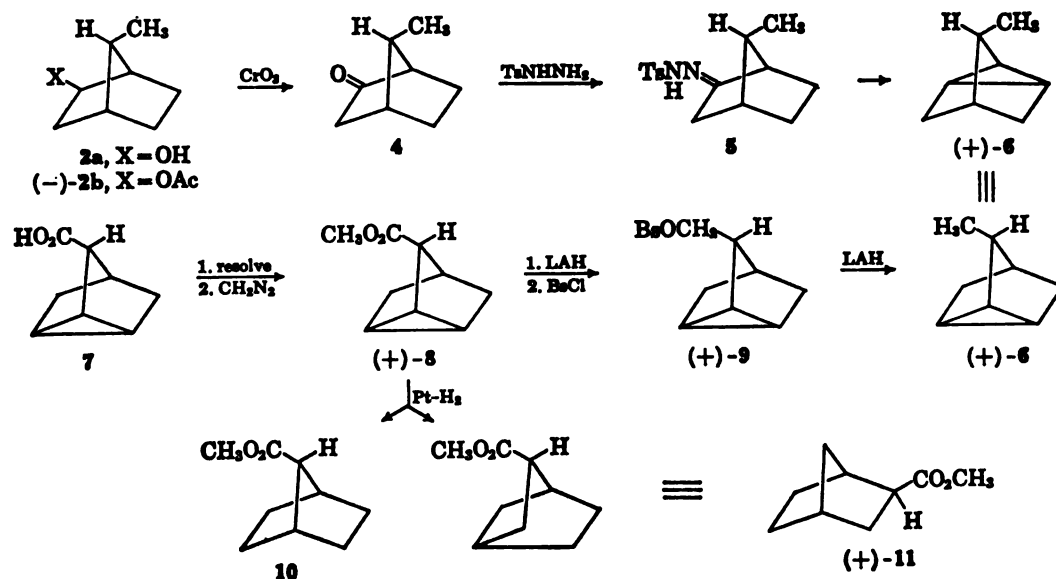
(a) *Cf.*, *inter alia*, J. A. Berson, J. S. Walla, A. Remanick, S. Suzuki, ynolds-Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, **83**, 3986 , and references cited therein; (b) K. Mislow and J. G. Berger, **14**, 1956 (1962); (c) J. A. Berson and A. Remanick, *ibid.*, **86**, 1749 .

Paper V of this series: J. A. Berson, R. G. Bergman, J. H. Ham- and A. W. McRowe, *ibid.*, **89**, 2581 (1967).

Acetolysis of the *p*-bromobenzenesulfonate (1b) of optically active 3-*endo*-methyl-2-*exo*-norborneol (1a) gives a mixture of products⁴ from which are isolated (–)-3-*endo*-methyl-2-*exo*-norbornyl acetate (1c), iden- tical in sign and magnitude of rotation with 1c obtained by direct acetylation of 1a, and (–)-7-*anti*-methyl-2- *exo*-norbornyl acetate (2b). (The rotatons refer to the sodium D line.) The absolute configuration of (–)-1c is established by oxidation and methylation to (+)- camphenilone (3).⁴ For reasons discussed elsewhere,⁴ a correlation of 1b and 2b is mechanistically significant but cannot be based on the assumption that (–)-1c and (–)-2b are related as simple Wagner–Meerwein



Scheme I



isomers. The configuration of 2b must accordingly be established by independent means. In the following reaction diagrams, which illustrate two such correlations, the indicated configurations are absolute.

Scheme I. The general objective of Scheme I is the correlation of *anti*-7-methyl-2-*exo*-norbornyl acetate (2b)⁴ with *exo*-norbornanecarboxylic ester (11). Oxidation of alcohol 2a, configurationally related to (–)-acetate 2b, gives a ketone 4, which is converted to the *p*-toluenesulfonylhydrazone. Pyrolysis of the *dry* sodium salt *in vacuo* smoothly converts it to (+)-3-methylnortricyclene (6).⁵ The same hydrocarbon is obtained by a reduction–arenesulfonylation–reduction sequence from (+)-methyl 3-nortricyclenecarboxylate (8), the corresponding active acid 7 being available by resolution *via* the cinchonidine salt. The ester (+)-8 serves as a relay for the entire series. Catalytic hydrogenation (40 psi, acetic acid solvent, platinum oxide catalyst) breaks the cyclopropane ring of (+)-8 to give a mixture of about equal parts of methyl 7-norbornanecarboxylate (10) and (+)-methyl 2-*exo*-norbornanecarboxylate (11). Very little of the epimeric methyl 2-*endo*-norbornanecarboxylate, the product of the third possible mode of ring cleavage, is formed under these conditions. A small amount of unreacted tricyclic ester 7 of undiminished rotation can be recovered; this gives assurance that partial epimerization (that is, racemization) of 7 does not accompany hydrogenation. From the known^{3a} configuration of (+)-11, the configurations of the substances of Scheme I follow.

This correlation, although straightforward in establishing configurational relationships, leaves something to be desired when quantitative comparisons of optical purities of solvolysis substrate 1b and product 2b are to be made. Thus, Scheme I correlates the magnitudes of rotation of 2b and 11, without reliance on an outside standard of optical purity, from the product of the three rotation ratios 2b:6, 6:8, and 8:11. However, the maximum rotation of 1b is correlated with that of camphenilone 3,⁴ a substance not included in Scheme I.

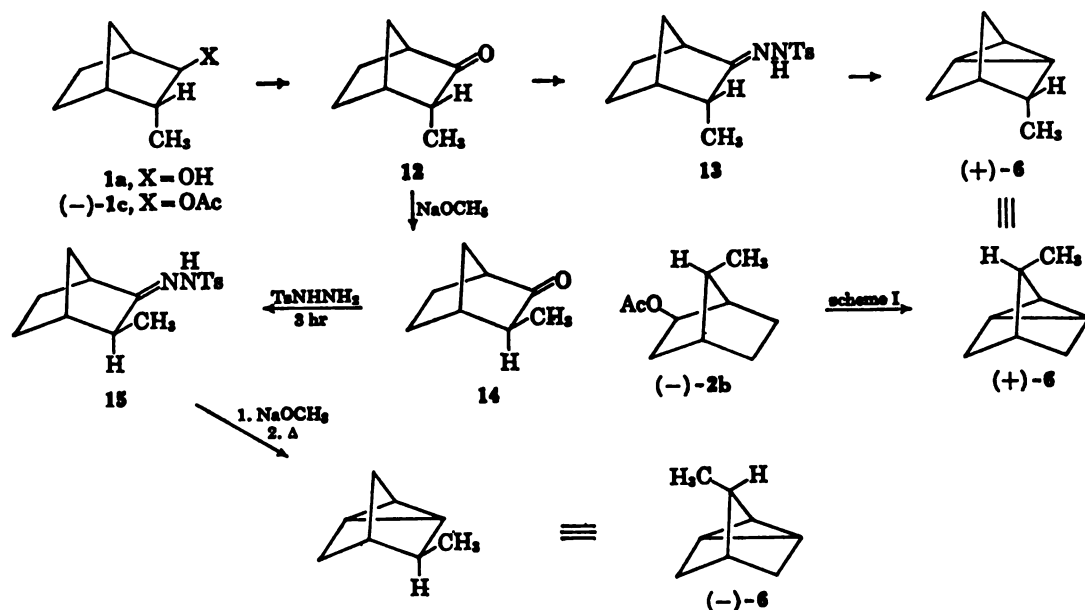
(5) (a) Cf. W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); (b) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, 81, 5512 (1959); (c) J. W. Powell and M. C. Whiting, *Tetrahedron*, 7, 305 (1959); (d) see, especially, G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *J. Am. Chem. Soc.*, 87, 935 (1965).

A comparison of maximum rotations of 11 and 3 is not now available by direct correlation. The maximum rotation of 11 rests on isotopic dilution analysis,⁴ whereas that of 3 has an entirely separate basis.^{3a} Therefore, since there is no common relay, the 11:3 rotation ratio and hence the crucial 2b:1b ratio is subject to a pyramiding of the errors inherent in each separate rotation. This is probably the cause of the somewhat low apparent value (92% retention) found⁴ when the data of Scheme I are used to calculate the stereochemical result of the 1b → 2b reaction. Furthermore, the exact magnitude of the absolute rotation of the *exo* ester 11 is subject to some question, since it was originally prepared⁶ from a sample of 2-*exo*-5-norbornenecarboxylic ester which was subsequently shown^{3a} to contain a small amount of impurity. It seems desirable therefore to provide a correlation free of these disadvantages. This is given in Scheme II, where the rotations of 1b and 2b are related through that of a common reference, the tricyclic hydrocarbon 6.

Scheme II. A sample of optically active 1a (at the same level of optical purity as the sulfonate 1b used for the solvolysis from which (–)-2b is isolated) is oxidized to the ketone 12 with Jones reagent (chromic acid–acetone). Although the oxidation proceeds in good yield, it is accompanied by epimerization, the product being a 90:10 mixture of the *endo*- and *exo*-methyl ketones, 12 and 14. The small amount of 14 is removed by vapor chromatography and the pure *endo* ketone 12 is transformed into the *p*-toluenesulfonylhydrazone (13). Hydrazone formation is slow, and if allowed to proceed too long in an effort to force complete conversion, is accompanied by partial epimerization. This becomes evident when the corresponding sodium salt is pyrolyzed to the tricyclic hydrocarbon (+)-6. The structural change converts epimerism to enantiomerism, and the rotation of the (+)-6 obtained in this way (+14.7°) is significantly lower than that (+16.3°) obtained from (–)-2b in Scheme I. This is a particularly awkward result because it is not obvious which of the two epimeric hydrazones the hydrocarbon product is derived from, and hence the correlation of (–)-1c

(6) J. A. Berson and D. A. Ben-Efraim, *ibid.*, 81, 4083 (1959).

II



(-)-6, already seen to be unreliable in magnitude, actually might be reversed in sign. (In this reversal of sign would be not inconceivable if the rotation were identical in magnitude.) A reversal of the epimeric *exo* ketone 14 to tricyclic carbon enantiomeric with that obtained from the ketone 12 is therefore needed to make a firm correlation. Deliberate epimerization of the above mixture of optically active ketones enriches the 14 content to 40%. Isolation of pure 14 by vapor chromatography, conversion to the *p*-toluenesulfonylhydrazone (under milder conditions than before), and reduction of the sodium salt give (-)-6 with an optical rotation (-16.4°) opposite in sign but essentially equal in magnitude to that obtained from (-)-2b. This rules out any possibility of a sign inversion in the correlation of (-)-1c and (+)-6. Since no obvious mechanism for racemization is available in the (-)-2b conversion of Scheme I, the production of (-)-6 of the same magnitude of rotation as (+)-6 from the ultimate source, (-)-1c, must mean that the (-)-2b, and (-)-6 samples all have the same optical

The data show that 2b (in 95% ethanol) has the same specific rotation of 1c (in absolute ethanol) at the same level of optical purity.

It shows that acetolysis of 1b gives 2b by simple *Wittig*-Meerwein change and with complete retention of optical purity. The mechanistic significance of this observation is discussed in an accompanying paper.⁴

Experimental Section

Details of vapor chromatographic and other standard techniques are given in paper II.⁷

1. Correlation of 7-anti-Methyl-2-exo-norbornyl Acetate with 3-Methylnortricyclene [(+)-6]. Acetate 2b (0.58 g) of $[\alpha]_{D}^{25} -3.19^\circ$ (95% ethanol)⁴ was reduced to the corresponding alcohol and oxidized with Jones reagent to 7-anti-norbornanone (4). The procedure used was identical with that employed in the oxidation of 3-endo-methyl-2-exo-norbornanol. An infrared spectrum of the ketone obtained in this way showed a strong C=O band at 5.72μ and no O-H absorption. The material was chromatographed on column B at 120° and ob-

tained 99.5% pure by capillary vpc. It was distilled bulb to bulb and used without further characterization. The ketone (0.156 g) was dissolved in 3 ml of absolute ethanol and 0.234 g of *p*-toluenesulfonylhydrazine was added. The resulting mixture was heated at reflux on a steam bath for 1.5 hr, after which it was cooled and allowed to stand overnight at room temperature. Addition of water caused precipitation of a white solid; this was removed by extracting three times with CHCl_3 . The combined chloroform extracts were washed with 5% HCl and saturated NaCl and dried over magnesium sulfate. Filtration and evaporation at the aspirator left 0.354 g of white solid (96% yield), presumed to be 7-anti-methyl-2-norbornyl *p*-toluenesulfonylhydrazone. An infrared spectrum of the material, showing bands at 3.1 (N-H), 6.01 (C=N), and 6.29μ (aromatic), was consistent with the proposed structure. The lack of C=O absorption indicated that the ketone had reacted completely. An nmr spectrum in CDCl_3 showed absorption from δ 7.2 to 8.0 (4 H) assigned to the aromatic protons, and a singlet at δ 2.4 (3 H) due to the aromatic methyl group. A doublet assigned to the 7-methyl group ($J = 7$ cps) was centered at δ 0.9, superimposed on complex absorption, arising from the nitrogen proton and the remaining protons of the norbornyl skeleton, running from δ 0.9 to 2.3 (total 13 H).

The sodium salt of the *p*-toluenesulfonylhydrazone was prepared by the following procedure. (It is extremely important that the sodium salt formation be carried out under scrupulously anhydrous conditions, since the salt is quite hygroscopic and the presence of water prevents the formation of tricyclic hydrocarbon in the subsequent pyrolysis.) The entire sample of *p*-toluenesulfonylhydrazone (0.354 g) was placed in a 25-ml, round-bottomed flask, which had been swept with dry nitrogen. A 15-ml portion of tetrahydrofuran, freshly distilled from lithium aluminum hydride, was added quickly to the flask, along with 0.143 g of sodium methoxide. The resulting mixture was stirred overnight at room temperature, protected by a blanket of dry nitrogen. Evaporation of the solvent and drying *in vacuo* overnight (0.2 mm) left a white solid caked to the walls of the flask. The vacuum was broken with dry nitrogen and the salt loosened from the sides of the flask with a spatula in a dry atmosphere.

The flask was then attached, *via* a Pyrex tube, to a receiver cooled in a Dry Ice-acetone bath, the system evacuated to a pressure of 18 mm (normal vacuum pump pressures, of the order of 0.2 mm, prevent efficient trapping of the volatile hydrocarbon), and the flask was heated with an air gun. At the reaction temperature (estimated to be about 110°), the salt decomposed completely in about 10 sec, evolving gas and bubbling off hydrocarbon. A slightly tan solid was left in the flask, and about 0.080 g of volatile product had collected in the trap. A vpc analysis of this material on column O indicated it to be almost completely (ca. 97%) 3-methylnortricyclene contaminated with a small amount of a second material. No diazo compound was detectable (infrared spectrum), but vpc analysis on column L at 125° indicated the presence of a small amount (ca. 1%) of 7-anti-methyl-2-norbornanone (4).

L. Berson, A. W. McRowe, R. G. Bergman, and D. Houston, *J. Am. Chem. Soc.*, **89**, 2563 (1967).

The tricyclic hydrocarbon (+)-6 was collected vpc pure from chromatography on column H-1 at 80°. Its specific rotation was found to be $[\alpha]^{25.7}_D +16.3^\circ$ (95% ethanol), and its infrared spectrum was identical with that of the hydrocarbon obtained from nortricyclene-3-carbinyl *p*-bromobenzenesulfonate (9).

Scheme I. Optical Activation of Nortricyclene-3-carboxylic Acid (7). The cinchonidine salt was prepared in methanol, 95% ethanol, and acetone, but crystals were obtained only from the latter solvent. A solution of 79.0 g of the acid⁸ in 250 ml of acetone was heated to boiling on a steam bath, and 189 g of solid cinchonidine was added. After having been heated at reflux for 0.5 hr, the mixture was filtered, concentrated on the steam bath, and cooled to room temperature. The solution was allowed to stand for 8 days at room temperature, and the crystals were collected on a Büchner funnel. Four recrystallizations from boiling acetone gave a total of 110 g (wet) of salt in the head crop. A 50.0-g portion of this material was reconverted to carboxylic acid in the manner described for the ephedrine salt of 3-*endo*-methyl-2-*exo*-norbornyl acid phthalate,⁴ yielding 14.6 g of optically active material as a greenish oil. Reaction with diazomethane in ether solution and evaporation of the solvent gave methyl 3-nortricyclenecarboxylate (8) which distilled as a clear oil shown to be 98.5% pure by capillary vpc. The nmr and infrared spectra were identical with those of the racemic compound. A sample was chromatographed on column E at 175° to give material of greater than 99.9% purity which was redistilled bulb to bulb. This material had $[\alpha]^{24.4}_D +15.3^\circ$ (95% ethanol).

Scheme I. (+)-Nortricyclene-3-carbinyl *p*-Bromobenzenesulfonate [(+)-9]. This derivative (13.5 g) was prepared from 6.4 g of optically active methyl 3-nortricyclenecarboxylate [(+)-8] as described by Gajewski⁹ and others¹⁰ for the racemic series. Spectral properties of the sulfonate, as well as of its carbinol precursor, were identical with those of the racemic compounds.

The carbinol was also converted to (+)-nortricyclene-3-carbinyl acetate (also shown to be identical with the racemic compound), which was distilled, chromatographed on column E at 180° to give material completely pure by capillary vpc on column N-1, and redistilled bulb to bulb to give material of $[\alpha]^{22.5}_D +17.9^\circ$ (methanol).

Scheme I. (+)-3-Methylnortricyclene [(+)-6]. A small sample of nortricyclene-3-carbinyl *p*-bromobenzenesulfonate [(+)-9], prepared as above, was dissolved in dry ether and treated with 0.15 g of lithium aluminum hydride in a dry atmosphere. The solution bubbled vigorously for about 15 min and was heated at reflux overnight. The flask was cooled and the mixture worked up with sodium sulfate in the standard way, except that the pentane extracts were washed thoroughly with 20% sodium hydroxide solution before drying. Careful removal of the pentane through a Vigreux column left 0.30 g of greenish oil which was chromatographed on column H-1 at 80°. This gave capillary vpc pure (column O) material; the infrared spectrum showed readings at: 3.25, 3.4, 3.45, 6.9, 7.3, 7.4, 7.7, 7.8, 8.0, 10.34, and 11.1 μ (CCl₄). An nmr spectrum showed complex absorption from δ 1.3 to 3.3; no other signals were observed.

Anal. Calcd for C₈H₁₂: C, 88.82; H, 11.18. Found: C, 88.79; H, 11.23.

A rotation was taken on the vpc pure material. It exhibited $[\alpha]^{24.4}_D +28.0^\circ$ (95% ethanol).

Scheme I. Correlation of (+)-Methyl 3-Nortricyclenecarboxylate (8) with (+)-Methyl 2-*exo*-Norbornanecarboxylate (11). A 1.0-g portion of the above sample of (+)-8, $[\alpha]_D +15.3^\circ$ (95% ethanol), was hydrogenated over 1.5 g of platinum oxide in 50 ml of dry acetic acid at 40 psi until uptake ceased. The resulting mixture was passed through diatomaceous earth, diluted with water, and extracted with pentane. The combined pentane fractions were washed with water and then with saturated sodium bicarbonate solution until the washings were basic. After washing with saturated brine and drying over magnesium sulfate, the pentane was carefully removed through a Vigreux column, leaving about 0.9 g of clear oil which contained (by capillary vpc) 5% unreacted methyl 3-nortricyclenecarboxylate (8), 47% methyl 2-*exo*-norbornane-

carboxylate (11), and 48% methyl 7-norbornanecarboxylate (10). The bicyclic esters were separated from the starting material on column E at 178°. The tricyclic ester 8 obtained was 99.0% pure by capillary vpc, and its rotation was unchanged compared with that taken before the hydrogenation, proving that it had not epimerized during the reaction. The active ester 11 was separated from its necessarily inactive isomer 10 by chromatography on column B at 120°. In this way 11 could be obtained 99.0% pure (contaminated with 1.0% of the 7-substituted isomer 10). After redistillation it had $[\alpha]^{22.7}_D +11.5^\circ$ (95% ethanol).

The relative amounts of each of the two norbornanecarboxylic esters produced were estimated by capillary vpc peak areas (column N-1), after calibration with mixtures of authentic samples of known composition. A mixture containing 49.3% of methyl 2-*exo*-norbornanecarboxylate 11 and 50.7% of its 7-substituted isomer 10 had a specific rotation of $[\alpha]^{22.5}_D +5.58^\circ$. Using the value of $+11.5^\circ$ (*vide infra*) for the specific rotation of 11 obtained on the 99.0% pure isomer as described above, the rotation of the 7-carbomethoxynorbornane could be calculated to be 0° within experimental error.

Scheme II. The 3-Methyl-2-norbornanones. Optically active 3-*endo*-methyl-2-*exo*-norbornyl acetate (1c) of specific rotation $[\alpha]^{24.4}_D -1.85^\circ$ (absolute ethanol)⁴ was reconverted to the corresponding alcohol 1a with lithium aluminum hydride. The alcohol obtained in this way (about 3.1 g), dissolved in 50 ml of acetone, was cooled to 0° in an ice bath, and 8 ml of Jones reagent¹¹ was added slowly with rapid stirring of the cold solution. The mixture was stirred for 2 min after the addition, poured onto cracked ice, salted heavily, and extracted four times with pentane. After combination, the organic extracts were washed with water and saturated sodium chloride and dried over sodium sulfate. Decantation of the liquid and careful removal of the pentane left 2.2 g (69% yield) of material which had a decidedly camphoraceous odor. The product was identified as a mixture of 90% 3-*endo*-methyl-2-norbornanone (12) and 10% of its 3-*exo*-methyl epimer 14,¹² along with minor amounts of other unidentified products.

Scheme II. Epimerization of 3-Methyl-2-norbornanones. A 0.70-g sample of the above ketone mixture was dissolved in 20 ml of dry methanol. Sodium was cut freshly under heptane and 0.115 g added to the solution; the resulting mixture was heated at reflux for 2.5 hr in a nitrogen atmosphere (it was found by trials with racemic samples of this mixture that longer reflux times produced only disappearance of product due to condensation, and no further equilibration of the monomeric ketones). The reaction mixture was quenched with water, salted heavily, and extracted four times with pentane. After the combined pentane fractions had been washed with water and brine, they were dried over magnesium sulfate and concentrated under a Vigreux column on the steam bath. Vpc analysis of the residue indicated the presence of about 40% 3-*exo*-methyl-2-norbornanone (14) and 60% of its 3-*endo*-methyl epimer 12. These were separated on column B at 130°; each was obtained pure by capillary vpc.

Scheme II. Optical Correlation of 3-*endo*-Methyl-2-*exo*-norbornyl Acetate [(+)-1c] with 3-Methylnortricyclene [(+)-6]. A sample of acetate (−)-1c of rotation $[\alpha]^{24.4}_D -1.85^\circ$ (absolute ethanol) was converted to the ketones 12 and 14 as described directly above. The *p*-toluenesulfonylhydrazide of 3-*endo*-methyl-2-norbornanone (12) was prepared from the ketone (purified by vpc) by the same procedure used for 7-*anti*-methyl-2-norbornanone (4), except that 1.5 hr of reflux time was insufficient to completely convert the ketone to its derivative. The reflux was, therefore, continued overnight, and the product worked up and converted to the hydrocarbon as described for 4. The pyrolysis reaction mixture from the sodium salt of 3-*endo*-methyl-2-norbornyl *p*-toluenesulfonylhydrazide consisted of 6% of an unidentified compound, 3.2% of a material whose retention time was identical with that of 2-methyl-2-norbornene, 1% 3-*endo*-methyl-2-norbornanone (12), and the remainder 3-methylnortricyclene [(+)-6]. The tricyclic hydrocarbon was separated on column G-1 at 95°. It was pure by vpc and had $[\alpha]^{25.0}_D +14.7^\circ$ (95% ethanol).

Pure 3-*exo*-methyl-2-norbornanone obtained from the same optically active source was converted to a *p*-toluenesulfonylhydrazide derivative in the same way as 12 except that the reaction mixture was heated at reflux only 3 hr; the infrared spectrum of the white solid obtained indicated contamination from about 5% of

(8) Racemic material was prepared according to J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

(9) J. J. Gajewski, Ph.D. Dissertation, University of Wisconsin, 1966.

(10) (a) R. R. Sauers and J. A. Beisler, *Tetrahedron Letters*, 2181 (1964); (b) K. B. Wiberg and G. R. Wenzinger, *J. Org. Chem.*, **30**, 2278 (1965).

(11) T. G. Halsall, R. Hodges, and E. R. H. Jones, *J. Chem. Soc.*, 3019 (1953).

(12) The racemates have been reported by S. Beckmann and R. Mezger, *Chem. Ber.*, **90**, 1559 (1957).

ketone. This mixture was carried through to the hydrocarbon as before. The pyrolysis product in this case, despite scrupulous vacuum drying of the sodium salt, was contaminated with about 30% of tetrahydrofuran. The other products consisted of about 6% 3-*endo*-methyl-2-norbornanone (12), 1.5% 2-methyl-2-norbornene, 1.5% of an unidentified compound, and the remainder 3-methylnorbornene. The tricyclic hydrocarbon was again

separated by preparative vpc on column G-1 at 130°, shown by infrared to be identical with material obtained from previous preparations, and its purity checked by capillary vpc. It had $[\alpha]^{25}_D -16.4^\circ$ (95% ethanol), a value essentially identical in magnitude and opposite in sign with that of hydrocarbon obtained above in Scheme I directly from 7-*anti*-methyl-2-*exo*-norbornyl acetate (2b).

The Chemistry of Methylnorbornyl Cations. IV. Ratios of Rates of Nucleophilic Capture of the Cations at Wagner–Meerwein-Related Sites¹

Jerome A. Berson, Arthur W. McRowe, and Robert G. Bergman²

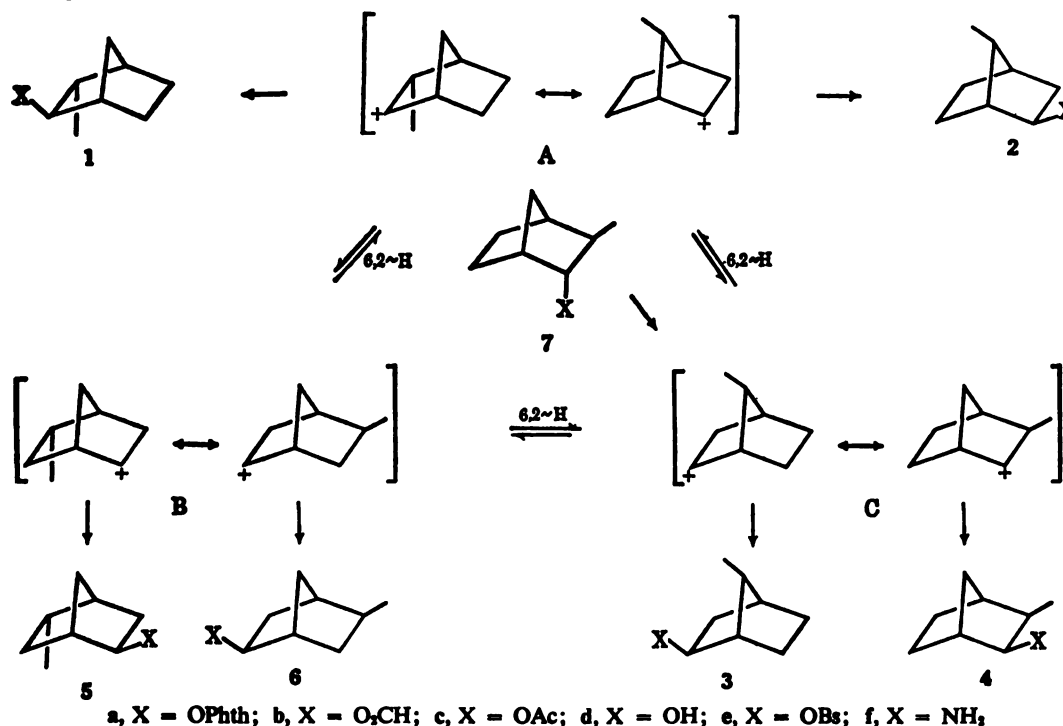
Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin. Received October 31, 1966

Abstract: A detailed study of the product distributions from solvolyses and deaminations of a number of precursors of methylnorbornyl cations permits the evaluation of the relative rates of capture of these species at each of the two Wagner–Meerwein-related sites. A direct steric effect on nucleophilic approach and another effect which opposes developing hydrogen–methyl repulsions in the transition state are noted. The characteristic capture ratios observed in the solvolytically produced ions apply also to the deaminatively produced ones, the major difference between the two processes being the excess of “direct substitution” observed in deamination. A comparison of the deamination results with those obtained earlier in the unsubstituted norbornyl case reveals that the “direct substitution” is very sensitive to a β -methyl steric effect, which causes a complete reversal of the stereochemistry of the process.

The summarizing rearrangement scheme given in paper I³ of this series outlines the interconversions of a set of “core” methylnorbornyl cations A, B, and C by 6,2-hydride shifts (Chart I) and their escape to

“periphery” cations A₁, B₁ (\equiv B₂), and C₁ by 3,2-hydride shifts. The present paper provides evidence for this scheme from studies of the products derived from solvolyses of various methylnorbornyl derivatives.

Chart I. “Core” System



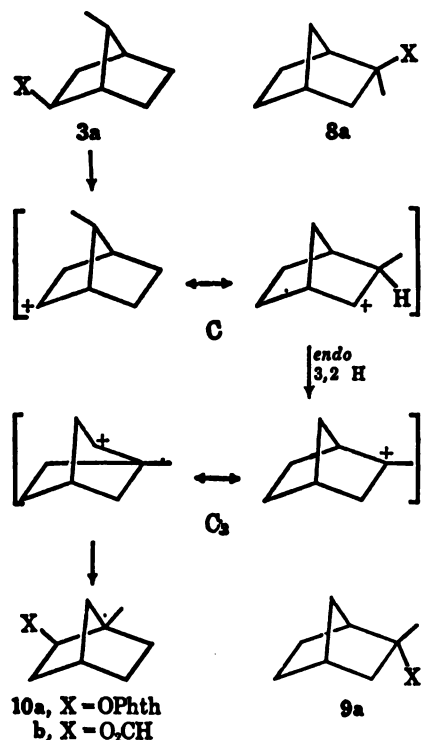
(1) (a) Support of part of this work by the National Institute of Arthritis and Metabolic Diseases through Grant No. AM-07505 and by the National Science Foundation is gratefully acknowledged. (b) A preliminary report of some of this work has appeared: J. A. Berson, A.

W. McRowe, and R. G. Bergman, *J. Am. Chem. Soc.*, **88**, 1067 (1966).

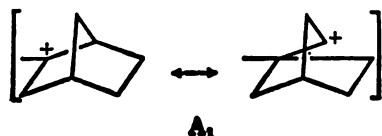
(2) National Institutes of Health Predoctoral Fellow, 1964–1966.

(3) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Am. Chem. Soc.*, **89**, 2561 (1967).

In a previous study,⁴ entry into the "core" set of cations was effected *via* cation C, generated by formolysis of *syn*-7-methyl-2-*exo*-norbornyl acid phthalate (3a). The major products reported⁴ were the formates

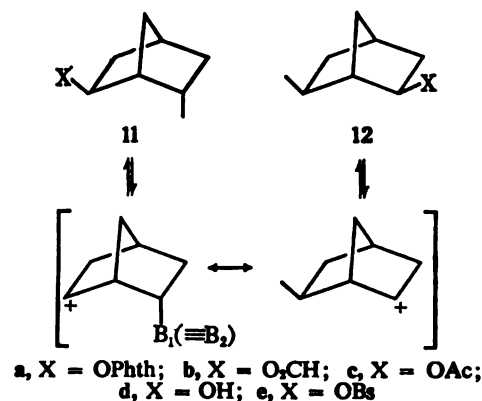


of 5-*exo*-methyl-2-*exo*-norborneol (6b), assumed⁴ to be derived by 6,2-hydride shift, and 1-methyl-2-*exo*-norborneol (10b), assumed⁴ to be derived by *endo*-3,2-hydride shift. Longer exposure of the products to the formolysis conditions caused conversion to 10b in high yield. It seemed likely, however, that a number of other products might be formed, at least under kinetically controlled conditions.⁵ Gas chromatography provides a means of demonstrating this and now reveals the presence in such solvolysis mixtures of all six products expected from the "core" set of cations as well as three additional ones with structures 10, 8, and 9 derived from the "periphery" cation A₁. The origin of the latter products from A₁ rather than from the enantiomerically related cation C₂ can be demonstrated in the optically active series,⁶ but for the present, the distinction between 10, 8, and 9 on the one hand and their respective enantiomers on the other is ignored.



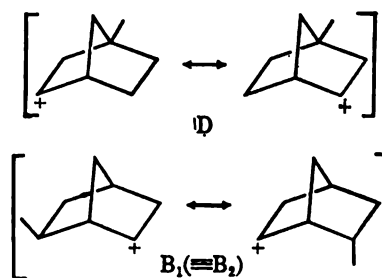
Entry into the "core" cycle is effected *via* cation A when 3-*endo*-methyl-2-*exo*-norbornylamine (1f) is nitrated or when the corresponding *p*-bromobenzenesulfonate (1e) is solvolyzed; *via* cation C by deamination of 3-*exo*-methyl-2-*endo*-norbornylamine (7f) or the corresponding *p*-bromobenzenesulfonate (7e); and *via* cation B by solvolysis of 5-*exo*- or 5-*endo*-methyl-2-*exo*-nor-

bornyl *p*-bromobenzenesulfonate (6e or 5e). The "periphery" cation A₁ (C₂) is encountered in solvolyses of 1-methyl-2-*exo*-norbornyl *p*-toluenesulfonate, in deamination of 2-*endo*-methyl-2-*exo*-norbornylamine,⁷ in solvolysis of the corresponding chloride,⁸ and also in leakage to the "periphery" from the "core" series. Solvolyses of 6-*endo*-methyl-2-*exo*-norbornyl *p*-bromobenzenesulfonate (11e) generate cation B₁ (≡B₂), which is captured to give 11c or 11d and the 6-*exo*-methyl isomer 12c, or 12d, in addition to products derived from 6,2-H shift.



Solvolyses. Table I lists the product distributions from solvolytic generation of cations A, B, and C (the "core" series) at 95–100° in several solvent systems. The cations generated at the points of entry into and exit from the scheme are indicated alongside each starting material and product. The percentages of products derived by capture of the *initial* cation (without hydride shift) are given in boldface type.

Very little leakage from the "core" to the "periphery" series of cations by vicinal hydride shift occurs under kinetically controlled conditions (excess of buffer). When the acid generated in solvolysis is allowed to accumulate, however, the kinetically controlled product composition shifts, and the "core" products are gradually converted to 1-methyl-2-*exo* product 10 derived from secondary-tertiary cation A₁, which represents a thermodynamic valley. The accumulation of product 10 under reversible conditions had been observed⁴ qualitatively in unbuffered solvolysis of 3a. The very low yield of products from cation A₁ (Table I) under buffered conditions results therefore from the escape of the bulk of the material at earlier exits in the mechanism. Under prolonged exposure of the 1-methyl-2-*exo* product 10 to equilibrating conditions, still slower processes occur. One of these is secondary-secondary 3,2-hydride shift to give cation D, which



(4) S. Beckmann and G. Eder, *Chem. Ber.*, **91**, 2878 (1958).

(5) J. A. Berson in "Molecular Rearrangements," Vol. I, Part 3, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963.

(6) Papers V and VI of this series: J. A. Berson, J. H. Hammons, A. McRowe, R. G. Bergman, and A. Remanick, *J. Am. Chem. Soc.*, **89**, 2581, 2590 (1967).

(7) S. Beckmann, R. Schaber, and R. Bamberger, *Chem. Ber.*, **87**, 997 (1954).

(8) N. J. Toivonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fennicae, Ser. AII*, No. 64 (1955).

Solvolyses

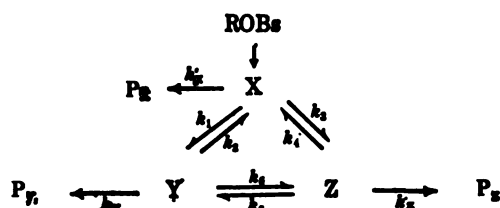
Product, exo	Cation	Starting material (ROBs) and conditions									
		5-endo-Me (B)	3-exo-Me (C)			3-endo-Me (A)	7-syn-Me (C)	1-Me (A ₁)	6-endo-Me (B ₁)		
		HOAc ^a	HOAc ^a	HCO ₂ H ^a	Aq EtOH ^d	HOAc ^a	Aq dioxane ^d	HCO ₂ H ^a	HOAc ^b	HOAc ^d	Aq EtOH ^d
6-Me	A	16	18	18	10	30	41	2	0	0	0
4-Me	A	14	17	15.4	9	31	41	3	0	0	0
2-Me	B	25	14	11	8	11	4	6	0	0	0
6-Me	B	33	16	12	10	12	6	3	0	0	0
2-Me	C	Trace	5	4	14	Trace	Trace	1	0	0	0
2-Me	C	9	28	34	49	8	4	1	0	0	0
6-Me	A ₁ (C ₂)	4	3.4	1	1.4	7	4	1	92.7	68	48
2-Me	A ₁ (C ₂)	0	Trace	?	0	0	0	?	2.8	Trace	0
2-Me	A ₁	0	Trace	5	0	0	0	73	0	3.1	Trace
2-Me	rs	0	0	0	0	0	0	10 ^e	0	29 ^a	52 ^f

phthalate. ^b *p*-Toluenesulfonate, fourfold excess sodium acetate buffer. ^c *p*-Nitrobenzenesulfonate, fourfold excess sodium formate. ^d *p*-Bromobenzenesulfonate, 25-fold excess pyridine buffer, 40–50% by volume ethanol or 50% by volume dioxane. ^e *p*-Nitrobenzenesulfonate, 2.5-fold excess sodium acetate buffer. ^f *p*-Bromobenzenesulfonate, 10% molar excess sodium acetate buffer. 50% of this fraction was 6-*exo*-methyl-2-*exo* product (12b). The remainder was a mixture of about equal parts of 6-*endo*-methyl-2-*endo*, 1-methyl-2-*endo*, and 1-methyl-3-*exo* products. ^a This fraction consisted of a 9.8:1 mixture of 6-*exo*-methyl-2-*exo*-norbornyl acetate. ^b A mixture (8.2:1) of the 6-methyl-2-*exo* norbornanols, the *endo* isomer 11d being the minor component.

1-methyl-3-*exo* product, and cation B₁ (≡B₂), leads to 6-*exo*- and 6-*endo*-methyl-2-*exo* products. Significantly, under buffered conditions in all media examined, only the first nine products listed in Table I are formed. These are the ones expected in Scheme I of paper I.

Hydride Shift vs. Solvent Capture. Table I shows that regardless of the point of entry into the reaction, products from each of the "core" cations A, B, and C are always found. Thus, 6,2-hydride shift is competitive with capture by solvent. The hydride shifts are intramolecular. Sodium acetate catalyzed acetolysis of 3-*exo*-methyl-2-*endo*-norbornyl *p*-nitrobenzenesulfonate (entry *via* cation C) in acetic acid gives the typical mixture of products, about 60% of which (Table I) arise from hydride shift, and 40% contain only about 0.03 D per molecule. In contrast, the 1-methyl-2-*exo*-norbornyl product that predominates in unbuffered medium incorporates substantial amounts of deuterium.

Percent of product derived from the cation generated at entrance (boldface entries in Table I) is higher in aqueous medium than in acetic or formic acid. In this sense, this effect suggests that capture by solvent becomes relatively more important as the nucleophilicity increases. Similar behavior is observed in the 7,7-dimethyl-3,3-dimethyl-5,5-dimethyl norbornyl and in the 2,3-di-¹⁴C-labeled norbornyl^{10a} and norbornyl cases.^{10b} In terms of the adjacent interpretation amounts to the proposal that the rate constant (which includes a solvent concentration term) for capture of the initial cation X, is higher in the more nucleophilic solvent. Strictly speaking, this is applicable to the observed result only for "unsubstituted" (isotopically labeled) norbornyl systems where the fractions of the total product derived from capture (F_x) and with ($F_y + F_z$) hydride shift are given in Table I and 2. If it is assumed that the hydride shift is insensitive to solvent, the fraction of X cap-



tured as P_x necessarily increases as k_x increases. The

$$F_x = P_x / (P_x + P_y + P_z) = (k_x) / (k_x + k_y + k_z) \quad (1)$$

$$F_y + F_z = (P_y + P_z) / (P_x + P_y + P_z) = \frac{k_y + k_z}{k_x + k_y + k_z} \quad (2)$$

simplicity of eq 1 arises from symmetry; in the "unsubstituted" norbornyl system, where X, Y, and Z are structurally equivalent, all the hydride shift rate constants (k_1 through k_4) are identical (except for a negligible isotope effect), as are all the capture rate constants (k_x , k_y , and k_z). Furthermore, these respond equally to a change of solvent. The symmetrical situation is discussed further elsewhere,⁶ but we note here that in the general case the equivalences are perturbed by substitution, and large changes in the rate constants result. The solvent effect is then less readily interpretable, since the fraction $P_x / (P_x + P_y + P_z)$ is a much more complex function of the rate constants, any or all of which (k_x , k_y , and k_z in particular) may have varying solvent sensitivity.

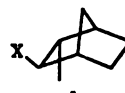
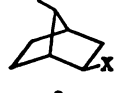
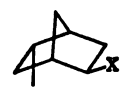
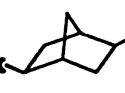
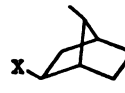
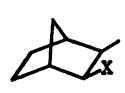
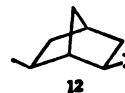
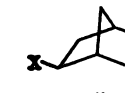
The general pattern of Table I makes it clear that the rates of solvent capture, 6,2-hydride shift, and tertiary-secondary 3,2-hydride shift are all competitive. Were 6,2 shift overwhelmingly fast relative to the other two processes, the product distribution would be insensitive not only to solvent variation but also to the point of entry into the "core" cycle. This is clearly not the case. Even with cation B₁ (≡B₂) derived from 6-methyl substrate, where 6,2-hydride shift is especially favorable because it leads to tertiary cation C₂, one still sees a substantial amount of direct solvent capture (Table I).

Tertiary cation C₂ (A₁), whether generated from the 6-methyl system B₁ by hydride shift or directly from 1-methyl-2-*exo* precursor, does not revert to any of the

Dolter, E. C. Friedrich, N. J. Holness, and S. Winstein, *J. Am. Chem. Soc.*, **87**, 378 (1965), and references cited therein.

J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *ibid.*, **76**, 4633 (1954); (b) W. G. Woods, R. A. Carboni, and J. D. Roberts, *ibid.*, **76**, 4633 (1954).

Table II. Products Derived from Capture of Methylnorbornyl Cations

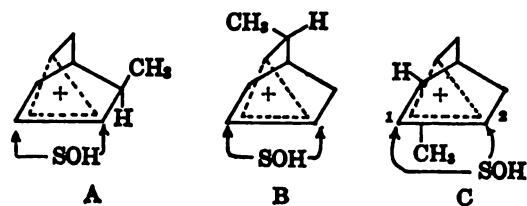
Wagner-Meerwein pair ^a		Starting material and conditions ^b								
		Cation	HOAc	HCO ₂ H ^c	HOAc	Aq EtOH	HOAc	Aq dioxane	HOAc	EtOH
		Product ratio								
		A	1.15	1.13	1.05	1.13	1.03	0.98
		B	1.33	1.10	1.13	1.30	1.1	1.4
		C	...	8 ± 2	5 ± 0.5	4 ± 0.5
		B ₁	9.9	8.1

^a In acetolyses, X = OAc; in aqueous ethanol or aqueous dioxane, X = OH. ^b Acetolyses at 95–100°, NaOAc buffered; hydrolyses at 95°, pyridine buffered. Product ratios do not change under reaction conditions. ^c Formolysis at 95–100°, sodium formate buffered. Product ratios do not change under reaction conditions.

secondary cations of Table I under kinetically controlled conditions.

Relative Rates of Capture of the Cations at Wagner-Meerwein-Related Sites. Each of the "core" cations A, B, and C can be captured at two nonequivalent Wagner-Meerwein-related sites. Arrangement of the products of Table I in Wagner-Meerwein pairs permits an inspection of the relative rates of capture at the two available positions in each. The data are given in Table II, where the results of solvolyses that generate the 6-methyl cation B₁ are also listed. Note that B₁ also suffers extensive hydride shift into the tertiary system (cation C₂).

With cations A and B, the capture ratios show virtually no position selectivity and, furthermore, are quite insensitive to solvent or to the point of entry into the "core" cycle. Thus, cation A gives 3-*endo*-methyl- and 7-*anti*-methyl-2-*exo* products (1 and 2) in the ratio 1.08 ± 0.06 , and cation B gives 5-*endo*-methyl- and 5-*exo*-methyl-2-*exo* products (5 and 6) in the ratio 1.23 ± 0.12 , the values being the averages of results obtained by generating the cations in six different ways each. The methyl group in both cations is remote from the reaction site and can exert little effect on the approach of a nucleophilic solvent molecule (SOH) from the *exo* direction.

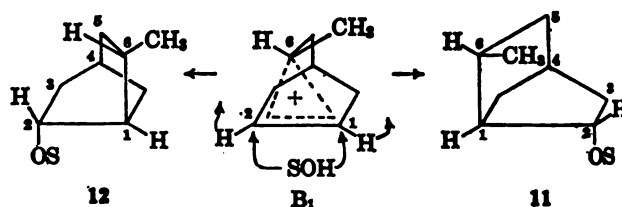


As an alternative, one might consider a trivial explanation for the constancy of the ratios based on the

assumption that equilibration of starting arenosulfonate *via* ion-pair return provides a common pool of mixed substrates regardless of the point of entry. This can be ruled out immediately, since it would require not only constant capture ratios for each cation but constant ratios of *all* products, in conflict with the data of Table I. The invariance of the product ratios from cations A and B is most simply explained in terms of characteristic ratios for cation capture. These seem to be quite insensitive to solvent.

Cation C shows a marked preference for attack at C-2 to give *syn*-7-methyl-2-*exo* product rather than at C-1 to give 3-*exo*-methyl-2-*exo* product, as would be expected from the more severe steric shielding of C-1 by the methyl group. The apparent fluctuation in the product ratio from C is probably attributable to the lower accuracy of analyses for these two products. The data also suggest a slower over-all rate of capture (or a higher rate of hydride shift) for cation C than for cations A or B, since the total amount of C-derived products (3 and 4) when entry is made at C is substantially less than the total amount of A-derived or B-derived products when entry is made at either of those points.

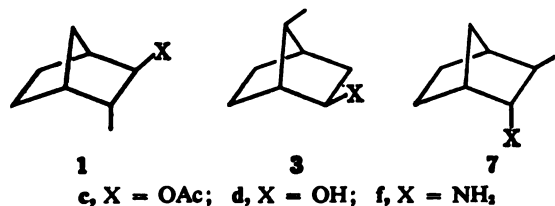
In cation B₁ even though the methyl group now does not interfere directly with the line of approach of solvent to the *exo* side of C-1 or C-2, there is an 8- to 10-fold preference for attack at C-2 to give 6-*exo*-methyl-2-*exo*



rather than at C-1 to give 6-*endo*-methyl-2-*exo* product. A simple interpretation of the preference is based on the repulsive interactions that develop in the transition states. One of these involves the site of attack, where a hydrogen is driven upwards toward another hydrogen or a methyl group at C-6. It is reasonable to assume that the H-CH₃ repulsion rated during attack at C-1 would be the more serious one, and that consequently attack at C-2 would dominate.

The steric effect in the product-forming step is associated with a difference in free energy between the transition states leading to 12 and 11, since the ground states are either the same or effectively the same (a non nonclassical ion B₁, or if the opponents of this species insist, a pair of rapidly equilibrating classical ions). Whatever its detailed nature, a kind of steric destabilization similar to that in the transition state leading to 6-*endo*-methyl-2-*exo* product must also be present, by virtue of an approximately microscopically-reversible relationship, in the solvolysis of a corresponding 6-*endo*-methyl-2-*exo* substrate. If this energy argument is the predominant one and if it is greater in the transition state than in the solvolysis ground state, the result would be a lower solvolysis rate for a 6-methyl derivative than for the unsubstituted norbornyl system itself. The observation¹¹ that 6,6-di-*isopropyl*-2-*exo*-norbornyl *p*-toluenesulfonate acetylates slower than the corresponding norbornyl derivative is consistent with these requirements. It is interesting to conclude, as a referee has urged, that the steric interference in question is greater in the transition state, which would be attributable to a decreased C-6 distance resulting from carbon bridging in a nonclassical structure. In our opinion, however, this is probably would be an overinterpretation, since substitution of methyl for hydrogen in the norbornyl system unavoidably introduces numerous steric interactions in addition to the one depicted in B₁ in both ground and transition states. The net increase or decrease in solvolysis rate as compared to the parent system is a resultant of these difficultly separable effects. For the present, we merely point out that the results given here provide experimental evidence for transition-state steric effects in 6-*endo*-methyl-2-*exo*-norbornyl solvolyses. The analyses of substituent effects on solvolysis rates of norbornyl derivatives must take factors of this kind into account.

Deamination of 3-*exo*-Methyl-2-*endo*-norbornylamine and 3-*endo*-Methyl-2-*exo*-norbornylamine (1f). Komppa and Beckmann¹³ prepared these two amines in essentially pure form from the corresponding acids. From deamination with sodium nitrite in aqueous acetic acid they reported isolation



(as acid phthalates) of two alcohols, *syn*-7-methyl-2-*exo*-norborneol (3d) and 3-*exo*-methyl-2-*endo*-norborneol (7d). In addition, they inferred that another product, *anti*-7-methyl-2-*exo*-norborneol (2d), was present in the reaction mixture from one (or both) of the amines.¹⁴ In our hands, substantial quantities of the *endo* alcohol 7d, the *syn*-7-methyl-2-*exo* alcohol 3d, or the corresponding acetates are formed only from *endo* amine 7f. The product distributions from the two amine hydrochlorides are given in Table III. The conditions for deamination of 1f are those of Komppa and Beckmann¹³ (aqueous acetic acid, sodium nitrite); these give a mixture of alcohols and acetates. Deamination of 7f is effected in dry acetic acid or in water, where the products are acetates or alcohols, respectively.

The most striking difference between the deamination (Table III) and solvolysis (Table I) results is the large amount of 3-*exo*-methyl-2-*endo*-norbornyl derivative (7d or 7c) formed in deaminations of 3-*exo*-methyl-2-*endo*-norbornylamine 7f. This product is not formed in deaminations of the 3-*endo*-methyl-2-*exo* amine 1f or in solvolyses of any of the substrates of Table I. Qualitatively, formation of 7c with retention of configuration from amine 7f recalls previous observations with the unsubstituted parent compound *endo*-norbornylamine.^{15,16} The deamination of that substance in acetic acid gave 16% acetate products 21–23% of which were formed by a path in which substitution (by some mechanism not yet clear¹⁶) occurred at the site of the original amino group and 77–79% of which came from “racemizing” processes involving nonclassical ions or their structural equivalents. The 21–23% “direct substitution” figure is matched fairly well by the 28% of product 7c, 3-*exo*-methyl-2-*endo*-norbornyl acetate. Another 4% of product with unrearranged structure, 3-*exo*-methyl-2-*exo*-norbornyl acetate (4c), is also formed, but it seems likely that most if not all of this material results from capture of the familiar cation C rather than by “direct substitution.” This conclusion is based on the demonstrably reasonable assumption that the characteristic cation capture ratios observed for Wagner-Meerwein pairs in solvolyses of arenesulfonates (Table II) apply, at least roughly, to deaminations as well. For example, the 1:2 ratios of Table III from amine 7f (where neither 1 nor 2 can be formed by direct substitution) are 1.28 and 0.94. Although measured on minor components and hence not very accurate, these are in agreement with the average value 1.08 of Table II. Similarly, the 5:6 ratio of 1.6, again measured on a minor pair of products, corresponds moderately well to the value 1.23 found in Table II. Thus, if any appreciable fraction of the *cis*-*exo* product 4 were being formed by “direct substitution,” the 3:4 ratio should be less than that found in solvolysis. This solvolytic value, which because of experimental difficulties is not very accurately measurable, ranges between 4 and 8 (Table II), whereas the deaminative 3:4 ratio (Table III) is in the range 11–12. Although the discrepancy, if real, is not readily interpretable, the data argue against the idea of an

(14) For further discussion, see paper II of this series: J. A. Berson, A. W. McRowe, R. G. Bergman, and D. Houston, *J. Am. Chem. Soc.*, **89**, 2563 (1967).

(15) E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *J. Am. Chem. Soc.*, **85**, 169 (1963).

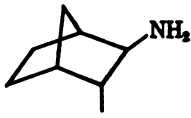
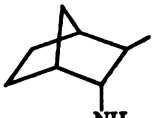
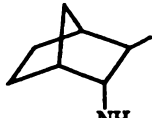
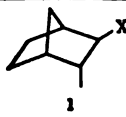


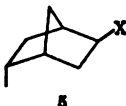
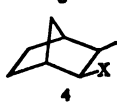
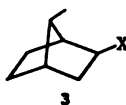
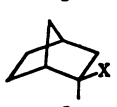

(16) J. A. Berson and A. Remanick, *ibid.*, **86**, 1749 (1964).

(11) P. von R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Am. Chem. Soc.*, **87**, 375 (1965).

(12) G. Komppa and S. Beckmann, *Ann.*, **523**, 68 (1936).

(13) S. Beckmann and R. Mezger, *Chem. Ber.*, **90**, 1559, 1564 (1957).

Table III. Deaminations of 3-Methylnorbornylamines

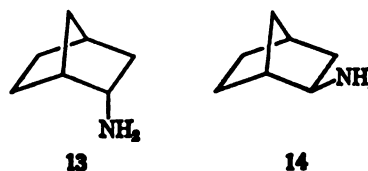
Starting material and conditions						
						
			1f	7f	7f	
			Aq HOAc	Dil HCl,	HOAc,	
			X = OH	X = OH	X = OAc	
	Me gp	Cation	Product, %			
	3-endo	A	34	21	4.5	5.7
1						
	7-anti	A	23	14	3.5	6.1
2						
	5-exo	B	~1	1	<1	3.5
6						
	5-endo	B	~1	1	3.7	5.5
5						
	3-exo	C	1	Trace	3.1	4.3
4						
	7-syn	C	1	1	38.4	46.4
3						
	2-endo	C ₁ (A ₁)	1	1	0	0
8						
	3-exo		0	0	46.8	28.4
7						

origin of a substantial amount of product 4 in a "direct substitution" path.

In the deamination of 3-*endo*-methyl-2-*exo*-norbornylamine (1f), at most a small amount of the product seems to arise from direct substitution. The ratios of products 2:1 in both the alcohols (X = OH) and acetates (X = OAc) are about 1.5, and if this is assumed to be meaningfully higher than the ratio 1.08 found in solvolyses (Table II), as much as 9% of the alcohol and 6% of the acetate of the 3-*endo*-methyl-2-*exo* structure (1d or 1c) might be "direct substitution" product. There is no 3-*endo*-methyl-2-*endo* product (less than 1% would have been detected), so that the 6-9% figures represent the total "direct substitution." Thus, "direct substitution" is considerably less important with the 3-*endo*-methyl-2-*exo* amine 1f than with the 3-*exo*-methyl-2-*endo* isomer 7f. This corresponds to the pattern in the unsubstituted norbornylamine case,¹⁶ where the *exo* amine gave less "direct substitution" product than the *endo*.

The division of the "direct substitution" products between inversion (*exo* amine → *endo* alcohol, *endo*

amine → *exo* alcohol) and retention modes for the two *trans*-3-methylnorbornylamines (7f and 1f) and for the two unsubstituted cases (13 and 14) are summarized in Table IV. The major effect of substituting a 3-*trans*-methyl for 3-hydrogen in both the *endo*- and *exo*-amino



compounds (13 → 7f, 14 → 1f) is to suppress the inverting deaminative "direct substitution." The result is consistent with several mechanistic rationalizations for the process and hence not decisive. Nevertheless, it does demonstrate a rather high degree of steric sensitivity to β substitution. This sensitivity is particularly pronounced in the case of 3-*exo*-methyl-2-*endo*-norbornylamine (7f), where the *exo*-methyl group forces virtually exclusive *endo* substitution (retention), a complete reversal of the result obtained¹⁶ in the unsubstituted

IV. Inversion and Retention in the Deaminative Substitution^a

Starting amine		Total % "direct subst" in		Fraction of "direct subst"	
R	NH ₂	X = OH	X = OAc	Retn	Invn
	<i>endo</i> (13) ^a	...	21-23	0.14-0.22	0.78-0.86
	<i>exo</i> (14) ^a	...	13	0.85	0.15
<i>exo</i> -CH ₃	<i>endo</i> (7f)	47 ^b	28 ^c	1.00, 1.00	0
<i>endo</i> -CH ₃	<i>exo</i> (1f)	9 ^d	6 ^d	1.00, 1.00	0

reference 16. ^b In water. ^c In dry acetic acid. ^d In aqueous acid.

The stereochemistry of "direct substitution" contrasts markedly with that in the lithium aluminum hydride reduction of the corresponding ketone, 3-methyl-2-norbornanone, which gives predominantly the product of *exo*-hydride attack, 3-*exo*-methyl-2-norbornanol (7d).^{13,14,17} The observed stereochemistry of hydride reduction of 2-norbornanones has been used^{6,18} as a model of the stereochemistry to be expected in the nucleophilic capture of hypothetical 2-norbornyl cations. The discrepancy between the results in the 3-*exo*-methyl system must mean that the model is not uniformly applicable or that a classical carbonium ion is not the product-forming intermediate in the "direct substitution." In view of the widespread intervention of ion pair or complex intermediates in deaminations¹⁹ which can well produce the observed stereochemical pattern, it seems unnecessary to abandon the stereochemical model.

Experimental Section

Acetic acid and formic acid were dried according to procedures in the literature.^{20,21}

Formolyses were carried out at 95–100° under the conditions given in Table I. Cold solutions of reactive substrates were injected into stirred solvolysis media. The preparation of the substrates is described elsewhere.²² Acetolyses and formolyses were carried out at initial concentrations of about 0.5 M buffer and 0.1 M substrate. Hydrolyses used about 2.5 M pyridine and about 0.1 M substrate. As has been shown elsewhere,⁶ the material balance in the solvolysis of 3-*exo*-methyl-2-*endo*-norbornyl *p*-bromobenzenesulfonate is essentially quantitative. Product identification was carried out for the runs of Table I by actual isolation⁶ and/or by comparison with known samples²³ on two different capillary columns and procedures already described. Detector response to isomers was considered uniform. Samples of 0.2 μl were injected with flow ratios of 100:1 to 400:1. Detector response was linear in this size sample if column "bleed" was not excessive.

^a S. Beckman, A. Durkop, R. Bamberger, and R. Mezger, *Ann.*, **99** (1955).

^b R. Howe, E. C. Friedrich, and S. Winstein, *J. Am. Chem. Soc.*, **87**, 9 (1965).

^c (a) E. H. White and C. A. Aufdermarsh, *ibid.*, **83**, 1179 (1961); White and F. W. Bacheler, *Tetrahedron Letters*, 77 (1965); (b) T. J. and E. Jankowski, *J. Am. Chem. Soc.*, **86**, 4217 (1964); (c) R. E. and C. Rüchardt, *Ann.*, **601**, 1 (1956).

^d L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 281.

^e P. D. Bartlett, C. E. Dills, and H. G. Richey, Jr., *J. Am. Chem. Soc.*, **82**, 5414 (1960).

^f See ref 14.

Peak areas were determined by triangulation and were reproducible to better than 0.5% between two major well-resolved peaks and to 1–2% between minor ones. Comparisons between peaks of very different size were subject to greater error. Analyses were carried out with columns L and N²² on acetate mixtures. Alcohols were acetylated and formates were saponified to alcohols and acetylated for analysis. Most of the peaks were resolved to base line, but *syn*-7-methyl-, 5-*exo*-methyl-, and 3-*exo*-methyl-2-*exo*-norbornyl acetates emerged within 1 min of each other and were difficult to analyze with high accuracy. The tertiary acetate, 2-*endo*-methyl-2-*exo*-norbornyl acetate, separated from its epimer 2-*exo*-methyl-2-*endo*- and from its Wagner-Meerwein relative 1-methyl-2-*exo*-norbornyl acetate, whereas the alcohol 1-methyl-2-*exo*-norbornanol separated well from the two tertiary alcohols. All three of these separated well from the remainder of the product mixture. The amount of 2-*exo*-methyl-2-*endo* material was, therefore, determined by difference between the acetate and alcohol chromatograms.

Except for the slow conversion among these three "tertiary-related" acetates,⁶ the remainder of the product composition was essentially unchanged upon reexposure to the reaction conditions in buffered medium. In particular, no interconversion between the "tertiary-related" products and the group of secondary products derived from the "core" cations occurred, nor was there appreciable interconversion among the latter secondary products, at least in buffered acetolyses and hydrolyses. In formolysis, even in the presence of buffer, slow conversion to 1-methyl-2-*exo* product was observed. Entry *via* cation C in Table I was effected by a brief (5 min) formolysis of 3-*exo*-methyl-2-*endo*-norbornyl *p*-nitrobenzenesulfonate. This sufficed to achieve essentially complete reaction, but the product mixture was essentially unchanged after 20-min additional exposure and therefore presumably reflects rate control. After 2 hr of further exposure, however, the accumulation of 1-methyl-2-*exo* product became detectable. Unbuffered formolysis of the *p*-bromobenzenesulfonate gave 1-methyl-2-*exo* formate as the major product.

3-*exo*-Methyl-2-*endo*-norbornylamine (7f). A mixture of 13.1 g (85 mmoles) of pure racemic 3-*exo*-methyl-2-*endo*-norbornanecarboxylic acid, 95 ml of concentrated sulfuric acid, and 175 ml of reagent grade chloroform was chilled below 0°. In small portions, 6.5 g (100 mmoles) of sodium azide was added. The mixture was stirred at room temperature for 4 hr with a slow evolution of bubbles. Refluxing on a steam bath for 1.5 hr completed the reaction. The reaction mixture was cooled and 300 ml of 6 N sodium hydroxide solution was added to half-neutralize the acid; the addition of 350 ml of water was necessary to dissolve the salts formed.

The chloroform layer was drawn off from the chilled mixture, and the aqueous phase was washed with another 50 ml of solvent. The solution was made basic and more water was added. The free amine was extracted four times with a total of 600 ml of ether; the combined organic layers were washed once with 1 N sodium hydroxide solution and twice with saturated brine and dried over sodium sulfate.

The hydrochloride was precipitated by passing anhydrous hydrogen chloride gas over the chilled ether solution of the amine. The solid was filtered off and dried *in vacuo*. The yield of white, crystalline, nondeliquescent material was 12.5 g (91%). The material could be recrystallized from absolute ethanol.

The urea prepared in the manner described¹⁴ gave sharply melting platelets, mp 204–205° (lit.¹⁴ mp 200–201°).

3-*endo*-Methyl-2-*exo*-norbornylamine (1f) was prepared in a similar manner from the corresponding acid. The urea melted at 209–210° (lit.¹⁴ mp 206–207°).

Aqueous Deamination of 3-*exo*-Methyl-2-*endo*-norbornylamine (7f). A solution of 1.9 g (27.5 mmoles) of sodium nitrite in 8 ml of water was added over a period of 10 min to a solution of 2.0 g (12.3 mmoles) of amine hydrochloride in 20 ml of water and five drops of 10% hydrochloric acid at 0°. The mixture, which became cloudy after 1 hr, was allowed to stand at 25° for 4 hr. No reddish nitrogen oxide fumes were noticed throughout the reaction course.

The acid solution was extracted with pentane three times; the combined organic layers were washed with saturated brine twice and dried over sodium sulfate. Careful concentration of the pentane solution yielded 1.5 g (96%) of a yellow oil as crude residue with the characteristic alcohol odor. An intense infrared spectrum of the neat liquid film indicated very strong hydroxyl peaks, no acetate at 5.75 or 8.0 μ, and only a very weak nitrate ester peak (6.1 μ). Capillary vpc on columns L or N indicated only one major peak (≥90% of total area). No 5-*exo* alcohol was present.

The crude product was acetylated directly with excess pyridine and acetic anhydride for 1.2 hr at 98°. After the reaction mixture was cooled to 25°, the excess anhydride was hydrolyzed with water for 2 hr. The mixture was then extracted three times with pentane, and the combined organic layers were washed with 10% hydrochloric acid, 10% sodium carbonate solution, and twice with saturated brine and dried over sodium sulfate.

The solution was carefully concentrated to yield a yellow residue which was distilled bulb to bulb at room temperature (3×10^{-3} mm). The yield of colorless product was 1.8 g (90%) with the characteristically fruity odor. The infrared spectrum indicated it was all acetate; no hydroxyl absorptions remained. Analysis by capillary vpc on column L indicated two major peaks with small amounts of other acetate and unidentified olefins. The distribution of acetate products is given in Table III, in which the approximately 1% olefin formed is omitted. The errors in these percentages are estimated to be $\pm 0.5\%$ absolute, although similar sized components can be compared with greater accuracy. The 5-*exo*-methyl-2-*exo* acetate 6c emerges between 4c (3-*exo*) and 3c (7-*syn*), and while it may be present to some extent, the limit of the determination of this component is about 1% for this case.

The two major components 3c and 7c could be preparatively separated on column E. After two successive passes, component 7c was free of any contamination. Its infrared spectrum was identical with that of the acetate prepared by the Baeyer-Villiger oxidation of 3-*exo*-methyl-2-*endo*-acetylnorbornane. It was reduced to 3-*exo*-methyl-2-*endo*-norbornanol (7d) with lithium aluminum hydride. The acid phthalate was prepared with equimolar quantities of phthalic anhydride and pyridine at 100° for 2 hr. This product, recrystallized thrice from hexane-benzene, melted at 126.5–128.0° (lit.¹³ mp 131–132° for apocamphenyl acid phthalate). Mixture melting point with the acid phthalate from the Baeyer-Villiger product gave no depression.

Three passes of component 3c through column E still gave material contaminated with several per cent each of 4c and 5c. Reduction to the alcohols with lithium aluminum hydride and preparation of the acid phthalate were carried out in the usual manner. Four recrystallizations from hexane-benzene yielded material, mp 163.5–166.0° (lit.¹³ mp 165–166° for "isoaposenenyl acid phthalate"). Two more recrystallizations did not change the melting point. Saponification of the purified acid phthalate by alkaline steam distillation, ether extraction, drying, concentration, and acetylation in the usual manner gave back 7-*syn*-methyl-2-*exo*-norbornyl acetate (3c) contaminated with 3% 4c.

Deamination of 3-*exo*-Methyl-2-*endo*-norbornylamine in Acetic Acid. To 20 ml of dry acetic acid was added 0.43 g (2.66 mmoles) of amine hydrochloride. The solution was stirred and chilled to ca. 4° (solidification occurred at any lower temperature), and 0.43 g (6.2 mmoles) of finely crystalline sodium nitrite was added over a

20-min period. The solution became cloudy after 10 min and was allowed to stand at room temperature for 2 hr.

Ice water was added, and the mixture was extracted four times with pentane. The combined organic layers were washed once each with 2 *N* hydrochloric acid, saturated bicarbonate, and saturated brine, dried over sodium sulfate, and carefully concentrated. The pale yellow, mobile liquid product weighed 0.38 g (85%) and was directly analyzed on capillary columns L and N. Several per cent olefin and about 3% alcohols were formed in addition to the acetates. The minor classes of components were not readily identified. Only the relative acetate composition is reported in Table III.

A small portion of the acetate mixture was reduced with lithium aluminum hydride to the alcohol mixture. Analysis on capillary column L indicated the presence of a trace, estimated to be 0.02%, of the *t*-*exo* alcohol. No 1-methyl-2-*exo*-acetate or *t*-*endo* acetate was detected.

Deamination of 3-*endo*-Methyl-2-*exo*-norbornylamine Hydrochloride. A solution of 32.0 g of sodium nitrite in 100 ml of water was added dropwise to a stirred solution of 10.0 g of the amine hydrochloride in 75 ml of 50% (by volume) water-acetic acid at room temperature. Gas evolved at a moderate rate and an organic phase quickly separated. The mixture was allowed to stir at room temperature for 5 hr; it was then extracted four times with pentane. The pentane extracts were combined and washed with water and sodium bicarbonate until the washings were basic; they were then washed with saturated sodium chloride solution and dried over magnesium sulfate. Filtration and solvent evaporation with a Vigreux column left 6.0 g (67% yield) of a mixture whose composition is described in Table III. Distillation of the mixture bulb to bulb and acetylation of the distillate by the usual method gave a mixture of acetates whose composition was identical with the "acetate fraction" of Table III.

On column E at 180°, 3-*endo*-methyl-2-*exo*-norbornyl acetate (1e) and 7-*anti*-methyl-2-*exo*-norbornyl acetate (2e) could be separated from the minor products and obtained in relatively pure form. After reduction of 1e with lithium aluminum hydride, the alcohol 1d obtained was converted to its acid phthalate derivative 1a. Compounds 1e and 1d were identified by comparison of their infrared spectra and retention times on vpc with those of authentic materials.¹³ Compound 1a had mp 89.5–90°, alone or mixed with an authentic sample¹³ of 3-*endo*-methyl-2-*exo*-norbornyl acid phthalate. Compound 2e had a retention time on vpc different from that of 3-*exo*-methyl-2-*endo*-norbornyl acetate (7c) or 7-*syn*-methyl-2-*exo*-norbornyl acetate (3c). By lithium aluminum hydride reduction and treatment with phthalic anhydride, it was converted to 7-*anti*-methyl-2-*exo*-norbornyl acid phthalate (2a), mp 105.5–107.5° (from heptane).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.20; H, 6.57.

The Chemistry of Methylnorbornyl Cations. V. Solvent Capture and Hydride Shift in the 3-*endo*-Methyl Series¹

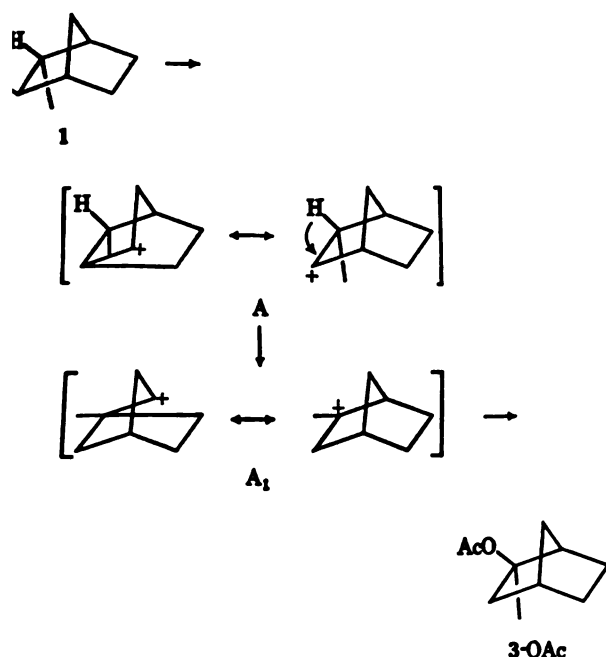
Jerome A. Berson,^{2a,b} Robert G. Bergman,^{2b,3} James H. Hammons,^{2c}
and Arthur W. McRowe^{2b,c}

Contribution from the Departments of Chemistry, University of Wisconsin,
Madison, Wisconsin, and University of Southern California, Los Angeles, California.

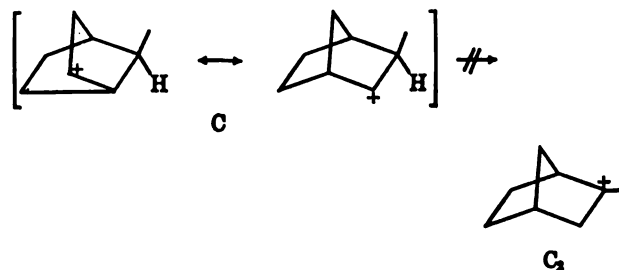
Received October 31, 1966

Abstract: By correlations of the configuration and absolute rotation of 3-*endo*-methyl-2-*exo*-norbornyl *p*-bromobenzenesulfonate with those of the corresponding acetate (1) and the acetates of *anti*-7-methyl-2-*exo*-norbornanol (7) and 2-*endo*-methyl-2-*exo*-norbornanol (3) it is established that acetolysis of the sulfonate occurs to give acetates 1, 7, and 3 with high retention of optical purity. Acetates 1 and 7 have the configurational relationship of simple Wagner–Meerwein isomers; acetate 3 has the configuration expected of a product derived by direct *exo*-3,2-hydride shift in the 3-*endo*-methyl-2-norbornyl cation. The hydride shifts are intramolecular. From the product distributions and optical purity data, it can be shown that 3,2-hydride shift from a tertiary to a secondary center is at least 14 times as fast as secondary–secondary hydride shift, which in turn is at least 122 times slower than solvent capture in acetic acid at 100°. Previous data in the literature are interpreted to give a competition ratio for secondary–secondary 6,2-hydride shift *vs.* solvent capture (0.27 in acetic acid at 45°). The corresponding ratio for the tertiary–secondary case is evaluated from the product distribution in 6-methylnorbornyl solvolyses as 1.23 in acetic acid at 100°. A method for estimating the temperature correction to be applied and the first estimate of the minimum activation energy for capture of the norbornyl cation in acetic acid (4.65 kcal/mole) are given in the Appendix. The enhancement by methyl substitution of the rate of 6,2-hydride shift is estimated to be between 5- and 15-fold. The weakness of this effect in comparison to that in other systems is attributed to charge distribution in the transition state for the hydride shift, which is reasonably formulated as an edge-protonated cyclopropane.

The 3-*endo*-methyl-2-norbornyl cation (A)⁴ can escape from the "core" cycle⁴ of 6,2-hydride shifts a "periphery" system (A₁) by *exo*-vicinal hydride



shift. The present paper demonstrates the occurrence of this reaction. The process serves as a standard of comparison for the 3-*exo*-methyl-2-norbornyl case (C), where stringent stereoelectronic prohibition of *endo*-vicinal hydride shift (to C₂) is observed.⁵ The chemistry of cation A also provides measures of the com-



petition between solvent capture and vicinal hydride shift and between secondary–secondary and tertiary–secondary vicinal hydride shift.

Configurational Correlations. The stereochemical relationships that provide the experimental basis for this study are established by a set of correlations anchored on (+)-camphenilone (2). Although the absolute configuration⁶ (as shown) and approximate absolute rotation⁷ of camphenilone are known, they become matters of no concern when both starting material (1,

(a) Support of part of this work by the National Institute of Health and Metabolic Diseases and by the National Science Foundation is gratefully acknowledged. (b) Presented in part at the Anniversary Meeting of the Chemical Society, Birmingham, England, April 1964, Abstracts, p 19; *Proc. Chem. Soc.*, 204 (1964). A preliminary report appeared: J. A. Berson, R. G. Bergman, J. H. Hammons, and A. W. McRowe, *J. Am. Chem. Soc.*, 87, 3246 (1965).

(c) (a) To whom inquiries should be directed; (b) University of Wisconsin; (c) University of Southern California.

(d) National Institutes of Health Predoctoral Fellow, 1964–1966.

(e) The nomenclature of the various cations follows that of paper I: J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Am. Chem. Soc.*, 89, 2561 (1967).

(5) Paper VI: J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *ibid.*, 89, 2590 (1967).

(6) A. J. Birch, *Ann. Rept. Progr. Chem.* (Chem. Soc. London), 47, 191 (1950), and references cited therein.

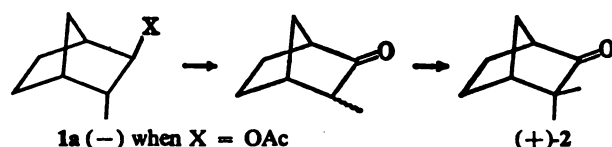
(7) Camphenilone prepared from camphene of $[\alpha]_D + 102.5^\circ$ (ether) has $[\alpha]_D + 66.7^\circ$ (benzene).⁸ The highest reported rotation for camphene is 113.5° (ether)⁹ and thus, that for camphenilone is 73.8° (benzene).

(8) W. Hüchel, W. Doll, S. Eskola, H. Weidner, F. Neumann, and I. Schneider, *Ann.*, 549, 186 (1941).

(9) (a) Cf. J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, 83, 3986 (1961); (b) see especially footnote 14 of ref 9a and references cited there.

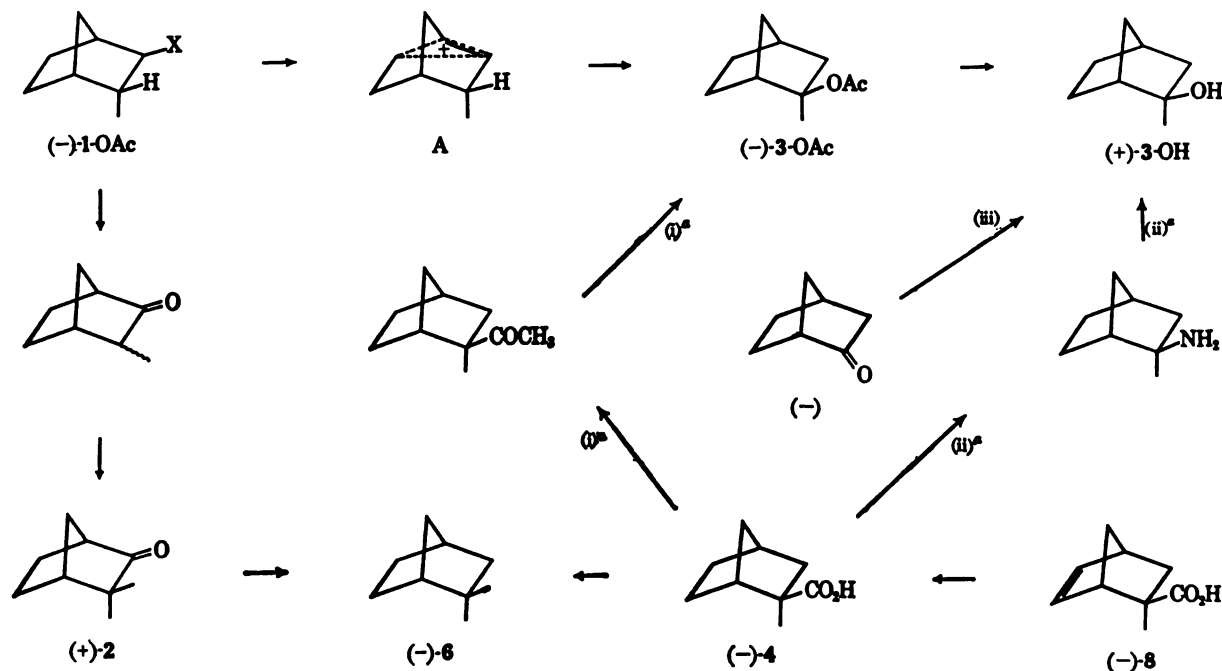
X = OBs) and product (3) are correlated to this ketone as a *common* relay.

Optically active 3-*endo*-methyl-2-*exo*-norbornanol (1) (X = OH) is obtained by conversion of the racemic alcohol¹⁰ to the acid phthalate and fractional crystallization of the ephedrine salt from acetone. Ten recrystallizations of the head crop, regeneration of the acid phthalate, and saponification give a 3-*endo*-methyl-2-*exo*-norbornanol (1, X = OH) which is converted on one hand to a levorotatory acetate (1, X = OAc), $[\alpha]_D -1.85^\circ$ (absolute ethanol), and on the other, by oxidation with chromium trioxide to a mixture of 90% 3-*endo*- and 10% 3-*exo*-methyl-2-norbornanone. Methylation of this mixture (potassium *t*-butoxide, dimethyl sulfoxide, and methyl iodide) gives camphenilone [(+)-2], $[\alpha]_D +16.5^\circ$ (benzene), which on the basis of the highest reported rotation⁷ is 22% optically pure. Since optical fractionations are carefully avoided



throughout the sequence, the starting (-)-1a (X = OAc), $[\alpha]_D -1.85^\circ$, has the same optical purity as (+)-2, $[\alpha]_D +16.5^\circ$.

Scheme I



* Experiment actually performed in enantiomeric series.

The tertiary product (3) expected from direct 3,2-hydride shift in cation A when the latter has the configuration related to that of (-)-1a (X = OAc) (Scheme I) might be derived conceptually from (+)-camphenilone (2) by reduction of the CO group to CH₂ and replacement of the *exo*-methyl group with acetoxy. This correlation can be achieved in practice by way of a relay compound, 2-*endo*-methyl-2-*exo*-norbornanecarboxylic acid, (-)-4, which had previously been correlated with (-)-camphenilane (6), which in turn

(10) Paper II: J. A. Berson, A. W. McRowe, R. G. Bergman, and D. Houston, *J. Am. Chem. Soc.*, **89**, 2563 (1967).


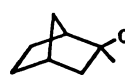
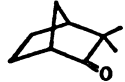
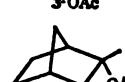




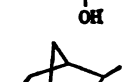
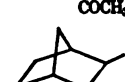
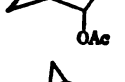
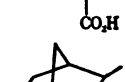

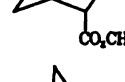

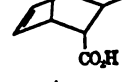

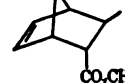
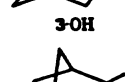


had been obtained^{8,11} from (+)-camphenilone (2). Acid (-)-4 now is correlated to (-)-3 by two sequences (shown for economy of presentation in Scheme I in the series enantiomeric with that in which the experiments were actually performed): (i) by conversion to the methyl ketone and Baeyer-Villiger oxidation; (ii) by conversion to 2-*endo*-methyl-2-*exo*-norbornylamine by the Hofmann rearrangement,^{12a} followed by nitrosative deamination^{12a} of the latter in aqueous acetic acid to give the tertiary alcohol (+)-3-OH corresponding in configuration to (-)-3-OAc. The ratio of rotations of the tertiary alcohols (-)-3-OH obtained from the two routes is 1.23, in good agreement with the ratio of rotations of the starting acids 4 (i:ii = 1.30). Thus, the deaminatively produced alcohol has lost at most about 5% more optical purity than the oxidatively produced one. The correspondence strongly suggests that both sequences proceed with complete or nearly complete retention of optical purity. It would not have been surprising if the deamination, which probably passes through cation A₁, actually did produce some racemization. At least under equilibrating conditions, this system rapidly loses all optical activity, presumably by intramolecular or intermolecular 6,2-hydride shift.^{8a} Under the strongly nucleophilic conditions used in the deamination, however, the cations probably are irreversibly captured, thus suppressing the competing

6,2 shift. Racemizing 6,2 shift is also slow even when cation A₁ is produced under the not completely irreversible conditions in the solvolysis experiments to be

(11) (a) Out of concern that the strongly basic conditions of the Wolff-Kishner reduction⁸ might have caused partial racemization of 2 or its hydrazone by homoenolization,^{11b} we have confirmed the previous work⁸ in both signs and magnitudes of rotation for the (+)-2 → (-)-6 correlation using conditions which, although basic, were quite different from the previous ones. The quantitative agreement between the results makes it highly unlikely that any racemization occurs. (b) A. Nickola and J. L. Lambert, *J. Am. Chem. Soc.*, **84**, 4604 (1962); **88**, 1905 (1966).

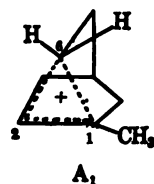
(12) Previously carried out in the racemic series by (a) R. R. Sauers, *ibid.*, **81**, 4873 (1959); (b) N. J. Toivonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fennicae, Ser. III*, No. 64 (1955).

Table I. Absolute Configurations and Rotations of Some Norbornane Derivatives

Compound	$[\alpha]_D$, deg	$[\alpha]_{488}$, deg	Solvent	Ref	Compound	$[\alpha]_D$, deg	$[\alpha]_{488}$, deg	Solvent	Ref
	-113.5	...	Ether	a-e		+4.0	+13.3	CHCl ₃	g
	-73.8	...	Benzene	a-e		+48.0	+146.3	CHCl ₃	g
(-)-2 	+13.6	...	Benzene	a,d		-8.53	...	MeOH	g
	-31.9	...	CCl ₄	f		+16.8	+347	CHCl ₃	f
	-56.8 -42.3	...	CHCl ₃ CCl ₄	f f		-48.7	-132	95% EtOH	f
	+8.04	...	Abs EtOH	g		-45.9	-124	95% EtOH	f
	+68.6	...	95% EtOH	a		-157	-521	95% EtOH	f
	+5.92	...	95% EtOH	a		-162	-536	95% EtOH	f
	-11.0 -11.8 -11.4	-33.2 ...	CHCl ₃ CCl ₄ Hexane	g g g		+48.7	...	Benzene	a
	+25.6	+69.1	CHCl ₃	g		-13.9	...	95% EtOH	f
	+31.5 +31.3	...	CHCl ₃ CHCl ₃	g,h i					

* Reference 9a. ^b J. P. Bain, A. H. Best, B. L. Hampton, G. A. Hawkins, and L. J. Kitchen, *J. Am. Chem. Soc.*, **72**, 3124 (1950). ^c For review, see J. A. Mills and W. Klyne, *Progr. Stereochem.*, **1**, 177 (1954). ^d Reference 8. ^e Reference 6. ^f Reference 5. ^g This work. Correlated with 2-norbornanol, the absolute rotation of which had been established by isotopic dilution analysis of its acid phthalate [J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959)]. ^h K. Mislow and J. G. Berger, *ibid.*, **84**, 1956 (1962). ⁱ Reference 17.

described.⁶ This behavior contrasts markedly with that of norbornyl cation¹³ and a number of substituted derivatives,¹⁴⁻¹⁶ in which 6,2 shift competes with capture of the cations by solvent. An interpretation is offered based on the nonclassical structure, which because of the tendency of the methyl group to localize charge at C-1 has a smaller fraction of the positive charge at C-2 than in the unsubstituted case. This ef-



(13) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).

(14) W. G. Woods, R. A. Carboni, and J. D. Roberts, *ibid.*, **78**, 4653 (1956).

(15) A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *ibid.*, **7**, 378 (1965), and papers cited therein.

(16) Paper IV: J. A. Berson, A. W. McRowe, and R. G. Bergman, *ibid.*, **89**, 2573 (1967).

fect would decrease the rate of 6,2-hydride shift. Obviously, a parallel explanation could be given in terms of an interconverting pair of classical ions, one tertiary and the other secondary.

Correlation of the configuration and rotation of tertiary alcohol (+)-3-OH with those of (-)-norbornanone are also effected (Scheme I, iii) via the epimeric tertiary alcohol, which gives (+)-3-OH upon successive treatment with hydrochloric acid and alkali.^{12b} The maximum rotation of 3-OH based on norbornanone is 11.0° (CHCl₃), the same as that obtained by correlation with camphenilone. Since the norbornanone value (Table I) is ultimately based on an "absolute" method (isotopic dilution), the highest reported value for camphenilone must represent the rotation of optically pure material.

The correlations established in these studies are summarized in Table I, which also lists for easy reference selected data from papers III¹⁷ and VI⁶ bearing on the present study.

(17) J. A. Berson and R. G. Bergman, *ibid.*, **89**, 2569 (1967).

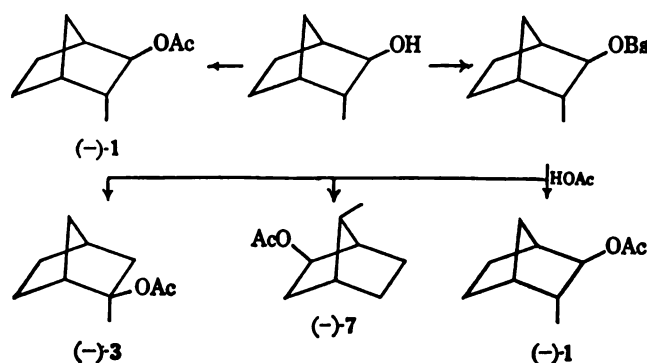
Acetolysis of Optically Active 3-endo-Methyl-2-exo-norbornyl *p*-Bromobenzenesulfonate. Prepared from the same enantiomer of 3-endo-methyl-2-exo-norbornanol that gives (–)-1 (X = OAc) on acetylation, the corresponding *p*-bromobenzenesulfonate (1, X = OBs) solvolyzes in sodium acetate buffered acetic acid to give the same mixture of products already described in the racemic series.¹⁶ Three of these acetates are isolated by preparative vapor chromatography with scrupulous precautions to avoid optical fractionation. The acetate of the starting 3-endo-methyl-2-norbornyl structure is isolated with the same sign and $99 \pm 1\%$ of the magnitude of rotation as that prepared by direct acetylation of the alcohol used to prepare the active substrate 1, X = OBs. (–)-7-*anti*-Methyl-2-exo-norbornyl acetate (7), the configuration and absolute rotation of which are established in paper III,¹⁷ is also isolated with complete preservation ($101 \pm 1\%$) of optical purity. Finally, the formation of (–)-2-endo-methyl-2-exo-norbornyl acetate (3) with complete retention of optical purity is demonstrated by isolation of the corresponding (+)-tertiary alcohol after lithium aluminum hydride reduction of the solvolysis reaction mixture. The rotation to be expected of the tertiary alcohol can be calculated as follows. The unsaturated acid 8 [(–)-2-endo-methyl-2-exo-5-norbornenecarboxylic acid] of $[\alpha]_D -41.4^\circ$ has been converted¹⁸ to (–)-camphenilane of $[\alpha]_D -8.20^\circ$. In Scheme I, (+)-8 of $[\alpha]_D +24.6^\circ$ gave (–)-3-OH of $[\alpha]_D -4.22^\circ$ by the Baeyer–Villiger route (i), whereas (+)-8 of $[\alpha]_D +32.1^\circ$ gave (–)-3-OH of $[\alpha]_D -5.20^\circ$ by the deamination route (ii). Also, (–)-1, X = OAc, $[\alpha]_D -1.85^\circ$, gave camphenilone (2) of $[\alpha]_D +16.5^\circ$, and 2 of $[\alpha]_D +11.6^\circ$ gave camphenilane (6) of $[\alpha]_D -2.20^\circ$. Using the results of the Baeyer–Villiger route (i), the rotation expected for 3-OH derived from the *p*-bromobenzenesulfonate corresponding to (–)-1a, X = OAc, of $[\alpha]_D -1.85^\circ$ is

$$[\alpha]_{\text{calcd}} = -4.22 \left(\frac{-41.4}{+24.6} \right) \left(\frac{-2.20}{-8.20} \right) \left(\frac{+16.5}{+11.6} \right) = +2.70^\circ$$

Using the data of the “deamination route” (ii)

$$[\alpha]_{\text{calcd}} = -5.20 \left(\frac{-41.4}{32.1} \right) \left(\frac{-2.20}{-8.20} \right) \left(\frac{+16.5}{+11.6} \right) = +2.56^\circ$$

If these figures are taken to represent the limits of experimental error, the observed value $[\alpha]_D +2.64^\circ$ corresponds to $100 \pm 3\%$ retention.



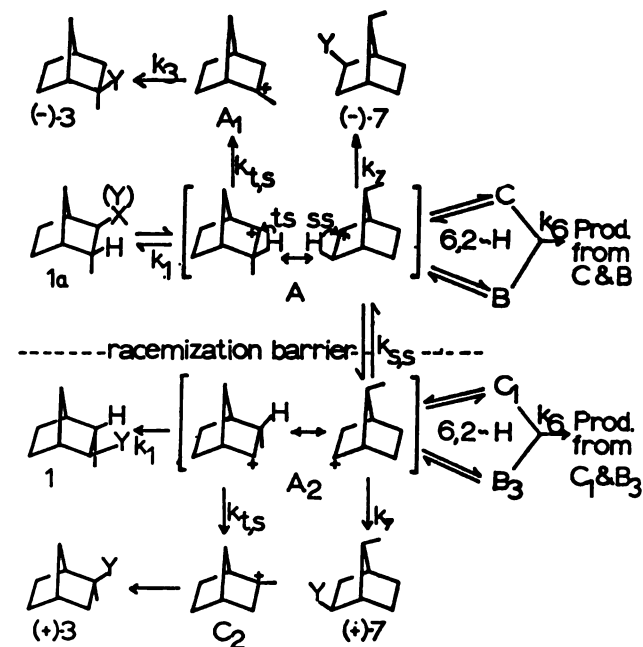
The configuration and optical purity of tertiary product (–)-3 show that it belongs entirely to the stereochemical series that results from direct *exo*-vicinal hydride shift in cation A. The simplicity of this reaction is in striking contrast to the behavior of the epimeric 3-*exo*-methyl cation C.⁴

The hydride shift that converts secondary cation A to tertiary cation A₁ is at least predominantly intramolecular. Solvolysis of 3-endo-methyl-2-exo-norbornyl *p*-bromobenzenesulfonate in acetic acid-*O-d* under the same conditions used in the optically active series produces an acetate mixture from which tertiary acetate 3 is isolated containing only 0.23 atom of deuterium per molecule. This small amount of incorporation results from a reaction of the product 3 after its formation, as control experiments show.⁵ Thus, in processes that expose it only once, A₁ is formed by essentially completely intramolecular hydride shift. Re-formation of A₁, even in buffered medium, permits incorporation of deuterium,⁵ but, fortunately, racemization by 6,2 shift in A₁ is slow enough (see above) to be undetectable.

The 6,2 shifts that lead to the other solvolysis products from 1 (X = OBs)¹⁶ are also entirely intramolecular. The total secondary acetate mixture incorporates only 0.0084 atom of deuterium per molecule.

The uniformly high optical purities of the products from the acetolysis of 1, X = OBs, demonstrate the absence of secondary–secondary hydride shift and of vicinal methyl shift in cation A, both of which are racemizing events. This allows the construction of Scheme II for use in a more detailed scrutiny of part of the over-all mechanism discussed in paper I.⁴ The nomenclature of the cations follows that used there.⁴ From the stereochemical results and distributions of products, it is now possible to deduce two important rate constant ratios in terms of Scheme II.

Scheme II



Relative Rates of Vicinal (3,2) Hydride Shift and Solvent Capture. Assume that the concentrations of all of the carbonium ion intermediates can be expressed by steady-state equations. It is known¹⁶ that the con-

n of secondary ion A to its more stable hydride-1 tertiary isomer A_1 ¹⁸ is essentially irreversible. Optical purity (P) of product 3 or 1a ($X = \text{OAc}$) is given by eq 1 and 2. Significance of the rate constants is given in Scheme 1 for k'_6 , k'_{-6} , and k_6 which refer respectively to forward and reverse rate constants for 6,2-hydride shift in cation A (and its enantiomer A_2) and capture of the hydride-shifted cations C and B (and their enantiomers C_1 and B_1). Rate constants k_6 and k_7 include solvent concentration terms. Bracketed terms of eq 1 represent steady-state concentrations.

$$k_{s,s} + k'_6 + k_{t,s} + k_1 + k_7 - k'_6 k'_{-6} / (k_6 + k_{-6}) = k_{ss}[A]/[A_2] \quad (1)$$

Optical purity of 3 or 1a = $(1 - k_{s,s}/v)/(1 + k_{s,s}/v) \quad (2)$

Fraction (F) of the total acetate product represented by 3 is given by eq 3.

$$F = k_{t,s}/(v - k_{s,s}) \quad (3)$$

Manipulation of eq 2 and 3 gives the ratio of the migration of *exo* hydrogen from a tertiary to a secondary carbon ($k_{t,s}$) to that from a secondary to a tertiary carbon ($k_{s,s}$) (eq 4).

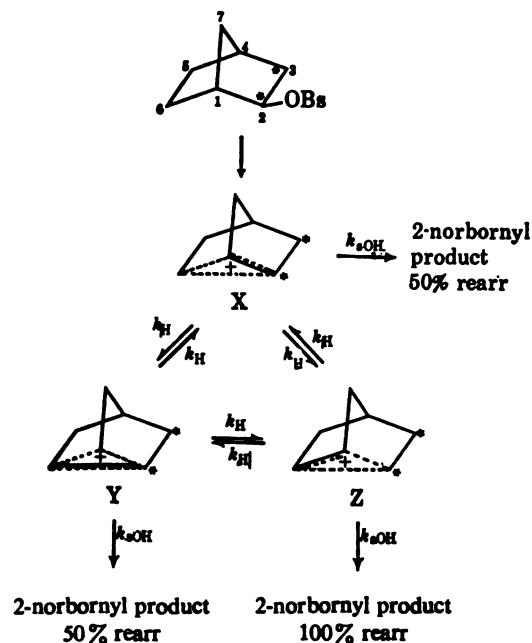
$$k_{t,s}/k_{s,s} = (2P/1 - P)F \quad (4)$$

Product distribution¹⁶ gives F as 0.07. The value is essentially unity whether determined from the optical purity of 3 or from that of 1, $X = \text{OAc}$, but the latter is more accurate since it is obtained by direct comparison of the rotations of a single substance. $P \geq 0.99$, $k_{t,s}/k_{s,s}$ has a minimum value of 14. The ratio of $k_{t,s}$ to the composite rate constant $k_{sOH} + k_7$ measures the competition between tertiary-hydride shift and solvent capture of ion A. It can be evaluated with the previously reported data¹⁸ for the ratio 3:(1 + 7) as 0.074 in aqueous ethanol, 0.18 in aqueous dioxane, 0.115 in formic acid, and 0.115/0.17 (average of ratios from three different modes of migration) in acetic acid. Thus, $k_{sOH}/k_{s,s}$, the competition between solvent capture and secondary-secondary hydride shift in A, is 14:0.115 or at least 122 in acetic acid at 0°. A factor this large would suffice to prevent formation of a detectable amount of 3,2-shifted product from norbornyl cation itself (2,3-¹⁴C-labeled).¹³ Usually, this ratio may be very much larger. As a migrating rate, we may use 6,2-hydride shift, which is known¹³⁻¹⁶ to be competitive with and hence of the order of magnitude as solvent capture in many norbornyl systems. A direct comparison between 6,2-secondary-secondary 3,2 shift in norbornyl cation is available from the proton magnetic resonance spectrum in solvent $\text{SbF}_5\text{-SO}_2\text{ClF-SO}_2$ at -120° , which shows¹⁹ that 6,2 shift is at least 8.8 powers of ten faster than 3,2 shift. If this rate ratio were largely due to difference in activation enthalpy and if it persisted

in hydroxylic media, 6,2 shift would be faster than 3,2 shift under the solvolysis conditions (water or acetic acid solvent, 25–100°) by factors in the range 4×10^3 – 3×10^4 . Thus, solvent capture should overwhelm secondary-secondary 3,2 shift by several orders of magnitude. Experimentally, no 3,2 shift was detected^{13,20a} in the acetolysis of *exo*-norbornyl *p*-bromobenzenesulfonate-2,3-¹⁴C, but Lee and Lam later reported^{20b} having found such a process in the acetolysis of the corresponding 2-tritio derivative. These authors interpreted^{20b} their data in terms of 1–2% of C-3 tritio product. The total per cent contribution of 3,2 shift would have had to be in the range 7–10% to account for this,^{20b} so that 3,2 shift and 6,2 shift, according to this interpretation, cannot differ very much in rate. Furthermore, 3,2 shift seems to be just detectable in formolysis of ¹⁴C-labeled material,^{13,20,21} although it is not clear whether the distribution there is completely kinetically controlled. If the reports of competitive 3,2 and 6,2 shifts in hydroxylic media are correct, one is forced to the conclusion that the relative and absolute magnitudes of these specific rates can vary by several powers of ten as a function of solvent. Since the rates observed by nmr techniques in nonhydroxylic media are being used as approximations to the rates under solvolytic conditions,²² it would seem imperative that the discrepancy be resolved. The closely related matter of absolute rates of capture of the cations in solvolytic media is briefly discussed in the Appendix.

Relative Rates of Transannular (6,2) Hydride Shift and Solvent Capture. Estimates of these relative rates for the secondary-secondary case can be made from studies of isotope-position rearrangement in solvolyses of 2,3-¹⁴C-norbornyl derivatives¹³ or from the more recent experiments in the 2-tritio-norbornyl series.^{20b} The adjacent diagram (Scheme III) outlines the basis for

Scheme III



Only one resonance form of A_1 is shown here. The argument is essentially changed whether A_1 is considered to be a resonance hybrid—secondary nonclassical ion or a tertiary classical ion. We are concerned here or in the sequel with the distinction.

(a) M. Saunders, P. von R. Schleyer, and G. A. Olah, *J. Am. Chem. Soc.*, **86**, 5680 (1964); (b) F. R. Jensen and B. H. Beck, *Tetrahedron*, **4287** (1966).

(20) (a) P. D. Bartlett and C. E. Dills, unpublished results; C. E. Dills, Thesis, Harvard University, 1955; (b) C. C. Lee and L. K. M. Lam, *J. Am. Chem. Soc.*, **88**, 2831 (1966); (c) *ibid.*, **88**, 5355 (1966).

(21) For a review, see J. A. Berson in "Molecular Rearrangements," Part 3, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963.

(22) S. Winstein, *J. Am. Chem. Soc.*, **87**, 381 (1965).

the calculations from the ^{14}C data. Vicinal shift is assumed to be slow.^{13b} Kinetic isotope effects in this type of marking are all secondary and are assumed to be small. The tritium-labeling data^{20b} must be handled in a different manner, which is described in the Appendix. The total per cent rearrangement of isotope position is given by $F_x(50) + F_y(50) + F_z(100)$, where F_x , F_y , and F_z are the fractions of product formed from cations X, Y, and Z. By symmetry, the steady-state concentrations of Y and Z are equal, and hence $F_y = F_z$. Thus, the total per cent rearrangement may be expressed as in eq 5.

$$F_x(50) + F_y(150) = \text{total } \% \text{ rear} \quad (5)$$

But $F_y = (1 - F_x)/2$, so that eq 5 can be put in the form of eq 6. From the previously derived¹⁶ relationships

$$F_x = 3 - \text{total } \% \text{ rearr}/25 \quad (6)$$

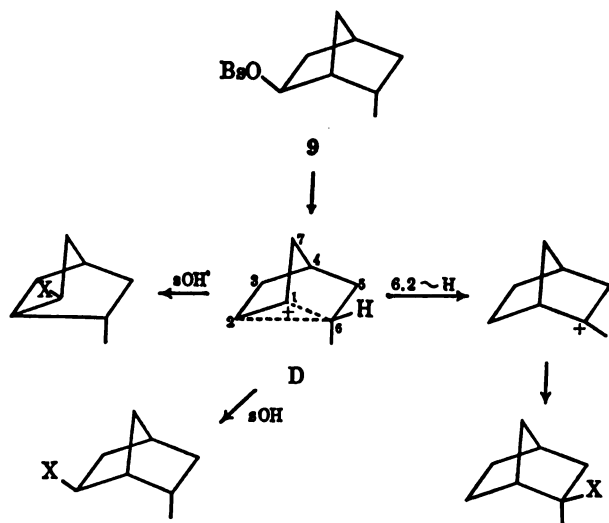
(eq 7 and 8), one obtains eq 9, which permits an experi-

$$F_x = (k_H + k_{\text{OH}})/(3k_H + k_{\text{OH}}) \quad (7)$$

$$F_y + F_z = 2k_H/(3k_H + k_{\text{OH}}) \quad (8)$$

$$k_H/k_{\text{OH}} = (1 - F_x)/(3F_x - 1) \quad (9)$$

mental evaluation of the competition between secondary-secondary 6,2-hydride shift and solvent capture of norbornyl cation. The corresponding competition ratio for a tertiary-secondary case is supplied by the product distribution¹⁶ from 6-*endo*-methyl-2-norbornyl *p*-bromobenzenesulfonate (9). Table II summarizes these ratios.



An estimate of the effect of methyl substitution on the absolute rate of 6,2-hydride shift would bear upon the question of charge distribution in the transition state. Although such an estimate based on the data of Table II is at best a rough one, it seems worth making. One should first make some attempt to relate the hydride shift rates to a common solvent capture rate k_{OH} . It seems reasonable to assume¹⁶ that k_{OH} would be roughly the same for attack at the favored position¹⁶ (C-1) of the 6-methyl cation (D) as for attack on norbornyl cation. Since attack at C-2 of D is only about one-tenth as fast,¹⁶ k_{OH} for D can be taken to be roughly one-half k_{OH} for norbornyl cation. The experimental k_H/k_{OH} values of Table II for the 6-methylnorbornyl cases are therefore divided by this statistical factor of 2.

Table II. Competition Ratios (6,2-Hydride Shift vs. Solvent Capture) for Secondary-Secondary (s,s) and Tertiary-Secondary (t,s) Systems

Structure	Type of shift	Solvent	Temp, °C	k_H/k_{OH}
Norbornyl	s,s	Aq acetone	45	0.12
Norbornyl	s,s	HOAc	45	0.27
6-Methylnorbornyl	t,s	Aq EtOH	100	0.92 (0.
6-Methylnorbornyl	t,s	HOAc	100	2.45 (1.

* The value in parentheses is an estimate derived from a statistical correction of the experimental value (see text).

If 6,2-hydride shift at both the ion-pair and separation stages occurred in the norbornyl cation²³ but in 6-methylnorbornyl, the norbornyl ratios of Tab derived upon the assumption of a "single pass" petition, would be too high. It is difficult to guess much correction should be applied for this,²³ but were large, the observed total per cent rearrange figures would have approached the "equilibrium" value of 66.7%. This is not found to be the case. The change in temperature (45–100°) between the norbornyl and 6-methylnorbornyl experiments might change the k_H/k_{OH} ratio in acetic acid by a factor of about 2 (see Appendix).

One concludes that the enhancement of the rate of 6,2-hydride shift by methyl substitution is a factor of about 5 and about 15 in acetic acid. This effect on the removal of "hydride ion" from the cation to the transition state distance contrasts strongly with the enormous change produced by methyl substitution on SN1 solvolyses,²⁴ where achievement of the transition state involves stretching a halogen-carbon bond. In reactions of bromides, for example, alteration of secondary structure (isopropyl) to tertiary (*t*-butyl) enhances the solvolysis rate by factors ranging between 10^3 and 10^5 . Although ground-state energy differences cannot be ignored, it seems likely that a major cause of the observed weakening of the methyl substituent has to do with charge distribution in the transition state. The transition state for halide solvolysis probably has a substantial amount of positive charge localized at the reaction site, and its energy would, therefore, be very responsive to alkyl substitution, but the transition state for 6,2-hydride shift if it resembles an edge-protonated cyclopropane,²⁵ consistent with the *endo-endo* geometry of the process,²⁶ might be expected²⁷ to have relatively little positive charge at the migration origin (C-6) or terminus (C-2). Much of the charge might well be localized on the migrating hy-

(23) For an earlier discussion, see J. A. Berson and A. Rembaum, *J. Am. Chem. Soc.*, **86**, 1749 (1964).

(24) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).

(25) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **74**, 1154 (1952).

(26) (a) J. A. Berson and P. W. Grubb, *ibid.*, **87**, 4016 (1965).

(b) M. Benjamin and C. J. Collins, *ibid.*, **88**, 1556 (1966). (c) As has been pointed out,²⁸ the possibility cannot be dismissed that substituent change the 6,2-shift intermediate or transition state from hypothetical face-protonated in simple norbornyl cation to edge-protonated (stereochemical equivalent leading to an *endo-endo* process) in the substituted examples actually studied.^{29a,b} However, this is not the content of the statement^{28d} that in the substituted cases, "either the protonated or the face-protonated intermediate could produce the experimental result." In the case of the 1-methyl-7-carboxynorbornyl cation, a single face-protonated intermediate of nominal *t*-symmetry was experimentally excluded.^{29a} (d) C. J. Collins and M. Benjamin, *J. Am. Chem. Soc.*, **89**, 1652 (1967).

(27) R. Hoffmann, *J. Chem. Phys.*, **40**, 2480 (1964).

as extended Hückel calculations suggest is the case cyclo- $C_8H_7^+$ itself.²⁷

Experimental Section

Optical Activation of 3-endo-Methyl-2-exo-norbornyl Acid Sulfate. A solution of 600 g of the racemic acid phthalate¹⁰ in acetone was brought to boiling on the steam bath and treated with an equimolar amount of ephedrine. After a short while the mixture was homogeneous; it was cooled to room temperature and stood overnight, after which time a large amount of the potassium salt had crystallized from the solution. The white crystals collected on a Büchner funnel and recrystallized ten times in acetone, yielding 165 g of salt in the head crop. A 50.0-g quantity of this material was stirred rapidly with about 200 g of crushed ice, 30 ml of 35% aqueous HCl, and 75 ml of ether. When there was no longer visible in the mixture, the phases were separated, the aqueous layer was extracted twice more with ether. The combined ether fractions were washed with 5% hydrochloric acid, water, and brine, and dried over sodium sulfate. They were then distilled and the solvent was evaporated at the aspirator, leaving 15 g (quantitative yield) of optically active acid phthalate, which had a specific rotation of $[\alpha]^{25}_D -3.98^\circ$ ($CHCl_3$).

The optically active acid phthalate was mixed with 40 ml of 15% sodium hydroxide and steam distilled. Optically active 3-endo-methyl-2-exo-norbornanol, **1a**, $X = OH$, distilled over completely in 10 min and crystallized in the aqueous distillate. To effect optical fractionation, the alcohol was collected completely by repeated extraction of the distillate with pentane, after saturation of the aqueous phase with salt. The combined pentane extracts were washed with 1% hydrochloric acid and brine and dried over sodium sulfate. The pentane solution was then concentrated to a manageable size, but the alcohol was not allowed to crystallize. An aliquot was removed and concentrated to dryness at the aspirator, and an infrared spectrum taken. It was identical with that of the pure racemic sample.¹⁰ A second aliquot was removed and converted to optically active 3-endo-methyl-2-exo-norbornyl acetate, which had an infrared spectrum and retention time on vpc identical with that of the racemic sample. Analysis by capillary vpc showed it to be 99% homogeneous. The rotation was $[\alpha]^{25}_D -1.85^\circ$ (absolute alcohol).

Resolution of Optically Active 3-endo-Methyl-2-exo-norbornyl Ketone ((-)-1a**, $X = OAc$) with (+)-Camphenilone (2).** The mixture of 3-methyl-2-norbornanones derived from the above active ketone, $[\alpha]^{25}_D -1.85^\circ$, has been described elsewhere.¹⁷ A portion (10 g) of the mixed ketones was dissolved in 5 ml of dry dimethyl sulfoxide (previously distilled from lithium aluminum hydride). The mixture was placed in a three-necked, round-bottomed flask was flamed out under a stream of nitrogen, cooled, and charged with 1.8 g of potassium hydroxide and 40 ml of dry dimethyl sulfoxide. The ketone solution was then added to the flask dropwise from a pressure-equalizing funnel, while the entire system was protected with a nitrogen blanket. Upon the addition the cloudy, off-white solution turned yellow.

After the mixture had been stirred for 20 min, 15 ml of freshly distilled methyl iodide was added dropwise while stirring was continued. The cloudiness and color disappeared immediately, and the mixture was allowed to stir for 2 hr at room temperature. The mixture was then added and the mixture was extracted four times with pentane. The combined pentane extracts were washed repeatedly with water and once with saturated brine, and dried over sodium sulfate. Decantation and evaporation left a greenish oil containing 15% (by capillary vpc) 15% 3-exo-methyl-2-norbornanone, 5% 3-endo epimer, 60% camphenilone (2), and the rest low-boiling products. After distillation bulb to bulb, the distillate was chromatographed on column D-1. By this procedure the optically active camphenilone could be obtained in better than 99.0% purity. It had a specific rotation of $[\alpha]^{25}_D +16.5^\circ$ (benzene).

Inversion of (+)-Camphenilone to (-)-Camphenilane.⁴ An aliquot of optically active camphenilone obtained from Light and Heavy Chemicals, $[\alpha]^{25}_D +11.6^\circ$, $CHCl_3$, and weighing 1.0 g was dissolved in 95% ethanol. Semicarbazide hydrochloride (0.9 g) and sodium acetate (1.1 g dissolved in 5 ml of water) were added, and the resulting mixture was heated at reflux for 4 hr on the steam bath with a water condenser. The semicarbazone separated as white crystals on cooling; it was extracted with three portions of $CHCl_3$, the combined organic extracts were washed with saturated sodium chloride and dried over magnesium sulfate. The solution was filtered and an aliquot was taken for an infrared spectrum. The spectrum showed the expected N-H (2.9, 3.0 μ) and C=N

(5.92 μ) bands, and a complete absence of C=O absorption (5.72 μ). The solution was therefore concentrated to dryness at the aspirator and all the product (5.5 g, 97% yield) was removed and mixed with 4.5 g of pulverized KOH. This solid mixture was placed in a 100-ml, round-bottomed flask and shaken to ensure homogeneity. A short-path distillation apparatus was attached, and the flask was heated in a Woods' metal bath from 170 to 260°. As the temperature rose, the solid fused and bubbled and a two-phase mixture collected in the receiver. When the distillation was complete, the material in the pot had solidified to a tan mass.

The organic layer was drawn off the top of the distillate with a pipet, a little pentane was added to the aqueous phase, and the pentane layer was drawn off and combined with the first fraction. After a small amount of magnesium sulfate was added to the organic mixture, it was centrifuged and the liquid was separated from the magnesium sulfate. The solid was washed with pentane and the pentane was combined with the rest of the hydrocarbon. As an infrared spectrum of this mixture showed a small C=O band, about 0.060 g of lithium aluminum hydride was added and the material was distilled bulb to bulb at atmospheric pressure. The hydrocarbon (2.5 g, 72% yield) came over as a clear liquid, solidifying in the Dry Ice trap. Chromatography on column D-1 at 135° gave camphenilane (6), which was again distilled bulb to bulb and thus obtained better than 99.0% pure by capillary vpc. Its specific rotation was $[\alpha]^{25}_D -2.20^\circ$ (benzene), and its infrared spectrum was identical with that of a racemic sample.¹⁰

Solvolysis of Racemic 3-endo-Methyl-2-exo-norbornyl p-Bromobenzenesulfonate (1a, $X = OBr$). A 0.1 M solution of sodium acetate in acetic acid was heated to thermal equilibrium in an oil bath at 95°. With rapid stirring, a suspension of 12.3 g of the sulfonate¹⁰ in another 50 ml of buffer solution was then added dropwise to the hot solution. The resulting mixture was stirred at this temperature for 15 min, after which time it was allowed to cool to room temperature and poured onto pentane and cracked ice. The phases were separated, the water phase was extracted twice more with pentane, and the combined organic layers were washed with water, saturated sodium bicarbonate solution, and brine, and dried over sodium sulfate. The solution was decanted, and the pentane was distilled away carefully with a Vigreux column, leaving a greenish, sweet-smelling oil. Bulb-to-bulb distillation of this material at 15 mm gave 5.0 g (83%) of acetates as a water-white oil. An analysis of this material by capillary vpc showed that it contained several products, whose identities and relative proportions are given elsewhere.¹¹

In another experiment, 0.9 g of the sulfonate was solvolyzed under the same conditions, but for a longer period of time. Aliquots were withdrawn periodically and worked up individually as above. Analysis of these aliquots by vpc indicated that the solvolysis was essentially complete after 5 min at 95°, and the relative proportions of the products remained constant for several hours afterward. At very long reaction times (greater than 4 or 5 hr) small amounts of other products, 1-methyl-2-exo-norbornyl acetate and 2-exo-methyl-2-endo-norbornyl acetate, could be detected.

A solvolysis of 3-endo-methyl-2-exo-norbornyl p-toluenesulfonate was carried out in a manner identical with that of the p-bromobenzenesulfonate solvolysis. The product pattern, analyzed by capillary vpc after work-up, was identical with that from the p-bromobenzenesulfonate.

Solvolysis of 1a in O-Deuterioacetic Acid. The procedure described for solvolysis of 1a, $X = OBr$, and isolation of tertiary product as alcohol 3-OH in the optically active series was repeated on a sample of racemic p-bromobenzenesulfonate, except that O-deuterioacetic acid was employed as solvent. Falling drop analysis on 3-OH showed it to contain 1.6 atoms % excess deuterium (0.23 atom of deuterium per molecule), and analysis of the remainder of the alcohols showed the mixture to contain 0.06 atom % excess deuterium (0.0084 atom of deuterium per molecule).

Solvolysis of Optically Active 1a, $X = OBr$. An aliquot of the same pentane solution of 3-endo-methyl-2-exo-norbornanol (1a, $X = OH$) used to prepare (-)-3-endo-methyl-2-exo-norbornyl acetate, $[\alpha]^{25}_D -1.85^\circ$, contained about 9 g of the alcohol. This was converted to the p-bromobenzenesulfonate in a procedure identical with that used to prepare the racemic derivative.¹⁰ The material obtained was identical in spectral properties with the racemic sulfonate, except that the infrared showed the presence of a small amount of residual starting alcohol. A preparative-scale solvolysis on 20.6 g of the optically active sulfonate was carried out under the same conditions as the racemic analog,¹⁴ and 7.6 g (75%) of acetates was obtained from the reaction. The entire mixture was reduced to alcohols with lithium aluminum hydride, and 2-endo-

methyl-2-*exo*-norborneol (3) was separated from the other products on vpc column B at 135° after bulb-to-bulb distillation of the mixture at 13 mm. The tertiary alcohol was collected as white needles, pure by capillary vpc. After bulb-to-bulb distillation, it had a specific rotation of $[\alpha]_D^{25} +2.64^\circ$ (CHCl₃). Its infrared spectrum was identical with that of a racemic sample.

The remainder of the solvolysis material was collected as a semi-solid and reconverted to acetates in the usual way. The two major products, 3-*endo*-methyl-2-*exo*-norbornyl acetate (1a, X = OAc) and 7-*anti*-methyl-2-*exo*-norbornyl acetate (7), were separated from the rest of the mixture on column E at 175°. Both were recycled on the same column to give acetate 1a in better than 99.0% purity and 7 in 98.0% purity. Acetate 1a obtained in this way was identical in infrared spectrum and capillary vpc retention time with authentic 1a. It was found to have specific rotation $[\alpha]_D^{25} -1.83^\circ$ (absolute ethanol) and is thus formed with $99 \pm 1\%$ retention of configuration. The sample of 7 obtained from this solvolysis was identical in infrared spectrum and retention time on vpc with material obtained from the deamination of 3-*endo*-methyl-2-*exo*-norbornylamine hydrochloride¹⁸ and had a specific rotation of $[\alpha]_D^{25} -3.19^\circ$ (95% ethanol).

Scheme I. Correlation of 2-*endo*-Methyl-5-norbornene-2-*exo*-carboxylic Acid (8) with 2-*endo*-Methyl-2-*exo*-norbornanol (3-OH). (i) Baeyer-Villiger Route, Racemic Series. Hydrogenation of pure racemic 8,^{28,29} conversion to the acid chloride, and reaction of the latter compound with dimethylcadmium were carried out in the manner described¹⁰ for similar transformations. Racemic 2-*endo*-methyl-2-*exo*-acetylnorbornane was a liquid, bp 95–98° (25 mm), $n_D^{25} 1.4759$.

Anal. Calcd for C₁₀H₁₈O: C, 78.89; H, 10.60. Found: C, 78.63; H, 10.66.

The 2,4-dinitrophenylhydrazones were recrystallized from ethanol and had mp 155.5–156°.

Anal. Calcd for C₁₀H₁₂O₄N₂: C, 57.82; H, 6.07. Found: C, 57.73; H, 6.19.

The racemic ketone reacted with perbenzoic acid in the usual manner¹⁰ to give 2-*endo*-methyl-2-*exo*-norbornyl acetate.

Optically Active Series. A sample of 8 obtained by resolution²⁸ had $[\alpha]_D^{25} +24.6^\circ$ (95% ethanol). It was hydrogenated over platinum oxide in methanol to the saturated acid which then was converted to the ketone as in the racemic series. The ketone had $[\alpha]_D^{25} +9.25^\circ$ (CHCl₃), $n_D^{25} 1.4751$, and was homogeneous by vpc. Its infrared spectrum was identical with that of the racemate.

Oxidation with perbenzoic acid as in the racemic series followed by reduction with lithium aluminum hydride gave a mixture of alcohols which was purified by preparative vapor chromatography on column C to give pure 2-*endo*-methyl-2-*exo*-norbornanol (3-OH), $[\alpha]_D^{25} -4.22^\circ$ (CCl₄). This material had mp 84–85°. It was homogeneous on column L, and its infrared spectrum was identical with that of the racemate.

Scheme I. (ii) Deamination Route. A sample of 2-*endo*-methyl-5-norbornene-2-*exo*-carboxylic acid (8) obtained by resolution²⁸ had $[\alpha]_D^{25} +32.1^\circ$ (95% ethanol). It was hydrogenated and treated with thionyl chloride to give the corresponding saturated acid chloride. This material was dissolved in dry ether and treated with dry ammonia gas. Filtration of the solid, concentration of the filtrate, washing of the combined solids with water, extraction of the water wash with ether, evaporation of the ether, and drying of the combined solid gave 98.4% of the amide, $[\alpha]_D^{25} +5.65^\circ$ (methanol).³⁰ This material was subjected to the Hofmann rearrangement under the conditions reported by Sauers³¹ in the racemic series. The resulting amine hydrochloride had an infrared spectrum identical with that of the racemate (kindly supplied by Professor Sauers³¹).

The amine hydrochloride (3.8 g) in a mixture of 10 ml of water and 2.5 ml of acetic acid was treated with a solution of 2.5 g of sodium nitrite in 8 ml of water. The reaction mixture was allowed to stand 3 hr, poured into 150 ml of water, and extracted with pentane. Drying, evaporation of the pentane, lithium aluminum hydride reduction, reacylation, distillation, and reduction gave 2-*endo*-methyl-2-*exo*-norbornanol, $[\alpha]_D^{25} -5.20^\circ$ (CCl₄).

Scheme I (iii). Asymmetric hydroboration³² of norbornene with

diisopinocampheylborane (prepared from α -pinene of $[\alpha]_D -42.7^\circ$ [c 2.3, absolute EtOH], kindly supplied by Dr. H. Enos of Hercules Powder Co.) and acetylation of the crude alcohol obtained after oxidation gave (–)-*exo*-2-norbornyl acetate, $\alpha -3.31^\circ$ (neat, 1 dm), after distillation through a spinning-band column. This material contained less than 5% of the *endo* isomer as estimated by vpc (column N) of the alcohol derived from it by lithium aluminum hydride reduction. Jones oxidation³³ gave 2-norbornanone, $[\alpha]_D -7.95^\circ$ (chloroform), which was homogeneous (columns L and N).

Methyl Grignard reagent was prepared in 150 ml of ether in a 1-l., three-necked flask from 6.90 g (0.28 g-atom) of magnesium turnings and 15.9 ml (at 0°) of methyl bromide (0.29 mole). To this mixture was added a solution of 23.5 g (0.213 mole) of norbornanone, $[\alpha]_D -7.95^\circ$ (chloroform), in 100 ml of ether over a 20-min period. The light tan mixture was stirred for 1 hr at room temperature. The excess reagent was destroyed with a saturated solution of ammonium chloride. The solution and salts were cooled to 0° and almost all the precipitate was dissolved with 2 N hydrochloric acid; the solution was still alkaline as evidenced by the odor of ammonia.

The clear ether layer was separated from the aqueous phase and the latter extracted four times with pentane to give a combined organic solution of ca. 650 ml which was twice washed with saturated brine and dried over sodium sulfate. The solvent was carefully fractionated off, to give a slightly yellow oil.

The crude oil was distilled bulb to bulb at 95° (ca. 25 mm), to yield a white crystalline solid; the infrared spectrum and retention times on vpc were identical with those of a racemic sample of 2-*exo*-methyl-2-*endo*-norbornanol prepared by the method of Toivonen.^{12b} The yield was 25.5 g (95%). A representative sample was taken from the molten alcohol: $[\alpha]_D^{25} -6.45 \pm 0.09^\circ$; $[\alpha]_D^{25} -17.41 \pm 0.05^\circ$ (c 4.3, chloroform), average values and standard deviations given for four determinations.

The above alcohol was acetylated with excess acetic anhydride and pyridine at 100° for 24 hr to give, after the usual work-up and distillation, a 100% yield of the acetate, whose infrared spectrum and vpc retention times on vpc were identical with those of the authentic, racemic material. Capillary vpc on column N indicated the presence of ca. 0.05% *t-exo* acetate, rotation $[\alpha]_D^{25} -12.09 \pm 0.07^\circ$, $[\alpha]_D^{25} -36.84 \pm 0.08^\circ$ (c 6–7.8, chloroform). Treatment with lithium aluminum hydride regenerated the starting alcohol with unchanged rotation.

2-*endo*-Methyl-2-*exo*-norbornanol [(+)-3-OH]. A homogeneous sample of 3.00 g of the above optically active 2-*exo*-methyl-2-*endo*-norbornanol was stirred with concentrated hydrochloric acid for 2 hr at room temperature. The chloride was extracted with pentane, washed with brine, and evaporated to give a residue which was homogeneous on columns L and N except for traces of pentane. The crude chloride was stirred at 95° with 35 ml of 1 N sodium hydroxide for 4 days and extracted with pentane. Washing with brine, drying over sodium sulfate, removal of solvent, and sublimation gave 2.36 g (80%) of (+)-3-OH, infrared spectrum and vpc retention time identical with those of an authentic racemic sample.^{12b} The rotations were $[\alpha]_D^{25} +2.78 \pm 0.006^\circ$; $[\alpha]_D^{25} +8.38 \pm 0.02^\circ$ (c 5.0–5.3, chloroform).

The corresponding acetate (–)-3-OAc prepared in 94% yield from this sample had $[\alpha]_D^{25} -1.01 \pm 0.03^\circ$; $[\alpha]_D^{25} -3.36 \pm 0.01^\circ$ (c 5.2–5.4, chloroform), and contained 0.75% of the epimeric acetate. Lithium aluminum hydride regenerated (+)-3-OH with unchanged rotation which contained no 1-methyl-2-*exo*-norbornanol (0.05% could have been detected, column L).

By a previously described procedure,³⁴ 2-*exo*-methyl-2-*endo*-norbornanol, $[\alpha]_D^{25} -6.45^\circ$ (chloroform), was converted to 1-methyl-2-*exo*-norbornyl acetate, $[\alpha]_D^{25} +9.29 \pm 0.03^\circ$; $[\alpha]_D^{25} +28.0 \pm 0.005^\circ$ (c 5.2–5.4, chloroform), which was reduced with lithium aluminum hydride to 1-methyl-2-*exo*-norbornanol, $[\alpha]_D^{25} +0.21 \pm 0.02^\circ$; $[\alpha]_D^{25} -2.11 \pm 0.02^\circ$ (c 5.8–5.9, chloroform). Reacetylation gave back the acetate with unchanged rotation.

Appendix

6,2-Hydride Shifts in the 2-Norbornyl-2-*t* System. The threefold symmetry properties associated with 6,2-hydride shifts in 2-norbornyl-2,3-¹⁴C cations are perturbed in the 2-norbornyl-2-*t* analogs. In the 2,3-¹⁴C case (Scheme III), three successive transannular shifts in a given direction suffice to complete the symmetry operation by which the starting cation is trans-

(28) S. Beckmann, R. Schaber, and R. Bamberger, *Chem. Ber.*, **87**, 997 (1954).

(29) J. S. Meek and W. B. Trapp, *J. Am. Chem. Soc.*, **79**, 3909 (1957).

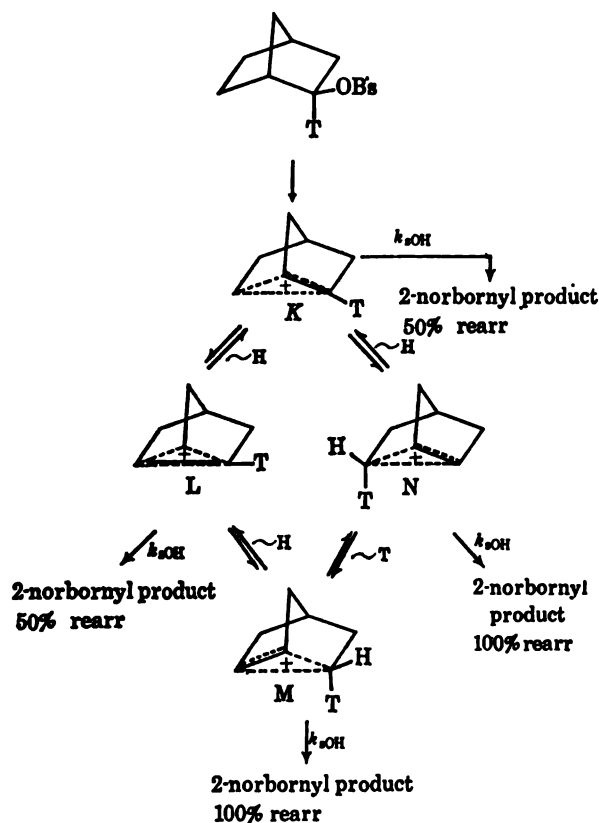
(30) For the racemate, see ref 31.

(31) R. R. Sauers, *J. Am. Chem. Soc.*, **81**, 4873 (1959).

(32) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, **86**, 397 (1964).

formed into itself. Although the 2-*t* case has also been discussed as if it were threefold symmetric,^{20b} this approach is not really justifiable. The number of successive transannular hydride shifts needed to complete the symmetry operation depends upon the stereochemistry of these shifts. If, as seems likely,²⁶ these are constrained to be *endo-endo*, four successive transannular shifts are required to complete a cycle (Scheme IV). The competition ratio $k_{\text{OH}}/k_{\text{H}}$ can be calculated

Scheme IV



from experimental data by means of eq 10, which is derived by treating all of the cationic intermediates by steady-state methods, assuming no isotope effect ($k_{\text{H}} = k_{\text{T}}$).

$$R_{\text{T}} = (F_{\text{M}} + F_{\text{N}})/(F_{\text{K}} + F_{\text{L}}) = \frac{4 + (k_{\text{OH}}/k_{\text{H}})}{4 + 5(k_{\text{OH}}/k_{\text{H}}) + (k_{\text{OH}}/k_{\text{H}})^2} \quad (10)$$

The quantities F_{M} , F_{N} , F_{K} , and F_{L} represent the fractions of product formed from each of the four cations, and the quantity R_{T} is evaluable from the experimental ratio of 5,6-tritiated to 5,6-untritiated product, these two ring positions being inseparable in the degradation scheme. Solution of the quadratic and rejection of the physically insignificant negative root give the desired ratio $k_{\text{OH}}/k_{\text{H}}$ (eq 11).

$$k_{\text{OH}}/k_{\text{H}} = \frac{1 - 5R_{\text{T}} \pm (9R_{\text{T}}^2 + 6R_{\text{T}} + 1)^{1/2}}{2R_{\text{T}}} = (1/R_{\text{T}}) - 1 \quad (11)$$

A cubic relationship (eq 12) is derived from the alternative extreme assumption of a large isotope effect ($k_{\text{T}} = 0$).

$$R_{\text{T}}(k_{\text{OH}}/k_{\text{H}})^3 + (5R_{\text{T}} - 1)(k_{\text{OH}}/k_{\text{H}})^2 + (6R_{\text{T}} - 4)(k_{\text{OH}}/k_{\text{H}}) + 2(R_{\text{T}} - 1) = 0 \quad (12)$$

The ratio R_{C} of 5,6-labeled to 5,6-unlabeled product in the case of 2,3-¹⁴C starting material is readily derived from eq 7 and 8 as

$$k_{\text{OH}}/k_{\text{H}} = (1/R_{\text{C}}) - 2 \quad (13)$$

As eq 11, 12, and 13 show, the product distributions from 2,3-¹⁴C and 2-*t* starting materials are different functions of the rate constants in question, and the apparent correspondences noted^{20b} between the two experiments in terms of "per cent contributions" of C-1, C-2 and C-1, C-2, C-3 equating processes are purely fortuitous. If the same rate constants apply to the two systems, eq 11, 12, and 13 show that, in principle, these "per cent contributions" cannot be the same. Expressed another way, the number of sequential steps required to achieve a given "per cent contribution" differs in the two cases. The proper cross-check is made *via* the rate constants. Thus, from the tritium experiments^{20b} and eq 11 one calculates $k_{\text{OH}}/k_{\text{H}} = 2.88$ in acetic acid at 45°. Using this value and eq 7, 8, and 13, one can calculate R_{C} and the distribution to be expected in the ¹⁴C experiment under the same conditions: C-5, C-6, 17.0%; C-2, C-3, 41.5%; C-1, C-4, 20.8%; and C-7, 20.8%. This is in quite good agreement with the experimental values of 15, 40, 23, and 22%. Conversely, one can calculate R_{T} from eq 10 and the ¹⁴C data, using the value 3.67 for $k_{\text{OH}}/k_{\text{H}}$ obtained from eq 13. This leads to a calculated distribution of 17.6% of tritium at C-5, C-6, which is to be compared with the experimental value^{20b} of 20.5%. Although the ratio $k_{\text{OH}}/k_{\text{H}}$ determined from the tritium data is about 20% lower than the ¹⁴C value, the distributions calculated in the cross-checks are rather insensitive to the discrepancy. The alternative assumption (eq 12) of a large isotope effect in the tritium experiments leads to $k_{\text{OH}}/k_{\text{H}} = 2.7$.

The Temperature Effect on the Competition Ratio. An Estimate of the Minimum Activation Energy for the Capture of Norbornyl Cation. From the $k_{\text{OH}}/k_{\text{H}}$ ratios of 2.88 at 45° and 1.76 at 25°, derived from the tritium-labeling data^{20b} and eq 11, one can calculate the Arrhenius activation energy difference between the processes of pseudo-unimolecular capture of norbornyl cation by the medium (solvent and/or lyate ion) and 6,2-hydride shift. Solvent capture has the higher activation energy by 4.65 kcal/mole. The $k_{\text{OH}}/k_{\text{H}}$ ratio at 100° is calculated on this basis to be 8.5. The calculation assumes that the observed temperature effect on the tritium distribution is not the result of a temperature-dependent isotope effect.

To the extent that the tritium data (which cover only a narrow temperature range) may be relied upon, the figure 4.65 kcal/mole represents the first estimate of the minimum value of the activation energy for capture of a norbornyl cation in solution. Since this energy is of extreme importance in present discussions of carbonium ion behavior, its confirmation or revision by further experiment would be valuable.

The Chemistry of Methylnorbornyl Cations. VI. The Stereochemistry of Vicinal Hydride Shift. Evidence for the Nonclassical Structure of 3-Methyl-2-norbornyl Cations¹

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Contribution from the Departments of Chemistry, University of Wisconsin, Madison, Wisconsin, and University of Southern California, Los Angeles, California. Received October 31, 1966

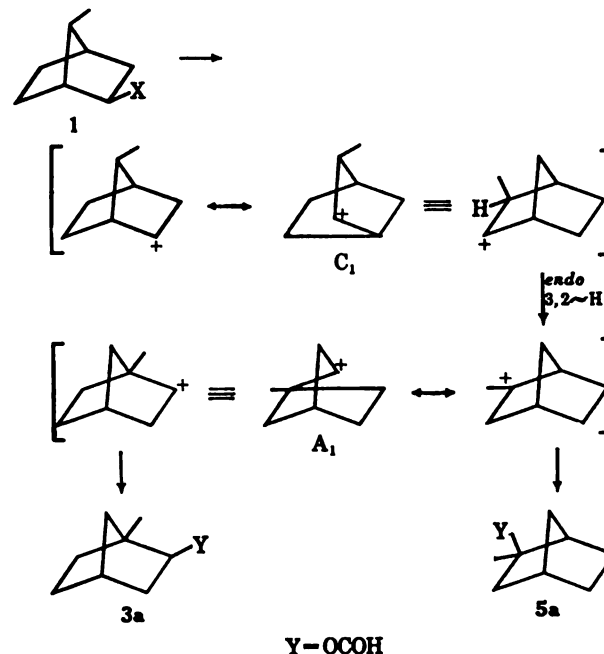
Abstract: The 3-*exo*-methyl-2-norbornyl cation scrupulously avoids rearrangement to the 2-methyl-2-norbornyl cation by *endo*-3,2-hydride shift, despite the large thermodynamic driving force of the reaction. Instead, it takes a more circuitous route involving preliminary 6,2-hydride shift to the 7-*anti*-methyl-2-norbornyl-3-*endo*-methyl-2-norbornyl system, which then suffers *exo*-3,2-hydride shift. The mechanism is elucidated with optically active reactants, since the competing paths lead to enantiomeric forms of 2-methyl-2-norbornyl product. The more circuitous path involving *exo*-3,2 shift is at least 100 times as efficient as the direct one relative to solvent capture and 6,2 shift. Comparison with the results in the 3-*endo*-methyl series shows that the preference for *exo*-3,2 shift inheres in a faster rate for this process rather than in extraneous factors proposed for other systems. Pinacolic rearrangement of 3-*endo*-methyl-2,3-*exo*-norbornanediol gives exclusively 3-*endo*-methyl-2-norbornanone. A number of other examples of vicinal shifts reported in the literature are examined, and the possibility of an alternative mechanism for the longifolene-isolongifolene rearrangement is pointed out. The extension of simple quantum mechanical arguments from primitive three-center displacements to four- and five-center openings of mesomeric bridges is discussed. The experimental findings are fully in accord with a nonclassical structure for 3-methyl-2-norbornyl cation.

One of the characteristic features of norbornyl cation chemistry is the highly stereospecific capture of external nucleophiles from the *exo* direction, even when *endo* attack is sterically about as favorable or more so. This behavior was⁴ and still is^{5,6} one of the major reasons for assigning nonclassical structures to the product-forming intermediates in such systems. A reasonable corollary of the nonclassical cation hypothesis suggests that *internal* nucleophiles, such as the migrating vicinal

groups in Nametkin rearrangements, might also show a large *exo* preference.^{5,7-9} The present paper reports a test that confirms this idea.

The formolysis of *syn*-7-methyl-2-*exo*-norbornyl acid phthalate (1) had been reported¹⁰ to give 5-*exo*-methyl-2-*exo*- (2) and 1-methyl-2-*exo*- (3) norbornyl formates. The latter product was of particular interest, since the mechanism proposed¹⁰ for its formation (Scheme I)

Scheme I



(7) J. D. Roberts and J. A. Yancey, *ibid.*, 75, 3165 (1953).

(8) P. D. Bartlett, E. R. Webster, C. E. Dills, and H. G. Richey, *Ann.*, 623, 217 (1959).

(9) D. C. Kleinfelter and P. von R. Schleyer, *J. Am. Chem. Soc.*, 83, 2329 (1961).

(10) S. Beckmann and G. Eder, *Chem. Ber.*, 91, 2878 (1958).

(1) (a) Support of part of this work by the National Institute of Arthritis and Metabolic Diseases through Grant No. AM-07505, by the American Cancer Society through a grant to the Interdepartmental Research Committee of the University of Southern California, and by the National Science Foundation is gratefully acknowledged. (b) Presented in part at the Anniversary Meeting of the Chemical Society, Birmingham, England, April 1964, Abstracts, p 19; *Proc. Chem. Soc.*, 204 (1964). (c) A preliminary version appeared: J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Am. Chem. Soc.*, 87, 3248 (1965).

(2) (a) To whom inquiries should be directed; (b) University of Wisconsin; (c) University of Southern California.

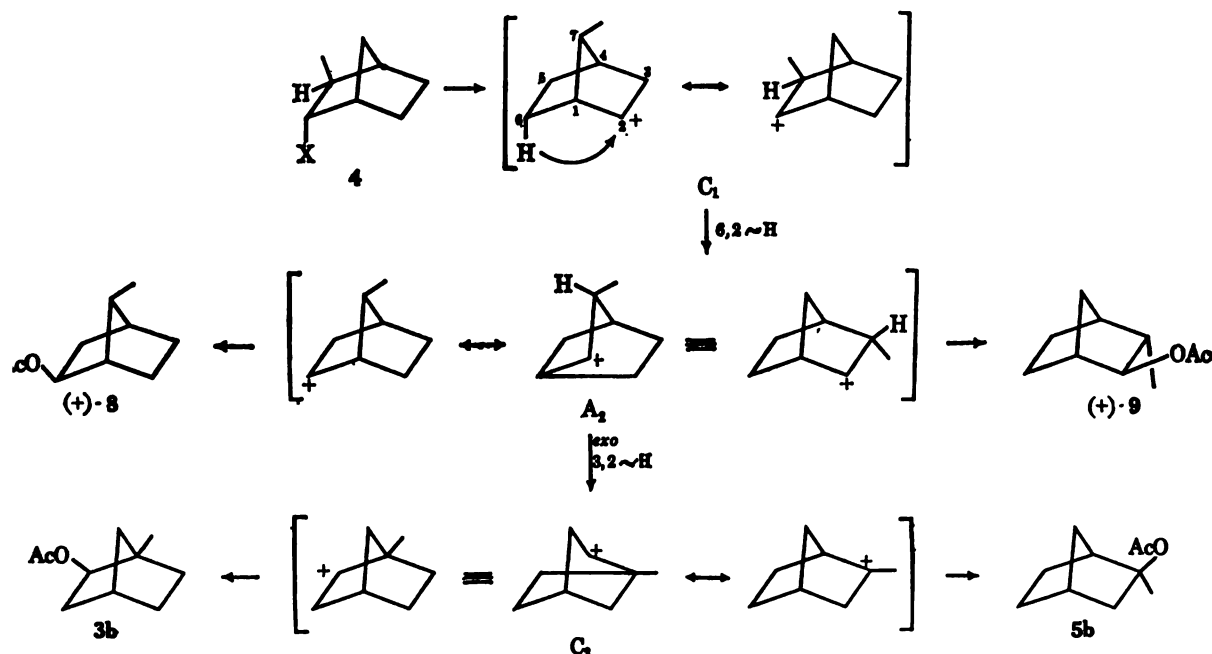
(3) National Institutes of Health Predoctoral Fellow, 1964-1966.

(4) T. P. Nevell, E. de Salas, and C. L. Wilson, *J. Chem. Soc.*, 1188 (1939).

(5) (a) J. A. Berson in "Molecular Rearrangements," Part 3, Vol. I, P. de Mayo Ed., Interscience Publishers, Inc., New York, N. Y., 1963. (b) B. Capon, M. J. Perkins, and C. W. Rees in "Organic Reaction Mechanisms, 1965," Interscience Publishers, Inc., London, 1966, p 14, ascribe to one of us^{4a} the view that in reactions of norbornyl derivatives, "kinetics alone give no information on the structure of the cationic intermediate" and conclude that adoption of this view necessitates abandonment of the *exo:endo* product ratio as a criterion also. However, the quoted passage^{4a} is irrelevant, since it refers to an outline of the complex kinetic problems of hydrogen chloride catalysis of the camphene hydrochloride-isobornyl chloride rearrangement, not to the question of *exo:endo* solvolysis rate comparisons. Our position on the connection between solvolysis rate and cation structure is expressed in the introduction to an extensive discussion of the matter: "Mesomerism stabilizes a bridged cationic intermediate relative to the corresponding 'classical' carbonium ion... the transition state... benefits energetically from similar mesomerism; it is therefore expected that a solvolysis in which bridging and heterolysis occur simultaneously will be accelerated relative to some standard solvolysis lacking such a feature."^{8d} (c) Reference 5a, p 118. (d) Reference 5a, p 175.

(6) R. Howe, E. C. Friedrich, and S. Winstein, *J. Am. Chem. Soc.*, 87, 379 (1965).

II



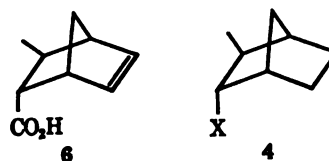
and an *endo*-vicinal hydride shift in the cationic intermediate C_1 ,¹¹ which violates the stereoelectronically disfavored^{6,7-9} prohibition. An alternative but more complex mechanism (Scheme II) employing only *exo*-hydride shifts is possible in principle, however.⁵ This is a preliminary 6,2-hydride shift converting C_1 to cation A_2 , followed by an *exo*-vicinal 3,2-hydride shift to produce cation C_2 , which is enantiomeric with A_1 . The mechanisms are clearly distinguished in the optically active series once the relative configurations of the starting material and product are established.

For a number of reasons, it is preferable to modify the form of the problem, first by entrance to the cationic ion scheme (see paper I¹²) at C_1 via a 3-*exo*-1 (4) rather than a 7-*syn*-methyl (1) precursor, and second by capture of the rearranged tertiary-second-order cation (A_1 or C_2) as tertiary product (5a or 5b) rather than secondary (3a or 3b). The first change is made by expediency, synthetic routes to optically active 1 and configurational correlation with 3 or 5 being active and/or difficult. The second is a response to experimental experience. Secondary product, the 1-methyl-norbornyl ester (3), is formed in appreciable amounts from either 1 or 4 only under conditions of negligible carbonium ion formation, that is, when the material accumulates during formolysis or acetolysis and is consumed by an added buffer. Under these conditions, there is danger of racemization by 6,2-hydride shift and/or reversible formation of 1-methylcyclohexene,¹³ and in fact, attempted acetolysis of 4 in the absence of sodium acetate leads to completely inactive 3. In the presence of sodium acetate as buffer, optical activity is preserved, but the kinetically controlled product mixture contains only 2.3% of the desired tertiary ester 5a or 5b. Despite the experimental

uninviting prospect of dealing with such a small amount of material, it was nevertheless clear that this product was of theoretical significance and did not represent a minor side path, since its Wagner-Meerwein relative 3 is a major product under reversible conditions. The low yield of 5a or 5b under kinetically controlled conditions results merely from irreversible capture of the bulk of the material at earlier points in the complex mechanism of the rearrangement. Since control experiments show that tertiary product 5a or 5b is not formed from the other acetates under the solvolysis conditions, this material represents carbonium ions that elude such capture.

Stereochemical Correlations. A distinction between the mechanisms involving *endo*-¹⁰ and *exo*-hydride⁵ shifts thus rests upon the configurational correlation of 3-*exo*-methyl-2-*endo*-norbornyl starting material (4) and 2-*endo*-methyl-2-*exo*-norbornyl product (5a or 5b).

(+)-3-*exo*-Methyl-2-*endo*-norborneol (4, X = OH) is prepared *via* the "acid \rightarrow acetate" sequence from (+)-3-*exo*-methyl-2-*endo*-norbornanecarboxylic acid¹⁴ (4, X = CO₂H), the acid chloride (4, X = COCl), and the methyl ketone (4, X = COCH₃), Bayer-Villiger oxidation of the latter to the acetate (4, X = OAc), and lithium aluminum hydride cleavage. The active acid (4, X = CO₂H) is derived by hydrogenation of the unsaturated acid 6,¹⁴ which is readily optically activated by fractional crystallization of the quinidine salt.



To minimize the accumulation of errors that inevitably accompanies a rotational correlation using two different relay compounds, it is desirable to correlate starting alcohol 4 (X = OH) with camphenilone (7), the same

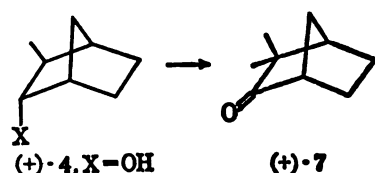
The nomenclature of the cationic intermediates is that given in I¹² and retained throughout this series.

¹² A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, R. E. Anick, and D. Houston, *J. Am. Chem. Soc.*, **89**, 2561 (1967).

¹³ A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds, and D. Willner, *ibid.*, **83**, 3986 (1961).

¹⁴ The racemic substance is reported by G. Komppa and S. Beckmann, *Ann.*, **523**, 68 (1936).

substance that had already served¹⁵ as reference in the correlation of product alcohol 5a or 5b. This is accomplished by oxidation and methylation of (+)-4 (X = OH), $[\alpha]_D +14.4^\circ$ (carbon tetrachloride), to (+)-7, $[\alpha]_D +33.4^\circ$ (benzene).



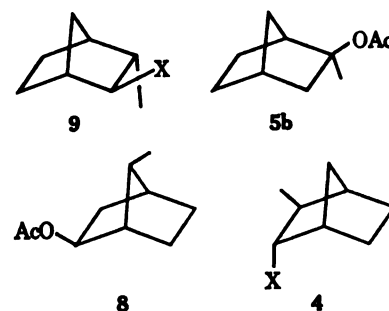
Acetolysis of Optically Active 3-*exo*-Methyl-2-*endo*-norbornyl *p*-Bromobenzenesulfonate (4, X = OBs). From the product mixture formed by sodium acetate buffered acetolysis of 4, X = OBs, prepared from (+)-4, X = OH, $[\alpha]_D +19.9^\circ$ (carbon tetrachloride), 62.4% optically pure, one can isolate by vapor chromatography (+)-3-*endo*-methyl-2-*exo*-norbornyl acetate (9), $[\alpha]_D +5.29^\circ$ (absolute ethanol), and (+)-7-*anti*-methyl-2-*exo*-norbornyl acetate (8), $[\alpha]_D +9.18^\circ$ (95% ethanol). Since 9 of $[\alpha]_D -1.85^\circ$ has the same optical purity as 7 of $[\alpha]_D +16.5^\circ$,¹⁵ whereas the starting alcohol 4, X = OH, corresponds to 7 of $[\alpha]_D (19.9/14.4) \times 33.4 = 46.1^\circ$, the rotation calculated for 9 isolated from the solvolysis with complete retention of optical purity is $(46.1/16.5) \times 1.85^\circ = 5.18^\circ$. The observed value of 5.29° thus corresponds to 102% retention. Similarly, 8 has^{15b} 1.72 times the rotation of 9 of equal optical purity in the indicated solvents. The calculated value of $1.72 \times 5.18^\circ = 8.91^\circ$ is matched by the observed value 9.18° , corresponding to 103% retention. The configurations are as shown^{15a,b} and are those expected for a Wagner-Meerwein related pair of products derived from cation A₂ which is in turn formed by 6,2-hydride shift in cation C₁ (Scheme II). The complete preservation of optical purity in these products generated from entry *via* cation C₁ in the present work and *via* cation A₂ in the previous work^{15c} shows that vicinal (3,2) secondary-secondary shift of hydrogen or methyl, whether *endo* or *exo*, is very slow relative to 6,2 shift and solvent capture. This is a desirable feature of the experimental system. It eliminates one conceivable source of racemization which, if it had occurred, could have complicated the issue, since it would have been superimposed upon any racemization caused by competition between Schemes I and II.

The optical purity of 8 and 9 (X = OAc) also excludes the possibility of another formally conceivable (although *a priori* unlikely) racemizing mechanism involving 5,2-hydride shift. In cation C₁, this would produce either the 6-methyl-2-norbornyl cation (products from which are not observed^{15a,b}) or the enantiomer of A₂. Hence if 5,2 shift were slower than 6,2 shift, the competition would cause some racemization in products 8 and 9; if the relative rates were in the opposite order, the configurations of 8 and 9 would be enantiomeric with those observed.

The tertiary product 2-*endo*-methyl-2-*exo*-norbornyl acetate is very difficult to isolate from the product mixture. It is present in small amounts and emerges in the early fraction from vapor chromatographic

columns with a retention time very close to those of 1-methyl-2-*exo*-norbornyl acetate and 2-*exo*-methyl-2-*endo*-norbornyl acetate, which also are present. The rotation of this three-component mixture, which is readily separable from all the other products by vpc, shows that the 2-*endo*-methyl-2-*exo*-norbornyl acetate in it is (+) (see Experimental Section) and hence that it has configuration 5b, consistent with its formation at least predominantly by Scheme II. Unfortunately, acetate 5b is not completely stable on the vpc columns (tricyanoethoxypropane stationary phase) most efficient for its separation from the remaining two contaminants unless extreme care is taken to deacidify the column and injector surfaces by injection of ammonia between passes. With considerable labor, (+)-2-*endo*-methyl-2-*exo*-norbornyl acetate (5b) can be obtained free of the other two persistently adhering isomers but now contaminated with decomposition products from the column stationary phase. The rotation of this material is $[\alpha]_{465} +6.18^\circ$ (chloroform), which confirms the configuration as 5b and represents 75% retention of optical purity.^{15a,b} This is a minimum value because of the presence of inert diluents, but still demonstrates that the more circuitous mechanism of Scheme II, involving only *exo*-3,2-hydride shift, accounts for at least 87.5% of the tertiary product acetate.

That this estimate is actually much too conservative is indicated by a comparison of the product ratios from the acetolysis of 3-*exo*-methyl-2-*endo*-norbornyl substrate (4, X = OBs) with those from the 3-*endo*-methyl-2-*exo*-norbornyl series 9 (X = OBs).¹⁵ In the latter



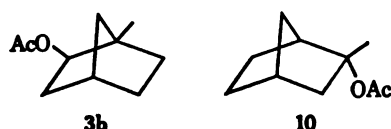
case, the ratios of tertiary product 2-*endo*-methyl-2-*exo*-norbornyl acetate (5b) to secondary products 9 (X = OAc) and 8 are 0.242 and 0.229.¹⁶ These ratios represent the partition of cation A₂ between solvent capture and *exo* tertiary-secondary 3,2-hydride shift to give cation C₂. Scheme II postulates that all of the tertiary product 5b from 3-*exo*-methyl substrate 4 (X = OBs) arises from C₂ which is derived solely from the same cation, A₂. If this is correct, the corresponding product ratios from 4 (X = OBs) should be identical with those from 9 (X = OBs). Any tertiary product 5a formed by direct *endo*-3,2-hydride shift in the alternative mechanism (Scheme I) would make the product ratios 5:9 and 5:8 from 4 (X = OBs) higher than those from 9 (X = OBs). In fact, since tertiary cation C₂ (or its enantiomer A₁) gives essentially all tertiary product under the acetolysis conditions,¹⁶ the excess of tertiary product from 4 (X = OBs) over that predicted by the 5b:9 and 5b:8 product ratios from 9 (X = OBs)

(15) (a) Paper V: J. A. Berson, R. G. Bergman, J. H. Hammons, and A. W. McRowe, *J. Am. Chem. Soc.*, **89**, 2581 (1967); (b) paper III: J. A. Berson and R. G. Bergman, *ibid.*, **89**, 2569 (1967); (c) actual experiment^{15a} in the enantiomeric series.

(16) Paper IV: J. A. Berson, A. W. McRowe, and R. G. Bergman, *J. Am. Chem. Soc.*, **89**, 2573 (1967).

is a direct measure of the incursion of any extra path, such as the *endo*-shift mechanism of Scheme I, by which tertiary product might be formed.

Experimentally, these ratios can be determined to about $\pm 1\%$ accuracy by direct capillary vapor chromatographic comparisons of peak areas.¹⁶ The determination is much more accurate than that involved in estimation of the yield of a minor constituent of a multi-component mixture, where summations of experimental errors become important. In the calculation of "tertiary product" from 4 (X = OBs), the 1-methyl-2-*exo* (3b) and 2-*exo*-methyl-2-*endo* (10) acetate products are combined with 5b since control experiments show that they are artefacts derived from it by prolonged exposure to the solvolysis conditions.¹⁶ In the case of the much

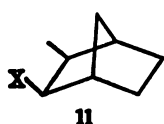


more reactive substrate 9 (X = OBs), 3b and 10 are not found since complete solvolysis is achieved in a shorter time.¹⁵

The ratios of "tertiary product" to 9 and 8 from 4 (X = OBs) are 0.247 and 0.233, which are in both cases identical within experimental error with those found from 9 (X = OBs).¹⁶ Thus, a maximum of 2% of the "tertiary product" can have been formed by the *endo*-shift path of Scheme I.

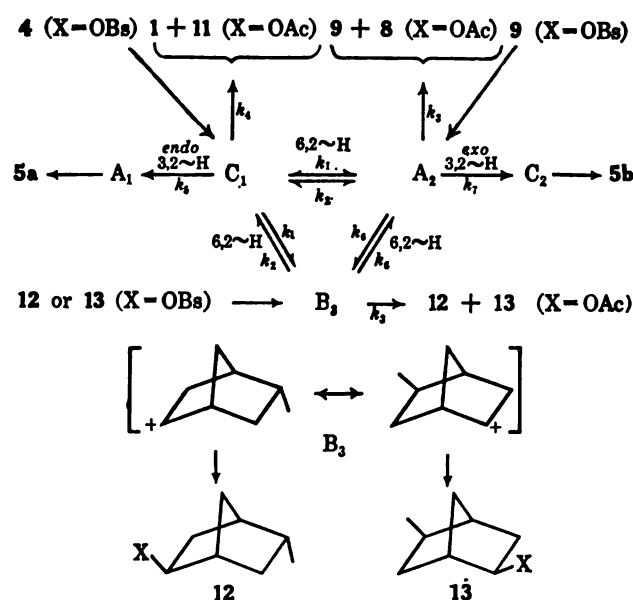
A more revealing estimate of the stringency of the interdiction against *endo*-3,2 shift is given by comparison of the relative importance of *exo*-3,2 shift in A₂ (Scheme II) with the relative importance of *endo*-3,2 shift in C₁ (Scheme I). Cation A₂ gives rise to 7% yield of tertiary product 5b, of which 100% comes from *exo*-3,2-hydride shift.¹⁶ Cation C₁ gives rise to 3.4% yield of "tertiary product" (5b + 3b + 10¹⁶) of which at most 2% comes from *endo*-3,2-hydride shift. Thus, relative to the competing processes 6,2-hydride shift and solvent capture, *exo*-3,2-hydride shift in A₂ is at least 100 times as efficient as is *endo*-3,2 shift in C₁.

Demonstration that *exo*-Vicinal Hydride Shift is Much Faster than *endo* ($k_7 \gg k_8$). In interpreting the high selectivity implied by these observations on two separate molecules, one must establish that they are attributable to an intrinsically greater rate of *exo*-hydride migration in cation A₂ than of *endo*-hydride migration in cation C₁ and not to some extraneous cause irrelevant to the test at issue. The misleading effects of failure to do this can be illustrated with the help of Scheme III, which shows the "core" cycle¹² of cations C₁, A₂, and B₃ interconnected by 6,2-hydride shifts. Entry or exit is effected *via* any of the cations from the structurally related substances: C₁ is connected with 4 (X = OBs) and with 1 and 11 (X = OAc), A₂ with 9 (X = OBs) and with 9 and 8 (X = OAc), and B₃ with 12 and 13 (X = OBs or OAc).¹⁶ Schemes I and II,



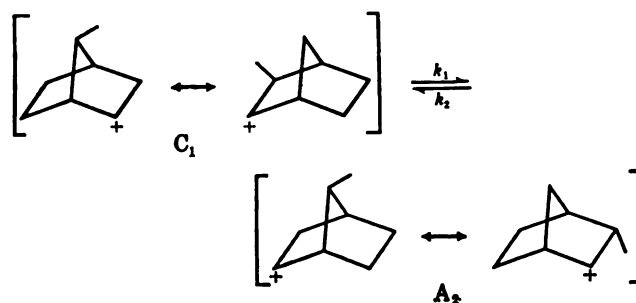
which involve cations C₁ and A₂, respectively, are excerpts from Scheme III. Escape from the "core" cycle

Scheme III



to the "periphery" (A₂ → C₂) has been shown to be essentially irreversible.¹⁶

The experiments of the present and preceding¹⁵ paper demonstrate that the ratio of product 5b derived from the sequence of cations A₂ → C₂ by *exo*-hydride shift to product 5a from the sequence C₁ → A₁ by *endo*-hydride shift is always high, regardless of the point of entry into the scheme. Although this result is consistent with the interpretation that the rate of *exo* shift is intrinsically much greater than that of *endo* shift ($k_7 \gg k_8$), in itself it does not require it. An alternative explanation would permit $k_7 \cong k_8$ but would attribute the predominance of *exo*-hydride shift to an entirely unrelated cause, namely a large discrepancy in stability between the "core" cations C₁ and A₂. If A₂ were in fact much more stable than C₁ ($k_1 \gg k_2$), the "core" cycle would have a built-in mechanistic gradient, so that points entering the energy surface at A₂ would have difficulty climbing to C₁ at a rate competitive with exit to product, and points entering at C₁ might slide down to A₂ fast enough to preclude appreciable competition from *endo* shift. Furthermore, it would not be difficult to construct a physically reasonable case for the idea that cation A₂ is more stable than cation C₁. For example, one might argue that the two sites of positive charge in the latter are shielded by the methyl group and hence perhaps the solvation energy is less. In fact, a similar argument has been invoked¹⁷ to account for certain behavior of 2-aryl-3-hydroxynorbornyl cations. We shall return to a discussion of these



(17) D. C. Kleinfelter and T. E. Dye, *J. Am. Chem. Soc.*, **88**, 3174 (1966).

cases but point out here that in principle the argument does not depend upon the assumption¹⁷ that 6,2-hydride shift is very fast relative to 3,2 shift (which clearly is not the case in our system¹⁶) but merely requires $k_1 \gg k_2$.

It can be shown that the requirements of the alternative explanation ($k_1 \gg k_2$ and $k_7 \cong k_8$) cannot be fitted to the rest of the product distribution in the present case and hence that the alternative is excluded. In particular, it is intuitively obvious by inspection that if A_2 and B_3 do not differ appreciably in energy (as seems reasonable), $k_1 \gg k_2$ requires that entry at A_2 preclude the formation of any appreciable amounts of products 3-*exo*-methyl-2-norbornyl acetate (11, X = OAc) and 7-*syn*-methyl-2-*exo*-norbornyl acetate (1, X = OAc), derived from C_1 . This can be shown analytically by a steady-state treatment of the cations of Scheme III, from which the product ratio 5b:5a from 3-*exo*-methyl-2-*endo*-norbornyl starting material (4, X = OBs) is given by eq 1.

$$(5b:5a)_4 = \frac{k_7 \left[\frac{k_1(2k_6 + k_2 + k_3)}{(k_2 + k_3)(2k_6 + k_2 + k_3) + k_7(k_6 + k_2 + k_3)} \right]}{k_8} \quad (1)$$

Since this ratio is experimentally at least 50, it follows from eq 1 that if the vicinal shift ratio $k_7:k_8$ is about unity, k_1 must be at least $50k_2$.

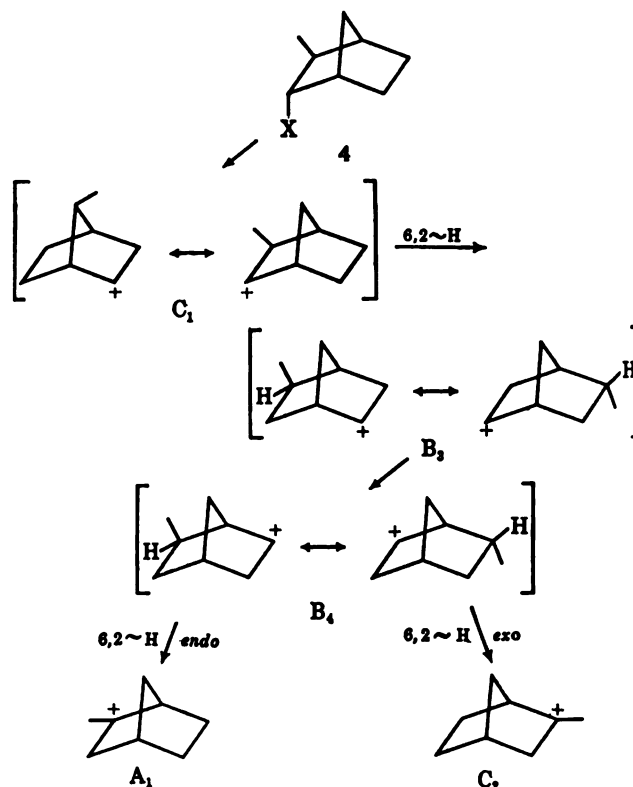
Equation 2 expresses the ratio of products 1 and 11 (derived from cation C_1) relative to 12, 13, 9, and 8 (derived from cations B_3 and A_2) when the core cycle is entered at A_2 via 9 (X = OBs) starting material. Since

$$[(1 + 11)/(8 + 9 + 12 + 13)]_0 = \frac{k_2 k_4}{[2k_1 k_3 + k_3(k_4 + k_5)]} \quad (2)$$

the rate constants for capture of the hindered cation C_1 at the two Wagner-Meerwein-related sites are in the ratio of about 5:1,¹⁶ it seems quite reasonable to suppose that a factor about half this large favors attack on unhindered cation A_2 relative to that on C_1 , i.e., $k_3/k_4 \sim 2.5$. Experimental support for this assumption is given by the detailed product distributions,¹⁶ which show that capture of C_1 must be considerably slower than capture of A_2 . With $k_1/k_2 \geq 50$, the maximum permissible value for the product ratio of eq 2 is thus 0.004. That is, *syn*-7-methyl-2-*exo* (1) and 3-*exo*-methyl-2-*exo* (11) products could not be formed from 3-*endo*-methyl-2-*exo* starting material (9, X = OBs) in any amount greater than 0.4% of the total of products 12, 13, 8, and 9 (X = OAc). But the experimentally determined¹⁶ product distribution is 9.2%. Thus, entry into the "core" cycle at cation A_2 produces much more product from cation C_1 than would be permitted if the equilibrium constant favoring A_2 over C_1 (k_1/k_2) were large enough to ensure the observed exclusive *exo*-hydride shift. Of course, as eq 1 shows, $k_1 > k_2$ reinforces $k_7 > k_8$; that is, the thermodynamic bias in question would increase the selectivity. However, even taking this into account, one cannot avoid having $k_7 \gg k_8$. Thus, with $k_3/k_4 \sim 2.5$, in order for the term $k_7 k_1 / k_8 k_2$ to be greater than 50 (see eq 1) the experimental product ratio can be fitted in eq 2 only by values of $k_7/k_8 \geq 23$. The heavy predominance of 3,2-*exo*- over 3,2-*endo*-hydride shifted product therefore signifies a large difference in the rates of the two processes themselves.

Elimination of a Hypothetical Alternative. In a purely formal sense, the stereochemical outcome of Scheme II ($4 \rightarrow C_2 \rightarrow 5b$) can be duplicated by a hypothetical alternative mechanism (Scheme IV). This in-

Scheme IV



volves 3,2-hydride shift in cation B_3 to produce the 6-methyl cation B_4 , followed by *exo-exo* hydride shift to give C_2 rather than *endo-endo* shift to give A_1 . This path is readily ruled out on the grounds that, first, the required exclusive *exo-exo* 6,2 shift ($B_4 \rightarrow C_2$) is highly implausible, since closely related cases of 6,2 shift are exclusively *endo-endo*,¹⁸ and, second, the required 3,2 secondary-secondary shift $B_3 \rightarrow B_4$ does not occur under the reaction conditions.¹⁶

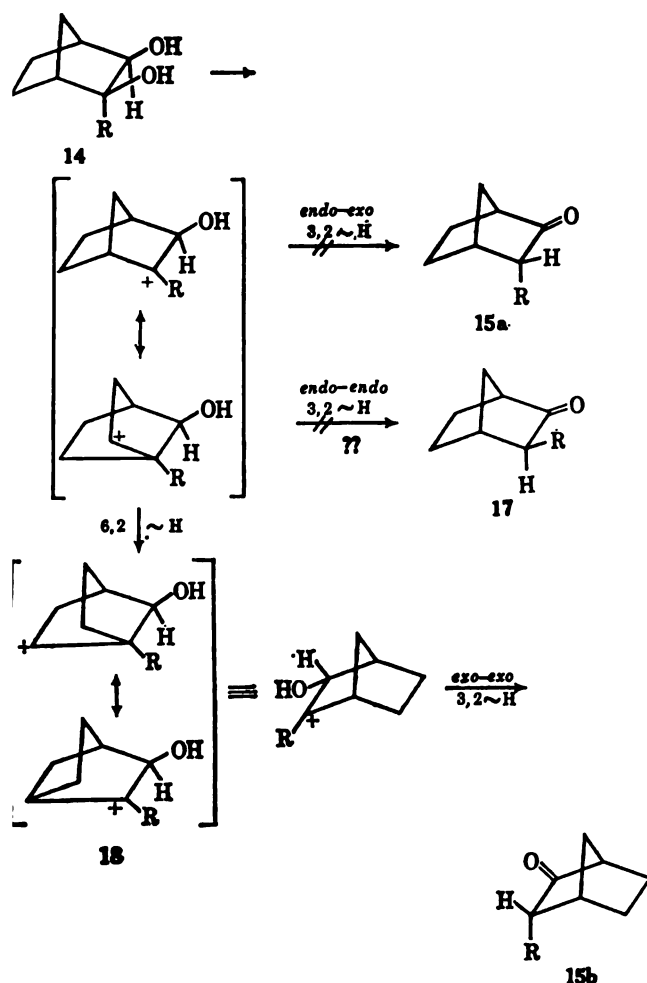
Comparison with Other Systems. An investigation based upon the observed¹⁹ rearrangement of 2-*endo*-phenyl-2,3-*cis,exo*-norbornanediol (14, R = C_6H_5) to 3-*endo*-phenyl-2-norbornanone (15a or b, R = C_6H_5) showed^{20a} that the reaction in the optically active series did not give 15a, the product of direct 3,2-hydride shift, but instead proceeded by way of preliminary 6,2-hydride shift ($16 \rightarrow 18$) followed by *exo-exo* 3,2-hydride shift to give 15b, enantiomeric with 15a. The formation of 15b thus uses a mechanism similar to that by which 3-*exo*-methyl-2-*endo*-norbornyl starting material (4, X = OBs) gives 2-*endo*-methyl-2-*exo*-norbornyl product 5b instead of its enantiomer 5a. The preference for *exo-exo* 3,2 shift is not quantitatively evaluable from this result since, in the system generated from 14, the products of the two competing kinds of 3,2-hydride shift are different substances (17 and 15b), and a measure of the relative importance of the two processes depends on the product composition, 15b:17, not the enantio-

(18) (a) J. A. Berson and P. W. Grubb, *J. Am. Chem. Soc.*, **87**, 4016 (1965); (b) B. M. Benjamin and C. J. Collins, *ibid.*, **88**, 1556 (1966).

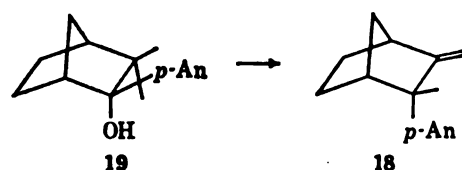
(19) D. C. Kleinfelter and P. von R. Schleyer, *ibid.*, **83**, 2329 (1961).

(20) (a) C. J. Collins, Z. K. Cheema, R. G. Werth, and B. M. Benjamin, *ibid.*, **86**, 4913 (1964); (b) C. J. Collins, personal communication.

neric composition, 15a:15b. The 15b:17 ratio previously^{20a} was implied to be large and now is estimated^{20b} as ≥ 200 .



It is difficult to evaluate the selectivity that obtains in the related case¹⁷ of 2-endo-*p*-anisyl-2,3-*cis*,*exo*-norbornanediol (14, R = *p*-MeOC₆H₄), where the authors,¹⁷ on the basis of the observation that "the only nonacidic compound isolable was 3-endo-*p*-anisylnorbornanone in *ca.* 50% yield," concluded that a large preference for *exo*-3,2 shift existed in their system. Such a preference may well exist but is not demonstrated by the facts disclosed. Similarly, the isolation⁸ of olefin 18 from *p*-anisylcamphenilol (19) does not of itself indicate a large preference for *exo*-3,2-methyl migration, and in fact was not so interpreted.⁸ Brown,²¹ in discussing the effect of substitution at the migration terminus on the stereoselectivity of 3,2 shift in norbornyl cation, has referred to the above examples (14,



R = C₆H₅, and 19) as demonstrating highly selective *exo*-3,2 shift and has stated that "the insensitivity of the stereoselectivity to the stability of the cationic center, even with a group as stabilizing as *p*-anisyl, suggests that the steric interpretation is to be preferred" (to the

(21) H. C. Brown, *Chem. Brit.*, 2, 199 (1966).

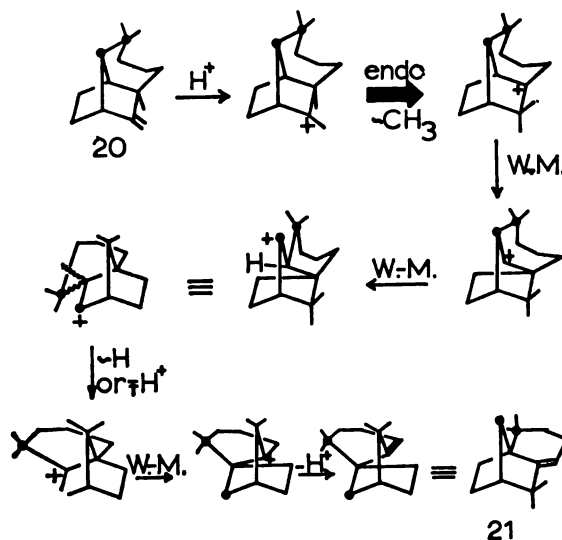
nonclassical interpretation). Regardless of what such invariance might mean if it were eventually established (as may well turn out to be the case), it is clear that in the light of the above discussion, an experimental basis for the argument is not yet available.

One must also keep in mind the more general admonition that any evaluation of "invariance" or "insensitivity" is on weak grounds if based upon a set of experimental data all of which show "complete" preference for one path over another. Wide variations in actual sensitivity may hide beneath an apparent "insensitivity" which is attributable to nothing more than a choice of systems that *all* have selectivities so high that they lie at the extreme edge of the available experimental techniques and thus cannot be ranked. Of course, even worse confusion results if one insists that actually observed variations are to be ignored. Thus, the observation²² that sodium borohydride attacks the 2-*p*-anisylbornyl cation with an *exo*:*endo* preference of 6.5 has been taken²² to represent "no major change" in selectivity as compared to the attack of acetic acid on norbornyl cation, which shows²³ an *exo*:*endo* preference of 9140.

A large preference for *exo*-3,2-methyl migration is demonstrated in the 2,3,3-trimethylnorbornyl,^{24a,b} 2,3,3-trimethyl-1-hydroxynorbornyl,^{24c} and 2,3-dimethyl-3- β -carboxyethylnorbornyl^{24d} cations since in those cases, like the 3-methylnorbornyl case reported here, *enantiomeric composition* is directly translated into product composition, and analysis for structurally isomeric substances is unnecessary. The trimethylnorbornyl cases,^{24a-c} which involve *intramolecular* competition between migrating groups, are also free of any ambiguity arising from built-in mechanistic bias caused by a large difference in stability between two different cationic intermediates.

We can now provide an additional example of the two-product type in the case of 3-endo-methyl-*cis*,*exo*-2,3-norbornanediol (14, R = Me), which rearranges

Scheme V

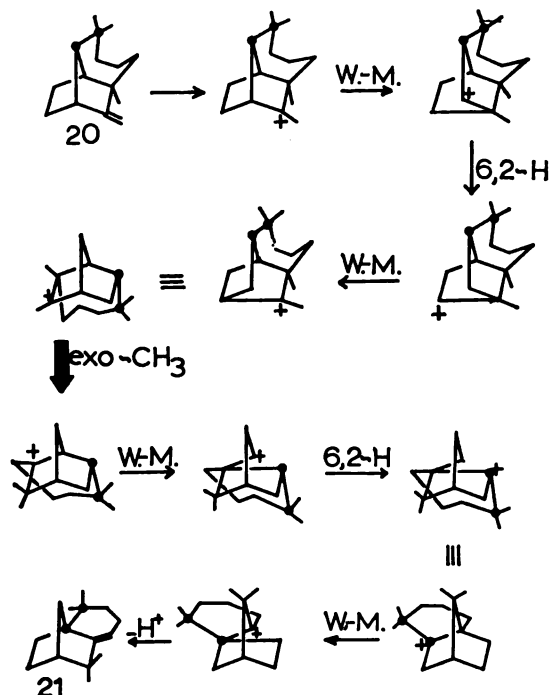


- (22) H. M. Bell and H. C. Brown, *J. Am. Chem. Soc.*, 86, 5007 (1964).
 (23) H. L. Goering and C. B. Schewene, *ibid.*, 87, 3516 (1965).
 (24) (a) P. Hirsjärvi, K. Heinonen, and L. Pirilä, *Suomen Kemistilehti*, B37, 77 (1964); (b) W. R. Vaughan, C. T. Goetschel, M. H. Goodrow, and C. I. Warren, *J. Am. Chem. Soc.*, 85, 2282 (1963); (c) A. M. T. Finch, Jr., and W. R. Vaughan, *ibid.*, 87, 5520 (1965); (d) G. E. Gream and D. Wege, *Tetrahedron*, 22, 2583 (1966).

in aqueous sulfuric acid to give exclusively 3-*endo*-methyl-2-norbornanone (15b, R = Me). This substance is readily separable by capillary vpc from its *exo* epimer (17), the presence of which to the extent of 0.03% would have been detectable. Although we have no direct evidence that the rearrangement is intramolecular and involves the route 14 → 16 → 18 → 15b demonstrated²⁰ for the phenyl case, adoption of such an assumption means that the *exo-exo* shift path is preferred to the *endo-endo* by a factor of at least 3300.

The acid-catalyzed rearrangement of the sesquiterpene hydrocarbon longifolene (20) to isolongifolene (21)²⁵ has been formulated²⁶ as in Scheme V with an *endo*-3,2-methyl shift (heavy arrow). In the present context, however, it would be plausible to postulate as an at least equally probable alternative the mechanism shown in Scheme VI, which employs a more cir-

Scheme VI



cuitous sequence involving instead an *exo*-3,2-methyl shift (heavy arrow). The two mechanisms are not distinguishable by ordinary methods of configurational correlation since both produce the same enantiomer of the rearranged product 21 from a given enantiomer of the starting material 20. They differ most directly in the relationship of the two carbon atoms indicated with heavy dots. These remain contiguous in Scheme VI but assume a 1,3 relationship in the product of Scheme V.

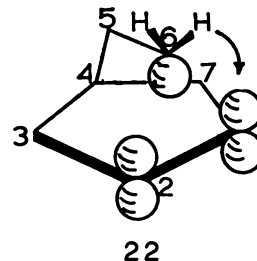
Contrasting Stereochemistry of 6,2- and 3,2-Hydride Shifts. The transition state or intermediate for the exclusively *endo-endo* 6,2- (or 6,1-) hydride shift observed in the known examples¹⁸ is readily achieved by a very minor adjustment of atomic positions in the norbornyl nonclassical ion 22. Thus, a slight movement of a C-6 hydrogen in the indicated direction produces the theoretically favorable²⁷ edge-protonated cyclopropane species and results in *endo-endo* shift stereochemistry.

(25) J. R. Prahlad, R. Ranganathan, U. R. Nayak, T. S. Santhanakrishnan, and S. Dev, *Tetrahedron Letters*, 417 (1964).

(26) G. Ourisson, *Proc. Chem. Soc.*, 274 (1964).

(27) (a) Cf. references cited by A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *J. Am. Chem. Soc.*, 87, 378 (1965); (b) R.

Brown²² comments that it is "remarkable" that 6,2 shift is fast enough to compete with solvent capture, since "normally it is considered that the nonclassical structure protects the ion from such attack in the *endo* direction." However, since the ground states of the *intramolecular* 6,2 shift and the *intermolecular* solvent capture are entirely different, a comparison of the rates of the two processes is difficultly interpretable.



Significance of the Preference for *exo*-3,2 Shift. The present demonstration that *exo*-3,2 shift is highly preferred to *endo* is completely in accord with the behavior expected of a nonclassical ion. Although opening of the mesomeric bridge with inversion by an external or internal nucleophile usually has been rationalized by stereochemical analogy to simpler nucleophilic displacements (S_N2), there are also strong quantum mechanical reasons for expecting this behavior. The argument can be given as an adaptation of one already put forward in another connection.²⁸ The transition state for the substitution reaction in its most primitive form is a three-center problem which can be treated by simple LCAO methods. Regardless of what orbitals are chosen for the basis set, the idealized case will be one with equal bond integrals (β) between the central atom and its two attached groups. For the linear (or approximately linear), inversion-producing relationship of these centers, A-B-C, one can assume a zero A-C integral, which leads to one bonding, one nonbonding, and one antibonding level, as has previously been noted.²⁹ For the retention-producing orientation, with an acute A-B-C angle, the A-C integral becomes finite ($k\beta$) and the system becomes cyclic. This has the consequences that the energy of the bonding level of the primitive linear case is lowered but that of the nonbonding level is raised (to antibonding) by a greater amount. Therefore, the four-electron (nucleophilic) system will prefer the linear geometry, but the two-electron (electrophilic) system will prefer the bent.³⁰ The assumptions of simple LCAO theory are so severe that one should not be surprised if other factors exert a large enough influence to cause occasional contraventions of the predicted behavior. Nevertheless, the underlying quantum mechanical effects are inescapably present.

An extension of the argument to nucleophilic attack on a nonclassical carbonium ion intermediate would treat the system as a four-electron, four-center case 23, with nonclassical bonding in the three-membered cycle

Hoffmann, *J. Chem. Phys.*, 40, 2480 (1964); (c) see also A. A. Aboderin and R. L. Baird, *J. Am. Chem. Soc.*, 86, 2300 (1964); (d) C. C. Lee, J. E. Kruger, and E. C. Wong, *ibid.*, 87, 3985 (1965); (e) C. C. Lee and J. E. Kruger, *ibid.*, 87, 3986 (1965); (f) G. J. Karabatsos, C. E. Orzech, Jr., and S. Meyerson, *ibid.*, 87, 4394 (1965).

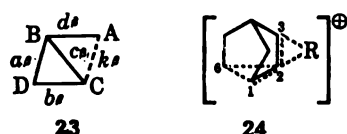
(28) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 483.

(29) A. Streitwieser, *Chem. Rev.*, 56, 571 (1956).

(30) Crudely, the linear system is related to allyl whereas the bent is related to cyclopropenyl.

BDC, and partial bonds A-B and B-C representing the onset of attachment of the nucleophile (A) to one terminus (B) and detachment of the bridging atom (C) from B. The inversion mode would correspond to the linear S_N2 case, with no A-C interaction ($k = 0$), but the retention mode would have $k > 0$. Simple LCAO calculations on this four-center problem give results qualitatively similar to those for the three-center case. (The system 23 with $c = 0$ is essentially the same used²³ to discuss the stereochemistry of additions to olefins or eliminations forming them). Over reasonable variations of the parameters a , b , c , and d of 23, the four-electron (nucleophilic) system is always destabilized by inclusion of a front-side interaction ($k > 0$).

Similarly, 3,2 shift in a norbornyl cation may be treated as a five-center, four-electron case 24. Migration of R on the *endo* side of the cation will correspond to front-side opening of the C-6-C-1-C-2 mesomeric



bridge and will introduce a C-6-R interaction which will be absent in *exo* migration. Again, simple LCAO calculations show this interaction to have a net destabilizing effect in the four-electron case. On this basis, *exo* migration should be favored, as is found experimentally.²¹

The preference for *exo*-3,2 shift is inexplicable in terms of the windshield-wiper effect, which has been postulated²² to account for *exo* capture of norbornyl cations by external nucleophiles.²³ This effect is supposed to operate by the rapid back-and-forth motion of C-6 between C-1 and C-2, which produces an abnormally low nucleophile concentration in the *endo* direction.²² In the case of 3,2 shift, however, the nucleophile, migrating hydride, is intramolecular and its "concentration" cannot be affected by the rapid motion. The present observations therefore require some other explanation.

One could argue²¹ that the results are caused by purely steric factors in the classical ion rather than stereoelectronic factors in the nonclassical one. Some such postulate is needed whether the classical ions are the dominant intermediates in solution²¹ or only present in small concentration.^{11b} However, it is not obvious that *exo* stereochemistry then should be heavily favored. Although the transition state for *endo* migration is thought to place the migrating hydrogen close to the 5,6-ethylene bridge,²¹ the transition state for *exo* migra-

tion would force the migrating hydrogen to brush past the *syn*-7-hydrogen. These effects presumably would be offset to some unknown extent by diminution of certain ground-state repulsive forces. The interactions relieved would include a 3,5 interaction in the *endo* case (similar to a 1,3-diaxial interaction in boat cyclohexanes) and a 3,4 interaction in the *exo* (similar to a 1,2-diequatorial interaction). At present, a reliable way to estimate the balance of these factors is lacking. It seems to us preferable, therefore, to employ the nonclassical formulation, which predicts the observations.²³

Experimental Section

Optical Activation of 3-*exo*-Methyl-5-norbornene-2-*endo*-carboxylic Acid. Combination of quinidine alkaloid in absolute ethanol with 1.15 molar equiv of the acid and storage of the resulting solution gave a precipitate of the mixed salts. If smaller proportions of acid were used, the free alkaloid tended to crystallize out. Three recrystallizations gave material from which 40% of the original weight of acid could be obtained with $[\alpha]_D^{25} -129^\circ$ (95% ethanol). Seven further recrystallizations from methanol gave material of $[\alpha]_D^{25} -151^\circ$. Dextrorotatory acid was obtained from the mother liquors. The resolution was not pressed further.

(-)-Methyl 3-*exo*-Methyl-5-norbornene-2-*endo*-carboxylate. The ester was obtained by treatment of a distilled sample of the corresponding acid with ethereal diazomethane. Distillation gave ester that was homogeneous on column L and had an infrared spectrum identical with that of the racemate. Acid of $[\alpha]_D^{25} -130.4^\circ$, $[\alpha]_{365}^{25} -434.1^\circ$, gave ester of $[\alpha]_D^{25} -134.2^\circ$, $[\alpha]_{365}^{25} -446.2^\circ$ (c 5.7, 95% ethanol).

Correlation with 3-*exo*-Methyl-2-*endo*-norbornanecarboxylic Acid. The above unsaturated acid, $[\alpha]_D^{25} -130.4^\circ$, was dissolved in methanol and hydrogenated at 40-20 psi with platinum oxide catalyst. Shaking in the Parr apparatus for 5 min was sufficient to complete the reaction. The saturated acid was distilled bulb to bulb at reduced pressure to produce a crystalline mass. The infrared spectrum in carbon disulfide was identical with that of the pure racemic compound. The rotation was obtained from an aliquot taken from a molten, homogeneous product, $[\alpha]_D^{25} -40.5^\circ$; $[\alpha]_{365}^{25} -110^\circ$ (c 10.8, 95% ethanol).

A homogeneous sample of the above acid, $[\alpha]_D^{25} -40.5^\circ$, was quantitatively converted to its methyl ester with ethereal diazomethane. The distilled product, pure on columns L and N, had an infrared spectrum identical with that of the pure racemic compound and $[\alpha]_D^{25} -38.2^\circ$; $[\alpha]_{365}^{25} -103^\circ$ (c 5.9, 95% ethanol).

Optically Active 3-*exo*-Methyl-2-*endo*-acetylnorbornane (4, X = COCH₃). Pure 3-*exo*-methyl-2-*endo*-norbornanecarboxylic acid, $[\alpha]_D^{25} +31.4^\circ$ (c 4.6, 95% ethanol), was converted to the acid chloride with thionyl chloride and distilled in 93.4% yield. The acid chloride was immediately converted to the methyl ketone *via* the methylcadmium reagent in ether and distilled to give a 91% yield. The product had infrared spectrum and retention times on vpc (columns L and N) identical with those of the racemic com-

(31) (a) Arguments^{11b} favoring the nonclassical structure for norbornyl cation based on the slower rate of 3,2 shift compared to vicinal shift in open-chain systems are debatable, since the alignment of either of the C-H bonds at C-3 in a hypothetical classical norbornyl cation may be much less favorable than that accessible in a more or less freely rotating open-chain case. (b) F. R. Jensen and B. H. Beck, *Tetrahedron Letters*, 4287 (1966).

(32) (a) H. C. Brown, "The Transition State," Special Publication No. 16, The Chemical Society, London, 1962, pp 140-157, 176-178. (b) Cf. H. C. Brown, J. K. Morgan, and F. J. Chloupek, *J. Am. Chem. Soc.*, 87, 2137 (1965), for this proposal applied to other systems.

(33) For experimental and theoretical objections to the windshield-wiper effect, see: (a) J. A. Berson and P. Reynolds-Warnhoff, *ibid.*, 86, 595 (1964); J. A. Berson and D. Willner, *ibid.*, 86, 609 (1964); (b) S. Winstein, *ibid.*, 87, 381 (1965); (c) M. J. S. Dewar and A. P. Marchand, *Ann. Rev. Phys. Chem.*, 16, 321 (1965); (d) G. D. Sargent, *Quart. Rev. (London)*, 20, 301 (1966); (e) G. E. Gream, *Rev. Pure Appl. Chem.*, 16, 25 (1966); (f) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 525.

(33g) NOTE ADDED IN PROOF. Although both steric and torsional effects have been proposed as alternative explanations for *exo* attack of nucleophiles [by H. C. Brown, *Chem. Eng. News*, 45, 87 (1967), and by P. von R. Schleyer, *J. Am. Chem. Soc.*, 89, 701 (1967), respectively], it is questionable whether quantitative estimates of the magnitudes of these effects can be given. For example, both Brown and Schleyer have used them to explain the reported demonstration [A. F. Thomas and B. Willhalm, *Tetrahedron Letters*, 1309 (1965); A. F. Thomas, R. A. Schneider, and J. Meinwald, *J. Am. Chem. Soc.*, 89, 68 (1967)], by an nmr method, that camphor exchange its 3-*exo*-hydrogen for deuterium much more rapidly than its 3-*endo*-hydrogen. Brown and Schleyer have argued that the preferred *exo* stereochemistry of carbonium ion capture, by analogy, does not demand a nonclassical explanation. However, additional observations on the exchange require quite a different interpretation. Thomas, *et al.*, report, without further comment, mass spectrometric data which show that camphor-3,3-*d*₂, 97% *d*-deuterated, exchanges with water to give a mixture of 21% *d*₁, 64% *d*₁, and 15% *d*₀ camphor. This composition is incompatible with a large difference in exchange rate for the 3-*exo*- and 3-*endo*-deuteriums. Since steric and torsional effects previously were postulated to be consistent in direction and magnitude with the reported highly stereospecific *exo* exchange, the observed low stereospecificity now necessitates a revision of the basis for quantitative estimation of the proposed effects.

pound, which had been prepared in the same way.¹⁴ Less than 0.5% impurity was detected, $[\alpha]^{25}_D -10.8^\circ$; $[\alpha]^{25}_{485} -224^\circ$ (c 4.6 chloroform).

Optically Active 3-*exo*-Methyl-2-*endo*-norbornyl Acetate. Methyl ketone 4, X = COCH₃, $[\alpha]^{25}_D -7.59^\circ$ (c 4.8, chloroform), was treated with a chloroform solution of peroxybenzoic acid with a catalytic amount of boron trifluoride etherate added. After 1 week, the mixture, consisting of 70% acetate 4, X = OAc, and 30% starting ketone, was worked up and resubjected to the same reagents for another 10 days to give 97% of the desired acetate and 3% unreacted ketone. The acetate was purified by preparative vpc on column C to yield homogeneous product (columns L and N) in a 58% over-all yield from ketone. Retention times on vpc and the infrared spectrum of this material were identical with those of the pure racemic material; $[\alpha]^{25}_D +19.1^\circ$ (c 6.8, carbon tetrachloride); $[\alpha]^{25}_{485} +25.6^\circ$ (c 5.4, chloroform).

Optically Active 3-*exo*-Methyl-2-*endo*-norbornanol (4, X = OH). Chemically pure acetate 4, X = OAc, $[\alpha]^{25}_D +35.5^\circ$ (chloroform), was reduced in high yield with lithium aluminum hydride to the alcohol whose infrared spectrum in carbon tetrachloride was identical with that of the racemic material.¹⁴ The material, which was pure by vpc (columns L and N), was solid at 0°, but became partially liquid at room temperature; rotations from a molten, homogeneous sample: $[\alpha]^{25}_D +19.87 \pm 0.09^\circ$ (c 4.5–5.3, carbon tetrachloride).

Correlation of 3-*exo*-Methyl-2-*endo*-norbornanol with Camphenilone [(+)-7]. A solution of 85 ml of acetone, reagent grade, and 3.51 g (27.8 mmoles) of alcohol 4, X = OH, $[\alpha]^{25}_D +14.4^\circ$ (c 5.0, carbon tetrachloride), was oxidized with a slight excess of Jones reagent. The reaction mixture was diluted with 350 ml of saturated brine and extracted six times with a total of 500 ml of pentane. The combined organic layers were washed twice with saturated brine and dried successively over sodium sulfate and calcium sulfate. The solvent was carefully distilled off through a short Vigreux column and the residue was distilled at 60–61° (10 mm). The yield was 2.38 g (69%) of product consisting of 96% 3-*exo*-methyl-2-norbornanol and 4% the *endo*-methyl isomer.

The above ketone mixture (ca. 19 mmoles) was directly taken up in 45 ml of dry tetrahydrofuran and heated with vigorous stirring for 12 hr with approximately 1.0 g of sodium hydride (pearls, not a fine dispersion). The addition of 13 ml (ca. 0.2 mole) of distilled methyl iodide was effected over 2 hr, and the stirring and refluxing were continued another 3 hr. On cooling, 50 ml of water was added, and the two resulting layers were extracted six times with a total of 200 ml of pentane. The combined organic layers were dried successively over sodium sulfate and calcium sulfate. The solvent was carefully distilled off, and the residue was distilled at 60° (10 mm) to yield 2.3 g (90%) of a waxy solid. Analysis on capillary column L indicated approximately 5% high-boiling hydrocarbon impurity; the remainder was camphenilone. Purification was achieved by preparative vpc on column C. The pure product (columns L and N) had an infrared spectrum and retention times on capillary vpc identical with those of pure commercial camphenilone (Light, Ltd., London); $[\alpha]^{25}_D +33.4^\circ$ (c 7.7, benzene).

Optically Active 3-*exo*-Methyl-2-*endo*-norbornyl *p*-Bromobenzenesulfonate (4, X = OBr). To a sample of 18.0 g (0.1428 mole) of alcohol 4, X = OH, $[\alpha]^{25}_D +19.87^\circ$ (carbon tetrachloride), dissolved in 100 ml of pure, dried pyridine, was added 36.5 g (0.1428 mole) of *p*-bromobenzenesulfonyl chloride, freshly recrystallized. The solution was allowed to stand at +5° for 4 days and then worked up with 1.5 l. of ether and 150 ml of water and ice. The ethereal solution was washed once with ice-cold 5% hydrochloric acid and thrice with saturated brine. The solution was dried twice over sodium sulfate and concentrated on a rotary evaporator to give a colorless residue containing pyridine. The residue was held under vacuum (0.2 mm) for 54 hr at room temperature. Besides pyridine, approximately 0.6 g of alcohol was recovered from the cold traps. The white, crystalline sulfonate had an infrared spectrum in carbon disulfide identical with that of the authentic material from the racemic series. No hydroxyl absorptions were present. The yield was 46.28 g (94%).

Preparative Solvolysis of Optically Active 3-*exo*-Methyl-2-*endo*-norbornyl *p*-Bromobenzenesulfonate. The above optically active *p*-bromobenzenesulfonate prepared from alcohol, $[\alpha]^{25}_D +19.87^\circ$ (carbon tetrachloride), was washed into a 1-l. flask with dry acetic acid (650 ml) and 26.0 g (0.317 mole) of anhydrous sodium acetate.

Under a reflux condenser and drying tube, the flask was plunged into an oil bath at 100°; the temperature of the stirred solution had risen to 98° within 1 hr. The temperature was maintained at 98–100° for an additional 9.5 hr.

At the end of this time, the reaction mixture was poured into 2.5 l. of water and ice and extracted six times with a total of 2 l. of pentane. The combined organic layers were washed with successive 150-ml portions of water, saturated sodium bicarbonate solution, and twice with saturated brine. The light yellow solution was successively dried over two portions of sodium sulfate and one of calcium sulfate with a little Norit. The clear solution was filtered and carefully fractionated through a Vigreux column. An intense infrared spectrum of a neat sample of the clear yellow residue contained none of absorptions of the arenesulfonate or hydroxyl compounds. The yield of crude product, which contained less than 2% each of solvent and unidentified olefins (column N), was 22.3 g (99%).

The crude acetate mixture was dissolved in 70 ml of ether and reduced with 3.2 g (0.084 mole) of lithium aluminum hydride in 100 ml of ether in a 1-l., three-necked flask equipped with a Dry Ice condenser. The excess reagent and alkoxide salts were decomposed with a freshly prepared saturated solution of anhydrous sodium sulfate. The clear solution was decanted from the granular precipitate and the latter washed with 1 l. of ether. The ethereal solution was dried over sodium sulfate and carefully concentrated to yield a clear colorless residue. The white granular salts were dissolved in ice-cold hydrochloric acid, but yielded no extractable material.

Enough ether and absolute ethanol were added to completely dissolve the total, combined alcohol mixture obtained from concentration of the ether solution. Analysis on capillary column N indicated at least eight alcohols were present, of which the "tertiary alcohol mixture," consisting of 1-methyl-2-*exo*-norbornanol (3b), 2-*exo*-methyl-2-*endo*-norbornanol (10), and 2-*endo*-methyl-2-*exo*-norbornanol (5b), was present as a group eluting well ahead of the bulk of the alcohol mixture. This "tertiary alcohol mixture" consisted of 3.4% of the total alcohols.

The "tertiary alcohol mixture" was separated from the main bulk by preparative vpc (column A) under conditions separately shown in control experiments not to cause any interconversion or racemization of the alcohols of concern. The first eluted material was distilled bulb to bulb at room temperature (0.03 mm) to remove eluted column packing.

Analysis of the "Tertiary Alcohol Mixture." This alcohol mixture was shown to be contaminated with less than 0.3% of the alcohols of longer retention time which, as a group, were present in the same proportions as in the original solvolysis mixture. Of the two major alcohol peaks, 1-methyl-2-*exo*-norbornanol (3b) was $13.0 \pm 0.7\%$ of the mixture as determined on capillary columns L and N. The standard deviation is given for four trials.

Two aliquots for the determination of the specific rotation of this mixture were carefully taken from the completely molten material to obviate any optical fractionation. The average specific rotations with the standard deviations were $[\alpha]^{25}_D -4.51 \pm 0.005^\circ$; $[\alpha]^{25}_{485} -13.93 \pm 0.016^\circ$ (c 5.5–6.6, chloroform).

The alcohol mixture was recovered from the rotation solutions, acetylated under the usual conditions, and distilled at 0.03 mm. The analysis of this mixture on capillary columns L and N gave the value for the 2-*endo*-methyl-2-*exo*-norbornyl acetate (15b) present as $71.3 \pm 0.7\%$ over six determinations. A single determination of the specific rotations of the liquid acetate mixture gave $[\alpha]^{25}_D -0.15^\circ$; $[\alpha]^{25}_{485} -0.55^\circ$ (c 5.24, chloroform). With the observed rotation of -0.008 and -0.029° , respectively, the sodium D rotation is hardly useful except to confirm the sign; the accuracy of the mercury 365-mμ rotation is only about 10%.

The composition of the mixture may be calculated from the vpc data on both mixtures: 1-methyl-2-*exo*, $13.0 \pm 0.7\%$; 2-*endo*-methyl-2-*exo*, $71.3 \pm 0.7\%$; and 2-*exo*-methyl-2-*endo*, $15.7 \pm 1.0\%$.

The Isolation of 2-*endo*-Methyl-2-*exo*-norbornyl Acetate (5b) from the "Tertiary Acetate Mixture." Under normal conditions the tertiary *exo*-acetate 5b was found to decompose to elimination products when passed through preparative vpc columns. It was shown, however, that column A could be conditioned with many large injections of anhydrous ammonia gas to pass this acetate through in relatively good yield and to separate it from 1-methyl-2-*exo*-norbornyl acetate (3b) and 2-*exo*-methyl-2-*endo*-norbornyl acetate (10). In trials, optically active *t*-*exo* acetate 5b-OAc was obtained, after bulb-to-bulb distillation, with the same rotation as that injected. It was found necessary to condition the column with more ammonia after each injection of acetate 5b.

(34) Paper II: J. A. Berson, A. W. McRowe, R. G. Bergman, and D. Houston, *J. Am. Chem. Soc.*, **89**, 2563 (1967).

From the acetylated tertiary alcohol mixture obtained from the acetolysis of optically active 3-*exo*-methyl-2-*endo*-norbornyl *p*-bromobenzenesulfonate, 28.5 mg of the 2-*endo*-methyl-2-*exo*-norbornyl acetate (5b-OAc) was obtained after distillation at room temperature (0.03 mm). A small amount of white crystalline material was observed in the colorless liquid acetate. The entire distillate was washed into a volumetric flask for the rotation. From the observed rotation of $+0.176^\circ$ at the mercury 365-m μ line, the specific rotation of $[\alpha]^{25}_D +6.18^\circ$ (c 2.85, chloroform) was calculated. This would be equivalent to *t*-*exo* alcohol 5b-OH of $[\alpha]_D -5.12^\circ$ (chloroform), or 46.5% optical purity.^{18a,b} While this sample was pure by vpc on capillary column L, containing less than 0.5% of both *t*-*endo* acetate 10 and 1-methyl-2-*exo* acetate 3b, it undoubtedly was contaminated with a significant amount of some volatile material from the preparative vpc column resulting from continual treatment of the latter with ammonia. This contamination was evident both from the small amount of crystalline material observed in the sample and from the fact that the infrared spectrum of the chloroform solution used for the rotation showed diffuse absorption in the 2.5–3.0- μ range which was not present in the infrared spectrum of a chloroform solution of pure *t*-*exo* acetate 5b-OAc; the rest of the spectrum was identical with that of pure 5b-OAc.

Isolation of 3-*endo*-Methyl-2-*exo*-norbornyl Acetate (9, X = OAc) and 7-*anti*-Methyl-2-*exo*-norbornyl Acetate (8). These two substances emerged first and last, respectively, from the vapor phase chromatogram on column E of the secondary acetate fraction. This fraction was obtained by reacetylation of the alcohols remaining after separation of the "tertiary alcohol mixture" fraction from the solvolysis of optically active *p*-bromobenzenesulfonate. Two passes sufficed to give material that in each case was homogeneous (column L). The infrared and nmr spectra and retention times on capillary vpc (columns L and N) were identical with each sample's respective racemic counterpart.

The specific rotations of the 3-*endo*-methyl-2-*exo*-norbornyl acetate (9, X = OAc) were $[\alpha]^{25}_D +5.29^\circ$; $[\alpha]^{25}_{365} +8.52^\circ$ (c 5.2, absolute ethanol); and those of the 7-*anti*-methyl-2-*exo*-norbornyl acetate (8) were $[\alpha]^{25}_D +9.18^\circ$; $[\alpha]^{25}_{365} +31.47^\circ$ (c 5.6, 95% ethanol).

A sample of unfractionated secondary acetate mixture, free of solvent, had the specific rotation of $[\alpha]^{25}_D -2.80^\circ$ (c 4.8, *l* = 4, chloroform).

The Stability of the Acetolysis Products. A stock solution of 5.88 g (30.9 mmoles) of *p*-toluenesulfonic acid monohydrate, 6.00 g (73.2 mmoles) of anhydrous sodium acetate, and 3.33 g (32.6 mmoles) of acetic anhydride in 150 ml of dried acetic acid was prepared to simulate closely the ionic concentrations at the end of the acetolysis of optically active *p*-bromobenzenesulfonate. Pure 1-methyl-2-*exo* acetate (3b), $[\alpha]^{25}_D +9.20^\circ$ (c 5.2, chloroform), was heated at 100° for 8 hr in the simulated solvolysis solution. The usual work-up gave back pure 3b, $[\alpha]^{25}_D +8.70^\circ$ (c 6.5, chloroform), a 6% loss of optical activity. Reduction of the acetate thus obtained with lithium aluminum hydride gave the corresponding alcohol which contained less than 0.5% tertiary alcohols 5b-OH or 10-OH.

Pure *t*-*endo* acetate 10-OAc, $[\alpha]^{25}_{365} -51^\circ$ (c 4.9, chloroform), was heated for 8.0 hr at 100° in the simulated solvolysis solution. The reaction mixture was worked up as in the acetolysis experiment. The acetate after bulb-to-bulb distillation (0.03 mm) was analyzed on column N and found to contain 7% *t*-*exo* acetate 5b-OAc and just a trace of 1-methyl-2-*exo* acetate 3b. The specific rotation was $[\alpha]^{25}_{365} -47^\circ$ (c 5.1, chloroform), a loss of 8.4% of the original optical activity. Since *t*-*exo* acetate 5b-OAc of the same relative configuration has the same sign of rotation, albeit only about 10% of the value of 10-OAc, a small amount of the *t*-*endo* acetate 10-OAc might also be racemized.

Similarly, pure *t*-*exo* acetate 5b-OAc, $[\alpha]^{25}_D -1.67^\circ$; $[\alpha]^{25}_{365} -5.29^\circ$ (c 4.9, chloroform), was subjected to the simulated solvolysis conditions for 8.25 hr at 100°. The distilled product was analyzed on column L and shown to contain 58.7% starting material 5b-OAc.

The acetate mixture was reduced with lithium aluminum hydride to alcohols in the usual manner. The alcohol mixture, when analyzed on column L, contained 22.9% 1-methyl-2-*exo* alcohol 3b-OH. The calculated concentration of the *t*-*endo* alcohol 10-OH was therefore 18.4%. The specific rotations of the alcohol mixture were: $[\alpha]^{25}_D +1.79^\circ$; $[\alpha]^{25}_{365} +4.55^\circ$ (c 6.0, chloroform). The unfractionated secondary acetate mixture obtained from the separation of the tertiary alcohols from the acetolysis products was subjected to the simulated solvolysis conditions for 10 hr at 100°.

The isolated acetate mixture was unchanged in composition as determined on capillary vpc columns L and N. No tertiary related material was detected (less than 0.1% of the total mixture would be observable). The specific rotation was unchanged from that of the original.

Acetolysis of 3-*exo*-Methyl-2-*endo*-norbornyl *p*-Bromobenzenesulfonate in Acetic Acid-O-D. Acetic acid-O-D was prepared from 99.8% deuterium oxide and slight excess of acetic anhydride by stirring at room temperature for 24 hr and distillation. A sample of 5.74 g (16.6 mmoles) of the pure *p*-bromobenzenesulfonate was added to 80 ml of acetic acid-O-D containing 3.22 g (39.3 mmoles) of sodium acetate. The reaction mixture was stirred at 100° for 10.0 hr and worked up in the usual manner. Analysis of the acetate mixture on capillary column L indicated the presence of 18.4% *t*-*endo* acetate and 1-methyl-2-*exo* acetate with 81.6% *t*-*exo* acetate in the "tertiary product mixture." The acetate mixture was reduced to alcohols with lithium aluminum hydride. The concentration of 1-methyl-2-*exo* alcohol 3b-OH was not determinable at that time because of capillary column degeneration. That some was present was evident from the preparative isolation. The tertiary alcohols were separated from the main solvolysis components on preparative vpc column E. The tertiary alcohol mixture contained 10.05 atom % excess deuterium as determined by the falling drop method, equivalent to 1.4 deuterium atoms per molecule. The components with longer retention time contained less than 0.03 deuterium atom per molecule. Deuterium analyses by the falling drop method were performed by Mr. J. Nemeth, Urbana, Ill.

Acetolysis of 3-*exo*-Methyl-2-*endo*-norbornyl-*p*-Bromobenzenesulfonate in the Presence of 2-*exo*-Methyl-2-*exo*-norbornyl Acetate in Acetic Acid-O-D. About 0.14 g (1.1 mmoles) of *t*-*exo* acetate 5b-OAc, 0.074 g (0.9 mmole) of sodium acetate, and 0.13 g (0.37 mmole) of *p*-bromobenzenesulfonate were added to 2.0 ml of dry acetic acid-O-D and heated at 100° for 10.0 hr. The usual work-up yielded acetates which were reduced to alcohols with lithium aluminum hydride. The tertiary alcohol mixture was separated from the alcohol mixture of longer retention time on column E and analyzed by the falling drop method. There was 12.70 atom % excess deuterium present, equivalent to 1.78 deuterium atoms per molecule. Since the tertiary products from the solvolysis of the *p*-bromobenzenesulfonate normally amount to only ca. 3% of the total mixture, the tertiary alcohols isolated from this particular run would be expected to be contaminated by only 1% of solvolysis product. Thus, deuterium incorporation clearly can occur after the formation of tertiary solvolysis product.

Optically active 2-*exo*-methyl-2-*endo*-norbornanol (10-OH) was prepared by adding an ether solution of norbornanone, $[\alpha]_D -7.95^\circ$ (chloroform), to ethereal methylmagnesium bromide. The ketone was prepared by Jones oxidation¹³ of active norbornanol.¹⁴ The product 10-OH had infrared spectrum and retention times on vpc identical with those of an authentic sample¹⁵ of the racemate. The alcohol had $[\alpha]_D -6.45^\circ$; $[\alpha]_{365} -17.4^\circ$ (c 4.3, chloroform).

Acetylation of the active alcohol with acetic anhydride in pyridine gave a quantitative yield of 10-OAc with infrared spectrum and retention times on vpc identical with those of the racemate. The sample, which contained 0.05% of 5-OAc, had $[\alpha]_D -12.1^\circ$; $[\alpha]_{365} -36.8^\circ$ (c 6.0–7.8, chloroform). Lithium aluminum hydride reduction regenerated 10-OH with undiminished rotation.

Optically Active 2-*endo*-Methyl-2-*exo*-norbornanol (5-OH). Following a procedure worked out in the racemic series,¹⁶ a homogeneous sample of *t*-*endo* alcohol 10-OH, $[\alpha]_D -12.1^\circ$ (chloroform), 3.00 g (0.024 mmole), was stirred with 15 ml of concentrated hydrochloric acid for 2 hr at room temperature. The chloride was extracted with pentane and the organic solution washed with saturated brine. The solvent was distilled off in a 100-ml flask. The colorless residue was homogeneous on capillary columns L and N with the exception of a small amount of residual solvent.

The chloride was stirred at 95° with 35 ml of 1 *N* sodium hydroxide for 4 days. The cooled mixture was extracted four times with pentane; the combined organic layers were washed twice with saturated brine and dried over sodium sulfate, and the solvent was distilled off. The clear, colorless residue crystallized immediately on cooling to room temperature and was completely sublimed at 85° (10 mm). The yield was 2.36 g (80%) of material whose rotations were: $[\alpha]^{25}_D +2.78^\circ$; $[\alpha]^{25}_{365} +8.38^\circ$ (c 5.0–5.3, chloroform).

(35) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Am. Chem. Soc.*, **86**, 397 (1964).

(36) N. J. Toivonen, E. Siltanen, and K. Ojala, *Ann. Acad. Sci. Fennicae, Ser. AII*, No. 64 (1955).

Optically Active 2-endo-Methyl-2-exo-norbornyl Acetate (5-OAc). A homogeneous sample of the *t-exo* alcohol, $[\alpha]_D^{25} +2.78^\circ$ (chloroform), was acetylated with excess acetic anhydride and pyridine at 100° for 13 hr in the usual manner and distilled to give a 94% yield of acetate 5-OAc, whose infrared spectrum and retention times on vpc were identical with those of authentic racemic material. Capillary vpc on columns L and N indicated 0.75% *t-endo* acetate 10-OAc was present; rotations: $[\alpha]_D^{25} -1.01^\circ$; $[\alpha]_{25}^{25} -3.36^\circ$ (c 5.2–5.4, chloroform). This acetate was reduced with lithium aluminum hydride in the usual manner to give alcohol 5-OH with the same rotation as that of the starting material. Analysis by capillary vpc on column L indicated the absence of 1-methyl-2-exo alcohol 3-OH where less than 0.05% could have been detected.

Optically Active 1-Methyl-2-exo-norbornyl Acetate (3-OAc). Following the method previously reported,¹¹ 6.08 g of *t-endo* alcohol 10-OH, $[\alpha]_D^{25} -6.45^\circ$ (chloroform), was solvolyzed in acetic acid-sulfuric acid for 1.0 hr at 98° . Under these conditions, a few per cent each of *t-exo* acetate 5-OAc and *t-endo* acetate 10-OAc were present in addition to 3-OAc. Preparative vpc on column D using a Wilkens Autoprep 700A with automatic 60- μ l injections converted the *t-exo* acetate 5-OAc to olefins and cleanly separated the desired product 3-OAc from the *t-endo* acetate 10-OAc. Distillation of the purified acetate separated it from the eluted column packing and gave 4.08 g (52%) of material whose infrared spectrum and retention times on vpc were identical with those of authentic racemic material. Capillary vpc on column N indicated a total of less than 0.2% of impurities; rotations: $[\alpha]_D^{25} +9.29^\circ$; $[\alpha]_{25}^{25} +28.0^\circ$ (c 5.2–5.4, chloroform).

Optically Active 1-Methyl-2-exo-norbornanol (3-OH). The above acetate, $[\alpha]_D^{25} +9.29^\circ$, 0.722 g (4.29 mmoles), was reduced with 0.16 g of lithium aluminum hydride in the usual manner. Complete sublimation of the crude residue yielded 0.47 g (87%) of colorless, crystalline alcohol 3-OH. The infrared spectrum and retention times on vpc were identical with those of pure, racemic material prepared in a similar manner; rotation: $[\alpha]_D^{25} +0.21^\circ$; $[\alpha]_{25}^{25} -2.11^\circ$ (c 5.8–5.9, chloroform).

The alcohol recovered from the rotations was converted to the acetate with excess pyridine and acetic anhydride at 100° for 24 hr to give product with a rotation identical with that of the starting material.

2-endo-Methyl-2,3-cis,exo-norbornanediol (14). A sample of 2-methyl-2-norbornene²⁷ (0.20 g) was dissolved in 25 ml of dry ether. A stirred solution of 0.50 g of osmium tetroxide in 25 ml of ether was cooled to 0° , protected by a drying tube, and the olefin solution was added dropwise from a pressure-equalizing dropping funnel. A black solid precipitated during the addition; afterwards the mixture was allowed to stir overnight at room temperature. The black osmate ester was collected by filtration and added to a reaction flask containing 5.0 g of sodium sulfite, 25 ml of ethanol, and 25 ml of water. After heating at reflux for 1 hr on the steam bath, this mixture was filtered, and the filtrates were concentrated to dryness at the aspirator. The solid residue was extracted nine times with methylene chloride, and the organic extracts were combined and dried over magnesium sulfate. After filtration, the solvent was evaporated at the aspirator, leaving a greenish oil which distilled bulb to bulb to give a waxy solid.

This material exhibited an intense, broad O-H band in the infrared as well as a small C=O band due to an unknown contaminant. The diol was characterized by its nmr, which showed a broad signal at δ 4.1 (2 H) assigned to the hydroxyl protons and a slightly broadened absorption at δ 1.3 (about 4 H). Superimposed on the δ 1.3 absorption was a sharp singlet due to the methyl group, deshielded by the *gem*-hydroxyl function.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.70; H, 9.82.

Rearrangement of 2-endo-Methyl-2,3-cis,exo-norbornanediol (14). A round-bottomed flask was charged with 4 ml of concentrated sulfuric acid and cooled to -8° in an ice-salt bath. The cold solution was stirred rapidly with a magnetic apparatus, and 0.040 g of the solid diol 14 was added and allowed to stir in the acid for 10 min. After this time the yellow reaction mixture was poured onto cracked ice and extracted three times with pentane. The pentane was washed four times with saturated brine and dried over sodium sulfate. Careful removal of the solvent left about 30 mg of material which showed only one peak on capillary vpc column N-1, identical in retention time with 3-endo-methyl-2-norbornanone (15b). Control experiments showed that (1) less than 0.03% of the *exo*-methyl epimer could have been detected, and (2) both epimeric ketones were stable under the reaction conditions.

(37) K. Alder and H. J. Ache, *Chem. Ber.*, **95**, 503, 511 (1962).

Studies on the Molecular Geometry of the Norbornyl Cation.

I. The Synthesis and Acetolysis of the *exo*- and *endo*-4,5-*exo*-Trimethylene-2-norbornyl *p*-Toluenesulfonates

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Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. Received January 3, 1967

Abstract: 4,5-*exo*-Trimethylene-2-norbornene (10) has been synthesized from a monosubstituted cyclopentadiene 9 using an intramolecular Diels-Alder reaction, and from this intermediate *exo*- and *endo*-4,5-*exo*-trimethylene-2-norbornyl *p*-toluenesulfonates (11, R = Ts, and 16, R = Ts) have been prepared. These sulfonates undergo acetolysis (25°) at relative rates of 8.6:1. The ratio of rate constants (25°) for acetolysis of the *exo*-sulfonate 11, R = Ts, and 2-*exo*-norbornyl *p*-toluenesulfonate is 1:85, whereas the corresponding ratio for the *endo*-sulfonate 16, R = Ts, and 2-*endo*-norbornyl *p*-toluenesulfonate is 1:2.5. The depressed rate for the tricyclic *exo*-sulfonate 11, R = Ts, relative to 2-*exo*-norbornyl *p*-toluenesulfonate is readily explained in terms of bridging of carbon in the transition state for ionization, but seems to be contrary to expectations based on ionization to a localized (classical) carbonium ion. Thus, the present results favor the *bridged-ion* mechanism for acetolysis of 2-*exo*-norbornyl arene-sulfonates.

A large body of data relating to the solvolysis reactions of various bicyclo[2.2.1]heptanes holding leaving groups such as halide or arenesulfonate at C_2 is now available.^{1,2} It is clear, especially from ex-

tensive investigations of the parent 2-norbornyl series, that these reactions exhibit characteristics which sharply differentiate them from simple aliphatic or monocyclic

(1) For an excellent recent review see G. D. Sargent, *Quart. Rev.* (London), **20**, 301 (1966).

(2) A collection of reprints of key papers in this field along with an authoritative commentary has been provided by P. D. Bartlett, "Non-classical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965.

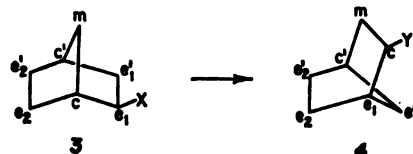
ogs. These properties, due in large part to special features of the norbornyl cation,³ include^{1,4-9} (1) extraordinary ease of Wagner-Meerwein rearrangement of C_4 from C_1 to C_2 (as compared with other reaction paths); (2) dependence of reactivity on orientation of substituents, specifically, generally higher solvolysis rates for 2-*exo* derivatives as compared with the corresponding 2-*endo* compounds; and (3) extraordinarily nonspecific formation of *exo*-substitution products arising from 2-*exo*-norbornyl derivatives. Similar behavior has been noted for a number of methyl-substituted norbornyl derivatives.^{1,5} These distinctive characteristics of the norbornyl cation have been interpreted by some^{1,4,5} in terms of a mechanism in which ionization is assisted by the rearrangement of C_4 from C_1 to C_2 to lead directly to an intermediate bridged ion 1 (*bridged-ion mechanism*), while others¹⁰⁻¹² have taken the view that the available data can be explained on the basis of rapidly rearranging localized norbornyl ions 2 (*classical-ion mechanism*). Additional evi-



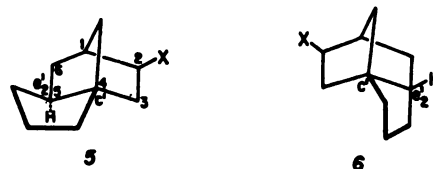
which can serve to exclude one of these alternatives is clearly desirable. One possible approach toward this end is the detection of positive charge at C_1 or C_4 in the transition state using kinetic measurements with substrates having electron-supplying groups at these centers. Although studies have been carried along these lines,^{1,13,14} they have not yielded the type of results which allow an unambiguous decision between the two theories. Another way of distinguishing between bridged-ion and classical-ion mechanisms is made possible in principle by the fact that the transition states for these paths should involve different geometries of the ring system. This paper describes the results of a part of an investigation aimed at revealing more fully the molecular geometry of the cationic species which intervene in the ionization reactions of 2-norbornyl *p*-toluenesulfonates. In general, a reasonable test for such a test could be the introduction of a bridge (or a set of bridges) into the bicyclo[2.2.1]heptane system in such a way as to produce either a large increase or decrease in total strain for the ring system during migration of C_4 from C_1 to C_2 while at the same time preserving to a maximum extent for the initial and rearranged structures the exact geometry of the bicyclo[2.2.1]heptane part and also the exact

environment of groups at the *exo* and *endo* orientations at C_2 .

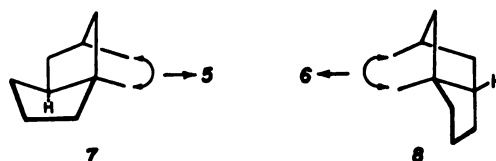
Before describing the specific molecular system which we have studied, a general consideration of the effect of Wagner-Meerwein rearrangement on the various positions of the norbornyl skeleton is appropriate. Let the various types of ring atoms in structure 3 be represented by descriptive letters as follows: common atoms 1 and 4 as *c* and *c'*, methano bridge as *m*, ethano bridge members as *e*₁, *e*_{1'} for the bridge bearing the leaving group, and *e*₂, *e*_{2'} for the other. After Wagner-Meerwein rearrangement of carbon, these atoms assume the locations indicated in 4. It will be noted that only two atoms, *c'* and *e*_{2'}, are both unchanged in type and



remote from the leaving and entering groups and also that *exo*- and *endo*-substituent interconversion occurs at *e*_{2'}. Therefore, if a chain of atoms is added to join *c'* and *exo-e*_{2'} in 3 with establishment of a new ring, the rearrangement 3 to 4 will produce a *stereoisomeric* system, in principle of different energy, without any essential interference with the environment of the leaving or entering groups. In the specific case of a trimethylene bridge, the stereoisomer *c'*-(CH₂)₃-*exo-e*_{2'} (5) can be formed with only a minor amount of additional angle strain. In contrast, the stereoisomer *c'*-(CH₂)₃-*endo-e*_{2'} (6) is formed with much angle strain in addition to the norbornyl strain. Crude estimates of



the difference in strain energy between 5 and 6 (principally angle strain) have been made in two different ways. In the first, the angle strain formula of Westheimer¹⁵ has been used, taking into account only the distortions of C-C-C angles and using the values for ring angles as measured from (a) Cenco Peterson molecular models and (b) Fieser-Dreiding molecular models; this gave strain energy differences of (a) 7.2 kcal/mole and (b) 8.1 kcal/mole, with the likelihood that both estimates are too high¹⁶ rather than too low. The second way for estimation of strain energy differences rests upon the recognition of 5 and 6 as derivatives of *cis*- and *trans*-pentalane, respectively. The ring systems of 5 and 6 can be formed by the joining of atoms in the hypothetical *cis*- and *trans*-pentalane derivatives 7 and 8. Simulation of the ring closure of



(15) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 533 *et seq.*

Unless otherwise indicated, the term norbornyl cation when used refers to the cation derived from heterolysis of appropriate 2-norbornyl derivatives.

S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **71**, 2953 (1949); **147**, 1154 (1952).

S. Winstein, *et al.*, *ibid.*, **87**, 376, 378, 379, 381 (1965).

S. Winstein, E. Vogelfanger, K. C. Pande, and H. F. Ebel, *ibid.*, **84**, 193 (1962).

H. Goering and C. B. Schewene, *ibid.*, **87**, 3516 (1965).

E. J. Corey, J. Casanova, P. A. Vatakencherry, and R. Winter, *ibid.*, **85**, 169 (1963).

S. Smith and J. P. Petrovitch, *Tetrahedron Letters*, 3363 (1964).

) H. C. Brown, "The Transition State," Special Publication No. 1, American Chemical Society, London, 1962, p 140.

) H. C. Brown, *Chem. Brit.*, **2**, 199 (1966).

) M. Rei and H. C. Brown, *J. Am. Chem. Soc.*, **88**, 5335 (1966).

) D. C. Kleinfelter, *Dissertation Abstr.*, **22**, 428 (1961).

) D. C. Kleinfelter and P. von R. Schleyer quoted by J. A. Berson in *Molecular Rearrangements*, Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 182.

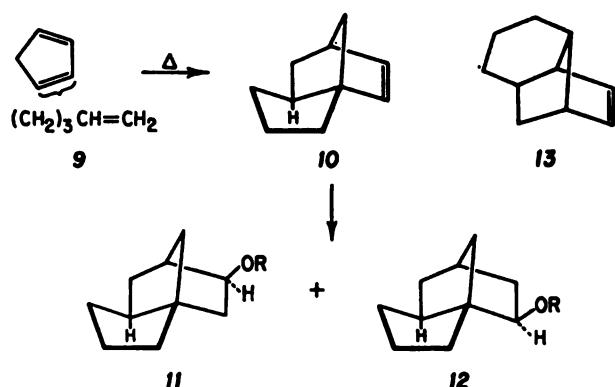


Figure 1.

7 and 8 with the above-named types of models indicates that the increase in angle strain upon ring closure is 10–20% greater with 7 than with 8, which probably amounts to a difference of 0.5–1 kcal/mole.¹⁶ This would roughly be offset by changes in torsional strain from 7 and 8 to 5 and 6, and, therefore, it appears that the difference in strain energy between 5 and 6 should be approximately the same as for *cis*- and *trans*-pentane systems, i.e., ca. 6–7 kcal/mole.¹⁷

Thus, there can be little doubt that 5 is substantially less strained than the isomer 6. This is also obvious simply by inspection of models which reveals additionally that the process of Wagner–Meerwein rearrangement of 5 to 6 results in a steady increase in strain. Therefore, it would be expected that if ionization leads to *bridging* in the transition state for solvolysis of 2-*exo*-norbornyl *p*-toluenesulfonate, the *p*-toluenesulfonates corresponding to 5 and 6 should react more slowly and more rapidly, respectively. On the other hand, the solvolysis rates for the three *endo*-*p*-toluenesulfonates should all be approximately the same, since presumably there should be little or no bridging of C₂ in the transition state and also no other differences for the three cases (e.g., steric acceleration or steric interference^{10–12} to ionization should be the same). A reasonable prediction on the basis of the *classical-ion mechanism* is that the rates of solvolysis of the *exo*-*p*-toluenesulfonates 5 and 6 should be essentially the same as for the 2-*exo*-norbornyl case and, similarly, that the rates for the *endo*-*p*-toluenesulfonate isomers of 5 and 6 should be approximately the same as 2-*endo*-norbornyl.

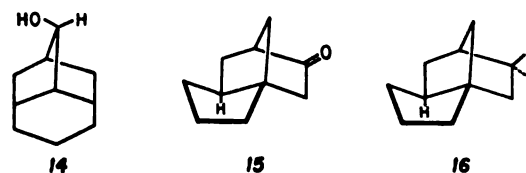
It should be noted that the C₁–C₇–C₈ angle in 5 and 6 as observed in models appears to have the value which is normal for the simple bicyclo[2.2.1]heptane ring system (further evidence on this point appears in the following section). The number of carbons in the extra bridge connecting c' and e₂' in 5 and 6 appears to be optimal for the purposes of revealing the molecular geometry of the norbornyl cation; fewer carbons would introduce too much strain and perturbation of the bicyclo[2.2.1]heptane system in *both* the *exo*- and *endo*-bridged structures, whereas a larger number of bridge atoms (>3) would diminish the differential strain be-

tween the *exo*- and *endo*-bridged structures to too a value.

Synthetic Studies

The synthesis of 4,5-*exo*-trimethylene-2-*exo*-norbornyl *p*-toluenesulfonate was accomplished in steps as outlined in Figure 1. Alkylation¹⁸ of pentadienylsodium by 5-bromo-1-pentene produced a mixture of monosubstituted cyclopentadienes with the substituent principally at C₁ and C₂ as indicated by nmr measurements. When a dilute solution of the mixture of Δ⁴-pentenylcyclopentadienes 9 was heated with tri-*n*-butylamine as solvent, 4,5-*exo*-trimethylnorbornene (10) was produced in good yield. The structure of the product from this reaction was indicated by physical, analytical, and chemical data. The alternative nonstereoisomeric internal Diels structure 13 could be excluded from consideration because the nmr spectrum of the product which exhibited a sextet consistent with the AB part of an ABX system centered at 6 ppm^{21,22} due to two olefinic protons, a broad band due to a *single* bridgehead (and allylic) proton at 2.8 ppm,²³ and the remaining aliphatic protons (found 11.0) between 2.0 and 1.0 ppm. Structure 13 can also be excluded from the nmr spectra of the transformation products of 10, e.g., the *exo*-2,3-diol and also on the basis of chemical data. The chemical evidence which excludes the structure stereoisomeric with 10 but having a 4,5-*endo*-trimethylene bridge is presented below.

Hydroboration of 10 with disiamylborane^{24,25} gave a mixture of the alcohols 11, R = H, and 12, R = H, in a ratio of 92:8. The same alcohols were also produced by using diborane as the reagent for hydroboration; the process was less useful for synthesis, since the products 11, R = H, and 12, R = H, were formed in a ratio of ca. 3:1; further, a third isomeric alcohol was produced in certain runs evidently because of use of more boron trifluoride than required for the generation of diborane reagent from sodium borohydride. The alcohol 11, R = H, was readily obtained from the 92:8 mixture *via* the crystalline 3,5-dinitrobenzoate ester. The crystalline alcohol so purified was converted to the crystalline *p*-toluenesulfonate 11



Ts, mp 66.5–68°, by exposure to *p*-toluenesulfonic acid chloride in pyridine. Oxidation of the alcohol

(18) K. Alder and H. J. Ache, *Ber.*, **95**, 503 (1962).

(19) See G. Brieger, *J. Am. Chem. Soc.*, **85**, 3783 (1963).

(20) A small amount (ca. 5%) of a second isomeric product formed; this by-product will be dealt with in later papers.

(21) All nmr data cited in this paper refer to parts per million downfield from tetramethylsilane as internal reference.

(22) Reproductions of this and other spectra are available.

Ph.D. dissertation of R. S. Glass, Harvard University, 1966.

(23) For reference nmr data on norbornenes see (a) P. Laszlo, *J. Am. Chem. Soc.*, **86**, 1171 (1964); (b) E. J. and B. Franzus, *ibid.*, **86**, 1166 (1964); (c) K. Tori, K. Aono, R. Muneyuki, T. Tsuji and H. Tanida, *Tetrahedron Letters*, **9** (1964).

(24) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(25) G. Zweifel, N. R. Ayyangar, and H. C. Brown, *J. Am. Chem. Soc.*, **85**, 2072 (1963), and references cited therein.

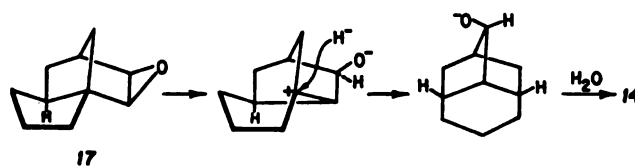
(16) A total closure strain energy from 7 and 8 to 5 and 6, respectively, is probably somewhat less than the strain energy of norcamphor (ca. 6 kcal/mole); see K. Alder and G. Stein, *Ber.*, **67**, 613 (1934); G. Becker and W. A. Roth, *ibid.*, **67**, 627 (1934); R. P. Linstead, *Ann. Rept. (London)*, **32**, 315 (1935).

(17) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 436 (1935); 611 (1936).

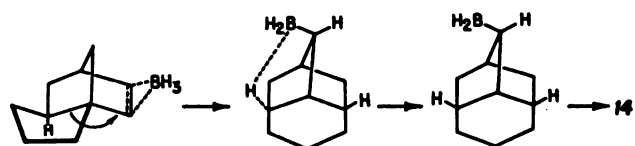
= H, by chromic acid afforded the corresponding ketone 15 (carbonyl absorption 1749 cm^{-1} , $5.72\text{ }\mu$ in CHCl_3), which was reduced with sodium borohydride in ethanol to yield the crystalline *endo* epimer of 11, R = H (16, R = H). Reaction of 16, R = H, with p-toluenesulfonyl chloride gave the corresponding p-toluenesulfonate 16, R = Ts, mp $50\text{--}51.5^\circ$.

The nmr spectra²² of the *exo* compounds 11, R = H, 11, R = CH_3CO , exhibit ROCH< proton resonance as a doublet of doublets centered at 3.88 and 3.92 ppm, respectively, whereas the nmr spectra of the *endo* compounds 16, R = H, and 16, R = CH_3CO , exhibit the ROCH< as much more complex multiplets centered at 3.23 and 4.98 ppm, respectively. Similarly, the p-toluenesulfonate 11, R = Ts, exhibits a ROCH< resonance as an overlapping doublet of doublets (pseudo-quartet) centered at 4.57 ppm, and the corresponding *endo* compound 16, R = Ts, is a broad, complex multiplet centered at 4.80 ppm. The more complex splitting observed with the derivatives of 16 as compared with those of 11 indicate additional coupling of *ca.* 3 cps with the bridgehead proton, therefore, the adjacency of a bridgehead proton places the alcoholic function at C_2 rather than C_3 , which confirms the assignment which follows from the known orientational tendencies of disiamylborane in addition to unsymmetrically substituted olefins.^{24,25} Hydroboration would also be expected to produce *exo* rather than *endo* alcohols, and this too is supported by the nmr data, since resonance for *exo*-ethanol protons occurs at lower field than for *endo*-ethanol protons in norbornane derivatives with characteristic differences in chemical shift of 0.3–0.6 ppm.^{26–29} The configuration for 16, R = H, also follows from the configuration of this alcohol by borohydride reduction to the corresponding ketone 15.

Oxidation of the tricyclic olefin 10 with monochloroacetic acid in ether produced the *exo*-2,3-oxide in good yield. The nmr spectrum of this substance is completely consistent with structure 17. The protons attached to the epoxide ring give rise to a sharp doublet at 2.79 ppm and a broadened doublet at 2.96 ppm; a bridgehead hydrogen is responsible for a broad doublet at 2.42 ppm (*one proton only*), and a doublet at 3.1 ppm is clearly assignable to the 7-*anti* proton.³⁰ Reaction of the epoxide 17 with lithium aluminum hydride produced three isomeric alcohols, 11, R = H, 11, R = H, and 14 in a ratio of 33:63:4, whereas the reaction of lithium aluminum hydride–aluminum chloride produced only 11, R = H, and 14 (ratio 24:76). The rearranged alcohol 14 must arise *via* a Wagner–Meerwein process which becomes more important than the competing process, SN_2 attack by hydride, with the more acidic “mixed hydride”³¹ as compared with lithium aluminum hydride. The rearrangement can be described (without regard for detail) as follows.

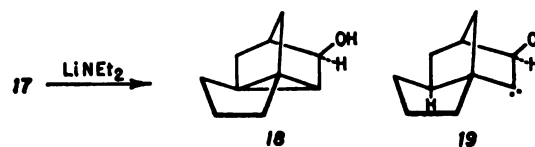


The occurrence of this rearrangement indicates clearly that the trimethylene bridge in 17 (and hence in 10, etc.) must be *c'-exo-e_2'* and not *c'-endo-e_2'*. The structure of 14 follows from physical and chemical data, including oxidation to a ketone which must possess the oxo function at the methano bridge, since the carbonyl stretching band is found at $5.63\text{ }\mu$ in the infrared.³² The formation of 14 from the tricyclic olefin 10 by reaction with mixtures of diborane and boron trifluoride followed by oxidation with alkaline hydrogen peroxide is a most interesting reaction which is deserving of further study. At present we can only speculate as to mechanism; one possibility is a process such as the following in which boron trifluoride (not shown) is coordinated (hydrogen bond) to a borane hydrogen.³³ This rearrangement also requires that the starting



tricyclic olefin be formulated as 4,5-*exo*-trimethylene-2-norbornene (10) rather than the *endo* isomer. In fact, we have observed a whole series of such rearrangements which proceed with remarkable ease (even more readily than with the parent norbornyl system); some of these are outlined in a later section.

Independent evidence for the structure 10 as opposed to the *endo*-trimethylene formulation comes from the reaction of the oxide 17 with lithium diethylamide, which leads to a saturated tetracyclic alcohol which can be assigned structure 18 on the basis of physical and chemical data, much of which is discussed below. The mechanism of this reaction would appear to be analogous to other base-catalyzed rearrangements of 1,2-epoxides^{34,35} which appear to proceed *via* β -alkoxy carbenes. The formation of 18 from such a carbene 19 appears only to be possible if the trimethylene bridge in the starting oxide 17 is *exo*.



A number of experiments directed at the synthesis of 4,5-*endo*-trimethylene-2-norbornyl derivatives (6, X = *endo*- or *exo*-OH) have been carried out, but members of this series have not been obtained to date. Synthetic efforts to produce these compounds are continuing.

(32) (a) C. F. H. Allen, T. Davis, D. W. Stewart, and J. A. Van Allan, *J. Org. Chem.*, **20**, 306 (1955); (b) C. F. H. Allen and J. A. Van Allan, *ibid.*, **20**, 323 (1955); (c) C. J. Norton, Ph.D. Thesis, Harvard University, 1955; (d) P. Wilder and A. Winston, *J. Am. Chem. Soc.*, **78**, 868 (1956); (e) W. R. Hatchard and A. K. Schneider, *ibid.*, **79**, 6261 (1957); (f) D. E. Applequist and J. P. Klieman, *J. Org. Chem.*, **26**, 2178 (1961).

(33) Possibilities such as reaction *via* fluoroborane (BF_3F) or separate action of BF_3 and BH_3 also deserve consideration.

(34) A. C. Cope, M. Brown, and H. H. Lee, *J. Am. Chem. Soc.*, **80**, 2855 (1958).

(35) A. C. Cope, H. H. Lee, and H. E. Petree, *ibid.*, **80**, 2849 (1958).

(1) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963).

(2) E. W. C. Wong and C. C. Lee, *Can. J. Chem.*, **42**, 1245 (1964).

(3) J. Meinwald, Y. C. Meinwald, and T. N. Baker, *J. Am. Chem. Soc.*, **86**, 4074 (1964).

(4) P. G. Gassman and J. L. Marshall, *ibid.*, **88**, 2822 (1966).

(5) For the interesting basis of this assignment see (a) K. Tori, K. Tanaka, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Letters*, 1964; (b) K. Tori, K. Aono, K. Kitahonoki, R. Muneyuki, Y. Tanaka, H. Tanida, and T. Tsuji, *ibid.*, 2921 (1966). The observation of a characteristic 7-*anti*-proton peak in the oxide 17 also is inconsistent with structure 13 for the olefinic precursor.

(6) (a) E. L. Eliel, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **39** (1961); (b) E. C. Ashby and J. Prather, *J. Am. Chem. Soc.*, **88**, 966.

Acetolysis Studies. Rates of acetolysis of 4,5-*exo*-trimethylene-2-*exo*-norbornyl *p*-toluenesulfonate (11, R = Ts) and 4,5-*exo*-trimethylene-2-*endo*-norbornyl *p*-toluenesulfonate (16, R = Ts) were measured at several temperatures in anhydrous acetic acid containing sodium acetate using the spectrophotometric method of Swain and Morgan,³⁶ which depends on the difference in intensity of absorption in the region 260–280 m μ between *p*-toluenesulfonate ion and *p*-toluenesulfonate esters. First-order kinetics were observed for both 11 and 16, R = Ts, and the infinity readings were found to be stable. The kinetic results are summarized in Table I, which also presents data³⁷ on 2-*exo*- and 2-*endo*-norbornyl *p*-toluenesulfonates for comparison.

Table I. Kinetic Data for Acetolysis in Anhydrous Acetic Acid

<i>p</i> -Toluenesulfonate	Temp, °C	10 ⁴ <i>k</i> ₁ , sec ⁻¹	Rel rate, 25°	ΔH^\ddagger , kcal/mole	ΔS^\ddagger , eu
4,5- <i>exo</i> -Trimethylene-2- <i>exo</i> -norbornyl (11, R = Ts)	90.65 ^a	847		25.6	-2.6
	82.60 ^a	382			
	67.68 ^a	73.9			
	25.00 ^b	0.283	3.4		
4,5- <i>exo</i> -Trimethylene-2- <i>endo</i> -norbornyl (16, R = Ts)	100.8 ^a	371		26.7	-3.1
	85.16 ^a	74.6			
	82.60 ^a	55.8			
	25.00 ^b	0.0328	0.4		
2- <i>exo</i> -Norbornyl	50.03 ^a	480			
	25.00 ^c	23.3	280	21.6	-7.2
2- <i>endo</i> -Norbornyl	100.4 ^c	0.0675			
	25.00 ^c	0.0828	1.0	25.8	-4.4

^a These runs made with 0.010 *M* sodium acetate and <0.005 *M* substrate. ^b Calculated from data at other temperatures. ^c Taken from ref 37 (also calculated from data at other temperatures).

The ratio of acetolysis rate constants for the *exo*- and *endo*-tricyclic *p*-toluenesulfonates 11, R = Ts, and 16, R = Ts, is calculated as 8.6 at 25° and 6.8 at 82.6°; these are much smaller than the *exo*:*endo* ratio for the 2-norbornyl system, e.g., 280 at 25°. The rate of acetolysis of the *exo*-tricyclic *p*-toluenesulfonate 11, R = Ts, is much smaller than that for 2-*exo*-norbornyl, the relative rates at 25° being 1:82.5, respectively. In contrast, the acetolysis rates of the *endo*-tricyclic *p*-toluenesulfonate 16, and 2-*endo*-norbornyl are very similar, the ratio at 25° being 1:2.5, respectively.

The lower rate of acetolysis of 4,5-*exo*-trimethylene 2-*exo*-*p*-toluenesulfonate (11, R = Ts) as compared with 2-*exo*-norbornyl might, for some obscure reason, be due to a difference in the tendency of the corresponding ion pairs to suffer acetolysis relative to internal return rather than to a difference in rates of ionization. This would seem unlikely *a priori*, but it also seems inappropriate because of data which have been obtained on the effect of added inert salt on the acetolysis of 11, R = Ts. The acetolysis rate constants observed for 11, R = Ts, in glacial acetic acid containing 0.01 *M* sodium acetate at 67.88° and varying molar concentrations of lithium perchlorate are: 76 (10⁻⁶) at 0.00 *M* LiClO₄, 89.4 (10⁻⁶) at 0.0098 *M* LiClO₄, 180 (10⁻⁶) at 0.05 *M* LiClO₄, and 320 (10⁻⁶) at 0.100 *M* LiClO₄. The evidence from other systems would tend to argue that as the concentration of LiClO₄ is increased to *ca.*

0.015 *M*, most of the internal return which can be prevented at all by this salt has been nullified (presumably this is return from "solvent-separated" ion pairs).³⁸⁻⁴⁰ Under these conditions the rate of acetolysis of 11, R = Ts, is still very much less than that of 2-*exo*-norbornyl. Further, the type of salt effect noted for the acetolysis of 11, R = Ts, does not appear to provide any basis for supposing an abnormal reluctance for "solvent-separated ion pairs"³⁸⁻⁴⁰ to react with solvent. It should also be noted that an argument can be given⁴¹ that acetolysis of 2-*exo*-norbornyl *p*-bromobenzenesulfonate probably does not occur directly from the "intimate ion pair," i.e., from the type of ion pair which is not subject to anion exchange with perchlorate. If such acetolysis could occur with 2-*exo*-norbornyl but not with the *exo*-tricyclic analog 11, R = Ts, the lower rate of the latter might conceivably be rationalized (quite unconvincingly) along such lines.

The major product from acetolysis of the tricyclic *exo*-*p*-toluenesulfonate 11, R = Ts, and the tricyclic *endo*-*p*-toluenesulfonate 16, R = Ts, was in each case the tricyclic *exo*-acetate 11, R = CH₃CO, which was formed to the extent of 91.5 and 92% of the total mixture of products, respectively. At least two more acetates were detected along with the major product from both 11, R = Ts, and 16, R = Ts; in each case these constituted *ca.* 4% of the total mixture. These were not identified due to the difficulty of separation from each other and from 11, R = CH₃CO.⁴¹ The vpc analyses indicated that one of the minor acetates could be the tricyclic *endo*-acetate 16, R = CH₃CO, on the basis of correspondence of retention times. However, additional investigation of this possibility is required and is planned. Two hydrocarbons were also formed in the acetolysis of 11, R = Ts, and 16, R = Ts, in a total yield of *ca.* 4%. The preponderant hydrocarbon exhibited the same vpc behavior as the tricyclic olefin 10.

Discussion

The results of this study are most simply interpreted in terms of the *bridged-ion mechanism* for the acetolysis of 2-*exo*-norbornyl sulfonates. This mechanism should lose much or all of its driving force in the case of the tricyclic *exo*-*p*-toluenesulfonate, 11, R = Ts (see introductory section), and so the slow acetolysis of this substrate relative to norbornyl is readily explained (and, in fact, was to be expected). In comparison, but also as predicted on the basis of the Winstein-Trifan arguments, 2-*endo*-norbornyl *p*-toluenesulfonate and the tricyclic *endo*-*p*-toluenesulfonate 16, R = Ts, for which bridging is not to be expected in the transition state for ionization on stereochemical grounds, show quite similar reactivity. Here it should be noted that the carbonyl stretching frequencies for 4,5-*exo*-trimethylenenorcamphor (15) and norcamphor, measured under the same conditions (CCl₄ solution) with a Cary-White Model 90 infrared spectrometer (with polystyrene for calibration), were found to be 1749 and 1750 cm⁻¹, respectively. This would indicate

(38) A. H. Fainberg and S. Winstein, *ibid.*, 78, 2763, 2767 (1956).

(39) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, and G. C. Robinson, *ibid.*, 78, 328 (1956).

(40) S. Winstein and G. C. Robinson, *ibid.*, 80, 169 (1958).

(41) Even the analytical resolution of the minor acetates from 11, R = CH₃CO, was extremely difficult and could only be accomplished by the use of vapor phase chromatography (vpc) with a long capillary column.

(36) C. G. Swain and C. R. Morgan, *J. Org. Chem.*, 29, 2097 (1964).
(37) P. von R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Am. Chem. Soc.*, 87, 375 (1965).

ferences in angle strain at C₂ cannot be responsible for the different acetolysis rates observed in the sulfonate series and also that the *endo*-sulfonates should be approximately the same.⁴³

Classical-ion mechanism, in a straightforward ionization, leads to the expectation that in acetolysis of 2-norbornyl $k(11, R = Ts) \cong k(2\text{-}endo\text{-}norbornyl) \cong k(16, R = Ts)$. This is *not* the case, and does not seem to be any obvious reason for the observed reactivity of the tricyclic *exo-p*-toluenesulfonate 11, R = Ts, keeping in mind the data on the *endo*-sulfonates. Substitution of simple alkyl at C₄ and/or methyl at C₂ would not be expected to produce a differential in the reactivities of 11 and 16, R = Ts, in a classical-ion mechanism, especially since the effect of methyl at C₂ and/or methyl at C₄ on the rates of ionization of 2-norbornyl series is small either with regard to *exo* rates alone or the *endo* rates alone.^{1,43} The arguments which have been given in support of the *bridged-ion mechanism*¹⁰⁻¹² include (1) greater steric hindrance to *endo* relative to *exo* group ionization to give the observed relative solvolysis rates of *exo*- and *endo*-norbornyl derivatives and (2) some kind of effect which causes *endo* attack by solvent on the bridged cation to be much slower than *exo* attack. There is little in these suggestions which helps to explain the results obtained in the present study.

We regard our results as providing clear support for the *bridged-ion mechanism* for solvolysis of 2-*exo*-norbornyl derivatives. However, it must be pointed out that confirmatory data from the study of the 4,5-dimethylene-2-norbornyl sulfonates is highly desirable.

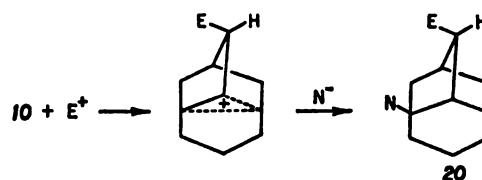
There is no evidence available at present which allows assignment of mechanism for the acetolysis of cyclic *exo-p*-toluenesulfonate 11, R = Ts. It is obviously possible that a part or even all of this reaction follows the classical pathway for ionization; again, further study is in order.

The results reported here add further evidence that the bridged norbornyl cation is especially stabilized relative to the classical ion, but they provide no information as to the origin of that stabilization. One possibility deserves mention in this regard. Normally, for aliphatic cations,⁴⁴ Wagner-Meerwein rearrangements proceed with low activation energies, perhaps in the order of a few kcal/mole. Assuming that the bridged ion which intervenes during such rearrangements has an energy very close to that of the transition state, it seems that only a small degree of extra stabilization (perhaps 3-7 kcal/mole) would be needed in certain cases to render the bridged ion more stable than a classical ion. At least part of this extra stabilization could be available in the bridged norbornyl cation from relief of angle strain. In the bicyclo[2.2.1]heptane cation a number of bond angles are distorted from their ideal values leading to considerable angle strain. Angles C₁-C₇-C₄ (ca. 95°), H-C₁-C₇, and H-C₄-C₇ (8°) are especially strained.⁴⁵ Much of this strain

would be relieved in going to a symmetrically bridged ion with C₆-C₁ and C₆-C₂ distances ca. 1.70 Å (i.e., about 10% longer than a normal C-C single bond), and essentially all the strain would be relieved in a bridged structure with C₆-C₁ and C₆-C₂ distances of 1.8 Å (only ca. 20% longer than normal for C-C).⁴⁶ Since the angle strain in the bicyclo[2.2.1]heptane ring appears to be ca. 6 kcal/mole,¹⁶ it is clear that considerable stabilization is available to the symmetrically bridged ion through relief of angle strain. Of course other factors may also contribute to the end result. For example, "I strain"⁴⁷ might destabilize the classical cation (C₁-C₂-C₃ angle ca. 104°) substantially. Finally, as is well known, the geometry of 2-*exo*-norbornyl derivatives is ideal for migration of C₄ to C₂ during the ionization process.

The only data currently at hand for which the *bridged-ion mechanism* does not provide a ready and cogent explanation, in our view, are those on the acetolysis of 1-aryl-2-*endo*- and 2-*exo*-norbornyl *p*-toluenesulfonates.⁴⁸ Using the Hammett equation,⁴⁹ it was found that the data on both *exo* and *endo* sulfonates were correlated better using σ^+ constants rather than σ^+ values of Brown and Okamoto⁵⁰ and further that the ρ values for the 2-*exo*- and 2-*endo*-sulfonates were similar and low; at 25° $\rho_{exo} = -1.36$ and $\rho_{endo} = ca. -1.14$.⁴⁸ There may be simple explanations of these data; these are not apparent at present, however.

Reactions of 4,5-*exo*-Trimethylenebicyclo[2.2.1]heptane Derivatives. In this section we record certain transformations of the tricyclic olefin 10 and its 2,3-oxide 17 which are of interest in connection with the development of the chemistry of this interesting system and which also serve to confirm the structural assignments indicated in the foregoing discussion. The tricyclic olefin 10 reacts with a number of electrophiles with rearrangement by a process which can be depicted as follows.



For example, reaction of 10 with aqueous mercuric perchlorate produces after addition of chloride ion 20, E = HgCl, N = OH, reduction of which with sodium borohydride⁵¹ affords the tertiary alcohol 21.⁵²

(46) For reference it is interesting that the bridged and nonbridged B-H distances in diborane are 1.33 and 1.19 Å, respectively. See W. N. Lipscomb, "Boron Hydrides," W. A. Benjamin, Inc., New York, N. Y., 1963.

(47) H. C. Brown and M. Gerstein, *J. Am. Chem. Soc.*, **72**, 2926 (1950).

(48) (a) D. C. Kleinfelter and P. von R. Schleyer, 3rd Delaware Valley Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1960, Abstracts, p 33; 138th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960, Abstracts, p 43P; *Dissertation Abstr.*, **22**, 428 (1961). (b) Private communication from P. von R. Schleyer.

(49) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp 184-207; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(50) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

(51) T. G. Traylor and A. W. Baker, *ibid.*, **85**, 2746 (1963).

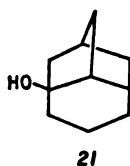
(52) The mercuration of norbornene under similar conditions proceeds substantially without rearrangement to afford the 3-*exo*-chloromercuri-2-*exo*-norborneol (ref 51 and earlier work there cited).

see C. S. Foote, *J. Am. Chem. Soc.*, **86**, 1853 (1964); P. von R. Schleyer, *ibid.*, **86**, 1854, 1856 (1964).

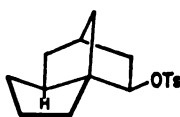
Dr. P. von R. Schleyer (personal communication) has informed us in his laboratory that methyl substitution at C₄ of *exo*- and *endo*-norbornyl sulfonates changes acetolysis rates only by a factor of 1.5 or less.

see M. C. Whiting, *Chem. Brit.*, **2**, 482 (1966).

see C. F. Wilcox, Jr., *J. Am. Chem. Soc.*, **82**, 414 (1960).



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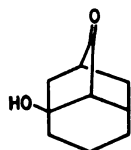


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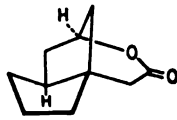
The nmr spectrum of 21 and the corresponding acetate indicate clearly that the hydroxyl function is tertiary. Hydrolysis of the *p*-toluenesulfonate 22 (from 12, R = H) in aqueous acetone containing calcium carbonate also leads to 21 cleanly. Interestingly, treatment of 21 with sulfuric acid produces 1-adamantanol.

Reaction of the tricyclic olefin 10 with bromine⁵³ gives a dibromide which is converted by heating with an aqueous suspension of silver oxide to the bromohydrin 20, N = OH, E = Br, which by further reaction with di-*n*-butyltin dihydride⁵⁴ yields the tertiary alcohol 21.

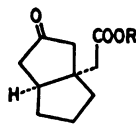
The *syn* relationship of N and E in the products of type 20 is assumed by analogy with the cases of stereospecific *exo* addition of various electrophilic reagents to norbornene. The diol 20, N = E = OH, is readily obtained by treatment of the epoxide 17 with acidic catalysts such as silica gel; chromic acid oxidation of this diol leads as expected to a keto tertiary alcohol (23) which shows characteristic bridge carbonyl absorption at 5.64 μ .



23



24



25

Along other lines, the tricyclic ketone 15 was converted by peracetic acid to the lactone 24 and thence by hydrolysis with base, oxidation with chromic acid, and subsequent reactions to a series of derivatives of the keto acid 25, R = H. The infrared and nmr spectra²² of 24 and the derivatives of 25 provide convincing evidence for the structures of these substances and, in consequence, for the precursors 15 and 10. For example, the lactone 24 shows low-field resonance due to a single proton (>CHO) in the nmr spectrum at 4.72 ppm (apparent quintet) and carbonyl absorption at 5.71 μ (CCl₄), and the ketonic carbonyl of the derivatives of 25 gives rise to absorption at 5.74 μ (CCl₄) as expected for a cyclopentanone.

A series of transformations starting from the tetracyclic alcohol 18 is also of interest. Evidence for the constitution 18 for the tetracyclic alcohol comes (a) from the characteristic cyclopropyl CH absorption in the infrared at 3.28 μ ⁵⁵ and in the near infrared at 1.676 μ ,⁵⁶ (b) the absence of olefinic CH peaks in the

nmr spectrum, and (c) oxidation by chromic acid to the corresponding ketone (26) which showed absorption in the infrared at 3.31 μ (cyclopropyl CH)⁵⁵ and 5.67 and 5.72 μ (cf. nortricyclanone carbonyl absorption at 5.66 and 5.70 μ).⁵⁷ Reaction of the ketone 26 with hydrogen bromide in methylene chloride produced a bromo ketone which from the mode of formation⁵⁸ and spectroscopic data is formulated as 5-bromo-4,5-trimethylene-2-norbornanone (27). This bromo ketone affords by reduction either with zinc-acetic acid, di-*n*-butyltin dihydride in tetrahydrofuran, or hydrogen and palladium on charcoal in ethanol the tricyclic ketone 15 cleanly; none of the isomeric *endo*-4,5-trimethylene-2-norbornanone could be detected.

Experimental Section

Melting points, determined using a Büchi melting point apparatus, are uncorrected. Infrared data were obtained with a Perkin-Elmer Infracord spectrophotometer, a Perkin-Elmer Model 137 sodium chloride spectrophotometer, a Perkin-Elmer Model 237 grating infrared spectrometer, and for high resolution a Cary-White Model 90 infrared spectrometer using polystyrene as a calibration standard. Near-infrared data were obtained using a Cary Model 14 spectrophotometer. Ultraviolet spectra were taken using a Cary Model 11 M ultraviolet spectrometer and a Cary Model 14 spectrophotometer. The nmr data were obtained at 60 Mc using a Varian Associates Model A-60 nmr spectrometer and are expressed as shift downfield from internal tetramethylsilane in parts per million. Vapor phase chromatography was performed using an F & M Model 300 unit with a thermal conductivity detector and an F & M Model 609 flame ionization unit. The mass spectra were recorded using a Consolidated Engineering Corp. Model 21-103 C mass spectrometer and an Associated Electrical Industries Ltd. Model MS-9 mass spectrometer. Microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Mülheim (Ruhr), Germany, and Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Δ^4 -Pentenylcyclopentadienes 9. A 1-l., three-necked flask was equipped with a mechanical stirrer having a glass blade, a two-way stopcock to let in ammonia, a three-way stopcock for maintaining a nitrogen atmosphere, and a Y tube fitted with a pressure-equalized dropping funnel and a dewar condenser. Sodium metal (11.5 g, 0.501 g-atom) was placed in the flask under nitrogen and dissolved in distilled ammonia (500 ml).¹⁹ The blue solution was cooled in a Dry Ice-acetone bath and stirred vigorously as dry, distilled cyclopentadiene (62 ml, 0.750 mole) was added dropwise from the pressure-equilibrated dropping funnel. As soon as the mixture became colorless, 5-bromo-1-pentene (74.5 g, 0.500 mole) was added over a 45-min period. The reaction mixture was cooled in a Dry Ice-acetone bath and stirred for 2.5 hr. After allowing the ammonia to evaporate, salt-water was added, and the aqueous mixture was extracted with ether. The ethereal layer was dried with anhydrous magnesium sulfate and filtered. The solvent was removed at room temperature with a water aspirator, and the yellow residue was distilled giving 57.9 g (86%) of the Δ^4 -pentenylcyclopentadiene (9): bp 50–53° (7 mm). The infrared spectrum²² of the product showed C=C stretching absorption at 6.08 and 6.23 μ ; the nmr spectrum²² showed olefinic proton peaks from 4.8 to 6.4 ppm (integrated ratio to upfield protons 5.7:8) and indicated that the mixture consisted largely of C₁ and C₂ substituted cyclopentadienes. Because of the reactivity of 9 no elemental analysis was performed. The product showed ultraviolet absorption at λ_{max} 248 m μ (ϵ 3200).

4,5-*exo*-Trimethylene-2-norbornene (10). A 300-ml, three-necked flask was equipped with a condenser, a three-way stopcock, a glass encased magnetized bar, and a pressure-equalized dropping funnel. Purified tri-*n*-butylamine (100 ml) was added to the flask under nitrogen, and the flask was placed in a silicone oil bath main-

(53) L. Kaplan, H. Kwart, and P. von R. Schleyer, *J. Am. Chem. Soc.*, **82**, 2341 (1960).

(54) (a) H. G. Kuivila in "Advances in Organometallic Chemistry," Vol. I, F. G. A. Stone and R. West, Ed., Academic Press Inc., New York, N. Y., 1964; (b) L. W. Menapace and H. G. Kuivila, *J. Am. Chem. Soc.*, **86**, 3047 (1964).

(55) (a) H. E. Simmons, E. P. Blanchard, and H. D. Hartzler, *J. Org. Chem.*, **31**, 295 (1966), and references therein; (b) F. J. Piehl and W. G. Brown, *J. Am. Chem. Soc.*, **75**, 5023 (1953); (c) A. R. H. Cole, *J. Chem. Soc.*, 3807, 3810 (1954); (d) M. Hanack, H. Eggensperger, and S. Kang, *Chem. Ber.*, **96**, 2532 (1963); (e) M. Horák, J. Šmejkal, and J. Farkaš, *Collection Czech. Chem. Commun.*, **28**, 2280 (1963).

(56) (a) W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 504 (1958); (b) J. Meinwald, A. Lewis, and P. G. Gassman, *ibid.*, **84**,

977 (1962); (c) P. G. Gassman, *Chem. Ind. (London)*, 740 (1962); (d) H. Hart and R. A. Martin, *J. Org. Chem.*, **24**, 1267 (1959); (e) H. Weitkamp and F. Korte, *Tetrahedron*, **20**, 2125 (1964); (f) H. Tanida, Y. Hata, Y. Matsui, and I. Tanaka, *J. Org. Chem.*, **30**, 2259 (1965); (g) P. G. Gassman and W. M. Hooker, *J. Am. Chem. Soc.*, **87**, 1079 (1965); (h) P. G. Gassman and F. V. Zalar, *J. Org. Chem.*, **31**, 166 (1966).

(57) R. Zbinden and H. K. Hall, *J. Am. Chem. Soc.*, **82**, 1215 (1960).

(58) H. Krieger, *Suomen Kemistilehti*, **34B**, 24 (1961); *Chem. Abstr.*, **55**, 23370f (1961).

at 200°. A solution of Δ^4 -pentenylcyclopentadienes 9 (0.112 mole) in tri-*n*-butylamine (100 ml) was added dropwise to solvent with stirring over a period of 1 hr. The cooled mixture was poured into ice-cold aqueous hydrochloric acid and extracted with two 150-ml portions of distilled trichlorofluoromethane (Freon 11). The combined organic layers were washed with dilute hydrochloric acid and then sodium carbonate and with anhydrous magnesium sulfate. The solvent was removed by distillation at atmospheric pressure through a column of silica gel, and the residue was distilled through a column of a reflux condenser through which water was passed at a rate so as to maintain good reflux. The residual yellow liquid was distilled from lithium aluminum hydride, giving 9.7–14.3 g (70%) of tricyclic olefin 10, bp 64–65° (26 mm). The molecular weight determined mass spectrometrically was 134. The nmr spectrum of 10¹³ exhibited peaks at 1–2 ppm (11 H), a broad singlet at 2.12 ppm due to the single bridgehead proton, and a six-peak multiplet (AB part of an ABX pattern, 2 H) due to the two olefinic protons. The infrared spectrum²² showed olefinic CH stretch at 3.0 μ , C=C stretch at 6.23 and 6.42 μ , and a *cis*-CH=CH out-of-plane deformation band at 14.18 μ . A small amount (3–5%) of an isomeric impurity which requires further study could be detected in the crude product by vpc analysis. A typical sample of 10 was prepared by vpc.

Calcd for C₁₀H₁₄: C, 89.48; H, 10.57. Found: C, 89.48; H, 10.57.

Reaction of Tricyclic Olefin 10 with Diborane. A solution of olefin 10 (1.34 g, 10.0 mmoles) in dry, distilled tetrahydrofuran (10 ml) was placed in a 25-ml, three-necked flask equipped with a glass stopper, a mercury sealed valve, and a glass tube with a side arm. The glass tube was connected to a diborane generator which consisted of a 25-ml, three-necked flask equipped with a magnetic stirring bar, a rubber serum cap, and a three-way stopcock. Distilled boron trifluoride etherate (780 mg, 5.5 mmoles) and diglyme (0.7 ml) were placed in the generator. The air in the entire assembly was displaced by nitrogen. Diborane, produced by dropwise addition of a 1 M solution of sodium borohydride in diglyme (2.75 ml, 2.75 mmoles) by means of a syringe to the boron trifluoride etherate solution, was passed as a slow stream of nitrogen into the tetrahydrofuran solution of 10 (cooled in an ice bath). After completion of the addition of the sodium borohydride solution, the diborane-producing flask was heated at 70–80° for 1 hr, and then the reaction flask was disconnected from the generator. The reaction solution was allowed to stand 6 hr at 0° and 36 hr at room temperature. To the solution, 2.86 M sodium hydroxide (1.10 ml, 3.15 mmoles) was added followed by 30% hydrogen peroxide (1.1 ml, 11 mmoles). The reaction mixture was allowed to stand for 1 hr at 0° and for 2 hr at room temperature, poured into water, and extracted with ether. The etheral extracts were stirred for 1 hr with 5% palladium on charcoal, dried (MgSO₄), concentrated, and distilled, giving 990 mg of a mixture of alcohols. The mixture was analyzed by vpc on a 12-ft 5% Carbowax 20M column and found to consist of 11 (70%), 12 (17%), and 14 (13%).

Another run only 11, R = H (74%), and 12, R = H, were obtained, but an aliquot of this reaction mixture to which boron trifluoride etherate was added gave 14 in addition to these alcohols.

Reaction of Tricyclic Olefin 10 with Diisobutylborane. In a dry, 25-ml flask equipped with a serum cap were placed 2-methyl-2-butene (23.1 g, 0.329 mole), dry, distilled diglyme (50 ml), and sodium borohydride (4.70 g, 0.124 mole) under nitrogen. The mixture was stirred vigorously and cooled in an ice bath as distilled boron trifluoride etherate (23.5 g, 0.166 mole) was added dropwise from a syringe over a period of 45 min. The mixture was allowed to stand at 0° for 15–18 hr. Tricyclic olefin 10 (5.52 g, 0.042 mole) dissolved in diglyme (5 ml) was added to the semisolid mixture. The mixture was stirred for 30 hr at 0° and for 24 hr at room temperature. The reaction mixture was oxidized by cautiously adding 3 N sodium hydroxide (50 ml) followed by dropwise addition of 30% hydrogen peroxide (50 ml). After stirring for 5 hr the mixture was diluted with water and extracted twice with ether. The combined extracts were washed four times with cold water, dried with sodium bisulfite solution, and once again with water, dried with anhydrous magnesium sulfate, concentrated, and distilled, giving 3.84 g (62%) of a mixture of alcohols, bp 62–63° (0.02 mm). The mixture was analyzed by vpc and found to consist of 12, R = H (8%), and 11, R = H (92%). Part of this mixture of alcohols (0.912 g, 6.0 mmoles) and 3,5-dinitrobenzoyl chloride (6.6 mmoles) were heated in dry, distilled pyridine (6 ml) and the solution was effected. The solution was stirred for 3.5 hr at room temperature, and the mixture was dissolved in benzene,

washed with cold, dilute hydrochloric acid (9.0 ml of concentrated HCl in 300 ml of water), water, and saturated sodium bicarbonate solution, dried (K₂CO₃), and concentrated, leaving 1.91 g (92%) of a mixture of esters. The mixture was recrystallized twice from *n*-hexane, yielding 1.31 g (70%) of the 3,5-dinitrobenzoate 11, R = (NO₂)₂C₆H₃CO₂, mp 121.5–122.5°; λ (CHCl₃) 3.22, 3.39, 3.49, 5.81 (C=O), 6.15 (C=C), 6.50, 7.49, 7.82, 8.59 μ .

Anal. Calcd for C₁₇H₁₈N₂O₆: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.96; H, 5.35; N, 8.10.

The purified 3,5-dinitrobenzoate of 11, R = H (1.23 g, 3.54 mmoles), methanol (5.9 ml), and 5 N sodium hydroxide (2.9 ml) were refluxed under nitrogen for 1 hr. The mixture was added to water and repeatedly extracted with ether. The etheral extracts were dried with anhydrous potassium carbonate and concentrated, leaving 11, R = H, in quantitative yield, mp 45–49°.

The infrared spectrum of 11, R = H (neat), showed hydroxyl absorption at 2.96 μ (broad); the nmr spectrum (CDCl₃) exhibited a doublet of doublets at 3.88 ppm due to >CHO (1 H), a sharp peak due to OH at 2.88 ppm, a broad singlet due to bridgehead CH (1 H) at 2.12 ppm, and many peaks due to the remaining protons at 2.0–1.0 ppm.

Anal. Calcd for C₁₀H₁₄O: C, 78.90; H, 10.59. Found: C, 78.62; H, 10.56.

The alcohol 12, R = H, was isolated as follows. The mother liquor from the first recrystallization of the mixture of 3,5-dinitrobenzoates of alcohols 11 and 12 was concentrated. Hydrolysis of the mixture of esters and preparative vpc of the mixture of alcohols gave 12, R = H: hydroxyl absorption at 2.65 and 2.8 μ ; nmr (CDCl₃): 1.0–2.3 (multiplet, 14 H), 2.65 (singlet, 1 H), and 3.60 ppm (broadened doublet, *J* = 6.5 cps, 1 H).²³

Anal. Calcd for C₁₀H₁₄O: C, 78.90; H, 10.59. Found: C, 78.60; H, 10.56.

exo-4,5-Trimethylene-2-exo-norbornyl *p*-Toluenesulfonate (11, R = Ts). To a solution of the tricyclic *exo* alcohol 11, R = H (76.9 mg, 0.506 mmole), in dry, distilled pyridine (1.25 ml), *p*-toluenesulfonyl chloride (250.6 mg, 1.32 mmoles) was added. The solution was allowed to stand for 24 hr at room temperature. Four drops of water were added, and the solution was allowed to stand for 0.5 hr without cooling. The solution was poured into water and ether, and the aqueous phase extracted again with ether. The combined extracts were washed with water, sodium bisulfate solution, and water again, dried (MgSO₄), and concentrated, leaving 150 mg (97%) of 4,5-*exo*-trimethylene-2-*exo*-norbornyl tosylate (11, R = Ts), mp 66.5–68°; $\lambda_{\text{max}}^{\text{NaOH, 0.01 M NaOH}}$ 262.3 μ (ϵ 554), 267.5 μ (ϵ 500), and 273.2 μ (ϵ 446). The infrared and nmr spectra²⁴ agreed with the assigned structure.

Anal. Calcd for C₁₇H₂₀O₂S: C, 66.61; H, 7.24; S, 10.47. Found: C, 66.75; H, 7.09; S, 10.63.

exo-4,5-Trimethylene-2-norbornanone (15). To a stirred solution of tricyclic alcohol 11, R = H (152 mg, 1.00 mmole), in acetone (2.5 ml) cooled in an ice bath, oxidizing agent (6.68 g of chromium trioxide and 5.75 ml of concentrated sulfuric acid diluted to 100 ml of solution with water) was added dropwise. The addition was continued until the color of the reagent was not discharged within 0.5 hr at room temperature. The excess oxidant was destroyed with isopropyl alcohol. The mixture was diluted with water and repeatedly extracted with ether. The etheral extracts were washed with saturated aqueous sodium bicarbonate solution and water, dried with anhydrous potassium carbonate, and concentrated, leaving 143 mg (95%) of tricyclic ketone 15; the infrared spectrum showed ν (CCl₄) 1749 cm⁻¹.

Anal. Calcd for C₁₀H₁₄O: C, 79.96; H, 9.39. Found: C, 80.13; H, 9.50.

To the tricyclic ketone 15 (24.3 mg, 0.162 mmole) dissolved in 95% ethanol (0.4 ml), a solution of acidic 2,4-dinitrophenylhydrazine (1.0 ml) reagent was added. The reaction mixture was allowed to stand for several hours at room temperature. Filtration of the mixture gave 48.1 mg (90%) of a yellow solid. Two recrystallizations from acetonitrile gave yellow crystals of the 2,4-dinitrophenylhydrazone of tricyclic ketone 15, mp 172–174°; λ (CHCl₃) 2.97, 3.35, 6.17, 6.29, and 7.50 μ .

Anal. Calcd for C₁₄H₁₈N₄O₄: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.14; H, 5.48; N, 17.13.

exo-4,5-Trimethylene-2-endo-norborneol (16, R = H). To a solution of the tricyclic ketone 15 (30.0 mg, 0.200 mmole) in methanol (1.0 ml) cooled in an ice bath was added sodium borohydride (37.1 mg, 0.981 mmole) dissolved in cold methanol (2.0 ml) with stirring over a period of 30 min. The solution was stirred at 0° for 1 hr and at room temperature for 2 hr. The mixture was poured into water and twice extracted with 2:1 *n*-pentane-methylene

chloride solution. The combined organic extracts were washed three times with water, dried (MgSO_4), and concentrated, giving 29.7 mg (97%) of tricyclic *endo* alcohol 16, $R = H$. The solid was dissolved in *n*-pentane at room temperature and cooled to 0° . Recrystallization twice in this manner gave colorless crystals, mp $56\text{--}58^\circ$. The molecular weight determined mass spectrometrically was 152.1200 (calcd for $\text{C}_{10}\text{H}_{16}\text{O}$: 152.1201). The nmr spectrum²² of 16, $R = H$, showed a multiplet (1 H) due to $>\text{CHO}$ at 4.23 ppm, a sharp peak due to hydroxyl at 3.2 ppm, and many peaks due to the remaining protons at 0.85–2.4 ppm; the infrared spectrum showed the expected OH stretching absorption at 2.65 and $2.95\ \mu$ in CCl_4 .

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}$: C, 78.90; H, 10.59. Found: C, 79.31; H, 10.65.

***p*-Toluenesulfonate 16, $R = \text{Ts}$.** The *endo* tricyclic alcohol 16, $R = H$ (39.4 mg, 0.259 mmole), dissolved in pyridine (0.65 ml) was allowed to react with *p*-toluenesulfonyl chloride (130.6 mg, 0.685 mmole) as described for the preparation of 11, $R = \text{Ts}$, giving 74.4 mg (96%) of a solid. Two recrystallizations from *n*-pentane gave colorless crystals of 4,5-*exo*-trimethylene-2-*endo*-norbornyl *p*-toluenesulfonate (16, $R = \text{Ts}$), mp $50\text{--}51.5^\circ$; $\lambda_{\text{max}}^{\text{A}_{\text{OH}, 0.01\text{M NaOAc}}}$ 262.4 μ (ϵ 544), 267.6 μ (ϵ 492), and 273.4 μ (ϵ 438). The infrared and nmr spectra²² were consistent with the assigned structure.

Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_4\text{S}$: C, 66.61; H, 7.24; S, 10.47. Found: C, 66.89; H, 7.14; S, 10.55.

Tricyclic *exo* Acetate 11, $R = \text{CH}_3\text{CO}$. To a solution of *exo* alcohol 11, $R = H$ (50.6 mg, 0.333 mmole), in dry, distilled pyridine (0.55 ml) cooled in an ice bath was added acetic anhydride (0.27 ml). After standing at room temperature for 74 hr, the solution was poured into water and twice extracted with *n*-pentane. The pentane extracts were washed with aqueous copper sulfate solution, water, aqueous sodium bicarbonate solution, and water, dried (MgSO_4), and concentrated, giving 61.0 mg (94%) of 4,5-*exo*-trimethylene-2-*exo*-norbornyl acetate (11, $R = \text{CH}_3\text{CO}$). The infrared spectrum²² showed carbonyl absorption at $5.73\ \mu$ due to acetate; the nmr spectrum showed a doublet of doublets (1 H) due to $>\text{CHO}$ at 4.70 ppm, a sharp acetyl singlet (3 H) at 2.02 ppm, a broad singlet at 2.23 ppm (1 H) due to the bridgehead proton at C_1 , and additional peaks upfield.

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$: C, 74.19; H, 9.34. Found: C, 74.42; H, 9.59.

Tricyclic *endo* Acetate 16, $R = \text{CH}_3\text{CO}$. The *endo* alcohol 16, $R = H$ (155.5 mg, 1.023 mmole), was acetylated as described above, giving 190.9 mg (96%) of 4,5-*exo*-trimethylene 2-*endo*-acetate 16, $R = \text{CH}_3\text{CO}$; the infrared (neat) spectrum showed an ester carbonyl at $5.73\ \mu$; the nmr spectrum showed a broad peak (1 H) due to $>\text{CHO}$ at 4.98 ppm and other peaks upfield including a sharp acetyl signal (3 H, 2.0 ppm). The molecular weight determined mass spectrometrically was 194.1301 (calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$: 194.1306).

Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.19; H, 9.34. Found: C, 73.74; H, 9.17.

Tricyclic Epoxide 17. A 0.30 *M* solution of monoperphthalic acid¹⁹ in ether (100 ml, 30 mmole) was added to tricyclic olefin 10 (1.79 g, 13.3 mmole) cooled in a salt-ice bath. After standing for 62 hr at 0° , the solution was poured into cold 10% aqueous sodium hydroxide solution. The ethereal solution was washed twice with 10% aqueous sodium hydroxide solution and water, dried (MgSO_4), concentrated, and distilled, giving 1.64 g (82%) of tricyclic epoxide 17, bp 45° (0.6 mm).

The nmr spectrum²² of 17 (CCl_4) showed one proton of the oxirane ring as a sharp doublet at 2.7 and 2.82 ppm and the other as a broadened doublet at 2.92 and 2.99 ppm and a broad singlet due to the bridgehead proton at C_1 at 2.41 ppm (1 H), as well as other peaks upfield.

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}$: C, 79.96; H, 9.39. Found: C, 80.01; H, 9.47.

Reduction of Tricyclic Epoxide 17 with Lithium Aluminum Hydride. A mixture of the tricyclic epoxide 17 (31 mg, 0.20 mmole), powdered lithium aluminum hydride (24 mg, 0.64 mmole), and dry, distilled glyme (1.0 ml) was stirred at reflux for 30 hr. Water was cautiously added, and the mixture was repeatedly extracted with ether. The ethereal extracts were dried (MgSO_4) and concentrated, giving an oil which was analyzed by vpc. The oil was found to be a mixture of 11, $R = H$ (33%), 12, $R = H$ (63%), and 14 (4%).

Reaction of Tricyclic Epoxide 17 with Aluminum Chlorohydride Reagent. A mixture of lithium aluminum hydride (86.6 mg, 2.28

mmole) and dry ether (2.0 ml) was refluxed for 30 min. cooled lithium aluminum hydride slurry was added to a solution of anhydrous aluminum chloride (262 mg, 1.97 mmole) in ether (2.0 ml) cooled in an ice bath. The mixture was stirred a period of 0.5 hr at room temperature. A solution of triepoxide 17 (14.7 mg, 0.0988 mmole) in dry ether (0.5 ml) was added to the mixed hydride reagent, and the mixture was refluxed 1 hr. The reaction mixture was hydrolyzed with water and extracted with ether. The ethereal extracts were dried (MgSO_4) and concentrated, giving 13.5 mg (90%) of a mixture of alcohols. The mixture was found to consist of 11, $R = H$ (24%), and 14 (76%) by vpc analysis.

Isolation of Rearranged Alcohol 14. Alcohols 11, $R = H$ and 14 were separated by preparative vpc using a 12-ft 5% Carl 20M column. The alcohol 14 was obtained as colorless crystals, mp $102\text{--}113^\circ$; the nmr spectrum (CDCl_3) showed peaks at 0 (multiplet, 14 H), 3.79 (singlet, 1 H), and 3.94 ppm (singlet, 1 H); in CS_2 it showed 0.8–2.5 (multiplet, 14 H), 3.83 (singlet, 1 H), 4.40 ppm (singlet, 1 H). The molecular weight determined spectrometrically was 152.1198 (calcd for $\text{C}_{10}\text{H}_{16}\text{O}$: 152.1200). *Anal.* Calcd for $\text{C}_{10}\text{H}_{16}\text{O}$: C, 78.90; H, 10.59. Found: 78.56; H, 10.73.

Oxidation of 14. Rearranged alcohol 14 (15.7 mg, 0.103 mmole) was oxidized as described for the oxidation of the *exo* alcohol 11, $R = H$, to the tricyclic ketone 15, giving 11.7 mg (76%) of the ketone, mp $119\text{--}130^\circ$; infrared (CCl_4) absorption due to carbonyl at $5.63\ \mu$. The molecular weight determined mass spectrometrically was 150.1047 (calcd for $\text{C}_{10}\text{H}_{14}\text{O}$: 150.1045).

Mercuriation of Tricyclic Olefin 10 to Give 20, $E = \text{HgCl}$, $N = \text{OH}$. To a stirred solution of tricyclic olefin 10 (134 mg, 1.00 mmole), 61.3% perchloric acid (164 mg, 1.00 mmole), water (0.8 ml), and acetone (0.8 ml), freshly prepared yellow mercuric oxide (21.1 mmole) was added portionwise. After stirring the mixture 5 hr, the mercuric oxide had completely dissolved. The mixture was removed by evaporation, and the mixture was added to a solution of sodium chloride (117 mg, 2.00 mmole) in water (1.0 ml). The mixture was shaken for a short time and then filtered by suction. The solid was washed with a small amount of water, dried under vacuum, giving 382 mg (99%) of a solid. Recrystallization from acetone gave colorless crystals of oxymercurial 20, $E = \text{HgCl}$, $N = \text{OH}$, mp 198° ; λ (KBr) 2.82, 2.92, 3.38, 6.83, 6.94, 7.51, 8.18, 9.02, 9.31, and 11.23 μ ; ν (CCl_4) 3596 (OH).

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{ClHgO}$: C, 30.99; H, 3.91; Cl, 15.81; Hg, 51.81. Found: C, 31.24; H, 3.92; Cl, 9.03; Hg, 51.7.

Reduction of Oxymercurial 20, $E = \text{HgCl}$, $N = \text{OH}$ with Sodium Borohydride. To a stirred mixture of the oxymercurial (350 mg, 0.90 mmole) and 0.1 *N* sodium hydroxide in methanol (5 ml) cooled in an ice bath was added sodium borohydride (1.2 mmole) in portions over a period of 1.25 hr. The mixture was refluxed for 3 hr, slowly poured into 10% aqueous hydrochloric acid solution, and extracted five times with methylene chloride. The extracts were dried (MgSO_4) and concentrated, giving 133 mg (98%) of a colorless, volatile solid. Sublimation at $1\ \text{mm}$ gave colorless crystals of tertiary alcohol 21, mp $161\text{--}162^\circ$; infrared absorption (in CCl_4) due to OH at 2.65 (sharp) and 2.92 (broad); nmr peaks (CCl_4) between 1.2 and 2.4 ppm (multiplet, no peaks downfield).

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}$: C, 78.90; H, 10.59. Found: 79.15; H, 10.63.

A solution of tertiary alcohol 21 (69 mg, 0.45 mmole), anhydride (460 mg, 4.5 mmole), and dry pyridine (360 mmole) under nitrogen was maintained at $78\text{--}80^\circ$ for 1 hr. The dark brown solution was poured into water and extracted with *n*-pentane. The pentane extract was washed twice with 2 *N* sodium sulfate solution and water, dried (MgSO_4), and concentrated, giving 76 mg (76%) of the acetate of 21; infrared absorption due to carbonyl at $5.73\ \mu$; nmr (CCl_4) 1.0–2.4 ppm (multiplet; singlet, 1.79 ppm) and no peaks downfield.

Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.19; H, 9.34. Found: 74.34; H, 9.42.

Tricyclic Tosylate 22. To a solution of alcohol 12, $R = H$ (12.5 mg, 0.0822 mmole), in dry, distilled tetrahydrofuran (ml) under nitrogen and cooled in an ice bath was added a *n*-butyllithium solution (0.06 ml, 0.096 mmole) in hexane. The solution was stirred at 0° for a period of 30 min. A solution of *p*-toluenesulfonyl chloride (19.3 mg, 0.10 mmole) in dry, distilled tetrahydrofuran (0.25 ml) was added. The solution was stirred for 5.7 hr at 0° and then poured into water. The mixture was extracted with ether, and the extracts were washed with water

(59) G. B. Payne, *Org. Syn.*, 42, 77 (1962).

us sodium bicarbonate solution and brine, dried (MgSO_4), concentrated, giving 25.3 mg (100%) of tosylate 22; λ (neat) 5.24, 7.22, 8.46, and 12.27 μ .

Hydrolysis of Tricyclic Tosylate 22. A mixture of tricyclic ketone 22 (25.3 mg, 0.0827 mmole), 75% aqueous acetone (1 ml), excess calcium carbonate was stirred at room temperature for a total of 20 hr. The reaction mixture was poured into water and readily extracted with ether. The ethereal extracts were washed with water, dried, and concentrated, giving 11.9 mg (95%) of essential oil 21. The product, as purified by preparative vpc, exhibited identical infrared absorption as the product obtained as described above from 20, $\text{E} = \text{HgCl}$, $\text{N} = \text{OH}$. Alcohols prepared by the two methods had the same melting point and the melting point of mixtures was undepressed. Both oils showed identical behavior on tlc on silica gel and vpc on 5% Carbowax 20M column.

Hydrolysis of Tricyclic Olefin 10. To a solution of tricyclic ketone 10 (134 mg, 1.00 mmole) in methylene chloride (0.5 ml) dissolved in a salt-ice bath was added a solution of bromine (160 mg, 1.00 mmole) in methylene chloride (0.5 ml) dropwise with stirring. The color of the reagent was immediately discharged with each drop added to the olefin solution. After completion of the addition of bromine, the solution was concentrated, giving 280 mg (97%) of a mixture consisting of a monobromide and mainly dibromide; λ 3.38, 6.81, 6.95, 7.70, 7.96, 9.03, 12.61, and 13.61 μ ; nmr (CDCl_3) 1.0–2.6 (multiplet, 19 H) and 4.07 ppm (singlet, 3 H). The mixture gave an immediate precipitate on exposure to alcoholic nitrate.

Hydrolysis of Bromohydrin 20, $\text{E} = \text{Br}$, $\text{N} = \text{OH}$. A mixture of γ -prepared silver oxide (200 mg, 0.87 mmole), crude dibromide (100 mg, 0.38 mmole), and water (2 ml) was refluxed for 17 hr. The mixture was filtered, diluted with water, and extracted with ether.

The ethereal extract was dried (MgSO_4) and concentrated, giving 50 mg (57%) of a mixture which consisted mainly of bromohydrin 20, $\text{N} = \text{OH}$, $\text{E} = \text{Br}$; λ (neat) 2.79, 2.90, 3.40, 5.89, 6.94, 7.32, and 9.01 μ .

The mixture gave a positive Beilstein test but did not give a precipitate on boiling for several minutes with a solution of silver nitrate in alcohol.

Hydrolysis of Bromo Alcohol 20, $\text{N} = \text{OH}$, $\text{E} = \text{Br}$. To a solution of bromo alcohol (36 mg, 0.16 mmole) in dry, distilled tetrahydrofuran (1.0 ml) under nitrogen was added di-*n*-butyltin dihydride (0.2 ml, 1.0 mmole) by means of a syringe. The solution was irradiated with light from a sun lamp for 5 min and allowed to stand at room temperature for 19 hr. 2-Bromopropane (0.1 ml) was added, and the solution was stirred for 1 hr. A 20% aqueous solution of sodium potassium tartrate (4 ml) and *n*-pentane was added, the mixture was stirred for 3 hr and filtered through Celite. The *n*-pentane layer was separated. The *n*-pentane solution was washed with aqueous sodium potassium tartrate solution and water, dried (MgSO_4), and concentrated, giving 24 mg (99%) of a mixture of compounds. The major product was isolated by preparative vpc (12 mg was collected) and shown to have identical behavior on vpc with tertiary alcohol 21 prepared by reduction of oxycyclohexanone 20, $\text{E} = \text{HgCl}$, $\text{N} = \text{OH}$. The two alcohols had identical infrared spectra and the same melting point; mixtures of the two oils had undepressed melting point.

Preparation of Tricyclic Epoxide 17 on Silica Gel. The tricyclic epoxide 17 (230 mg) was chromatographed over silica gel (Davison, 20 g) using a long column (10 \times 300 mm). The mixture was eluted by *n*-pentane (200 ml), 20% methylene chloride–*n*-pentane (100 ml), or 50% methylene chloride–*n*-pentane (100 ml). Methylene chloride (300 ml) eluted an oil (30 mg), and ethyl ether (100 ml) first (50 ml) an oil (22 mg) and then (100 ml) a colorless solid (73 mg). The colorless solid eluted by ethyl ether was the tricyclic epoxide 17, $\text{E} = \text{N} = \text{OH}$, mp 159–161°; λ (CH_2Cl_2) 2.93 (OH), 3.36, 7.03, 8.32, 8.95, 9.26, 9.53, and 11.03 μ ; nmr (CCl_4) 1.2–2.2 (multiplet, 13 H), 3.88 (singlet, 1 H), and 4.64 ppm (singlet, 2 H); (CDCl_3) 1.2–2.2 (multiplet, 13 H), 3.86 (singlet, 2 H), and 3.98 (singlet, 1 H).

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_3$: C, 71.39; H, 9.59. Found: C, 71.3; H, 9.63.

The diol 20, $\text{E} = \text{N} = \text{OH}$, did not react with periodic acid.

Acid-Catalyzed Hydrolysis of Tricyclic Epoxide 17. A stirring mixture of tricyclic epoxide 17 (150.3 mg, 1.00 mmole), water (0.6 ml), and 72% perchloric acid (1 drop) was maintained at 60° for a total of 1 hr. The mixture was neutralized with 0.1 *N* sodium hydroxide, diluted with water, and extracted three times with ether. The ethereal extracts were dried (MgSO_4) and concentrated; the solid residue was sublimed twice and recrystallized twice from

n-hexane, giving 22 mg (13%) of diol 20, $\text{E} = \text{N} = \text{OH}$, mp 148–150°, having the same infrared spectrum as the product from the previous procedure.

Hydroxy Ketone 23. Diol 20 (18.6 mg, 0.111 mmole) was oxidized as described for the oxidation of 11, $\text{R} = \text{H}$, to tricyclic ketone 15, giving 9.1 mg (50%) of hydroxy ketone 23, infrared absorption (CCl_4) 5.64 μ . The molecular weight determined mass spectrometrically was 166.0992 (calcd for $\text{C}_{10}\text{H}_{14}\text{O}_4$: 166.0994).

Lactone 24. Anhydrous sodium acetate (102 mg) was added to peracetic acid ("Becco 40%," 10 g), and this solution (5 ml) was diluted with methylene chloride (10 ml). The methylene chloride solution was filtered through cotton and titrated (4.50 *N*). To the tricyclic ketone 15 (115 mg, 0.769 mmole) was added buffered peracetic acid in methylene chloride (2.0 ml, 9.0 mequiv). After allowing the reaction mixture to stand for 85 hr at 26–28°, additional peracetic acid solution (1.0 ml, 4.5 mequiv) was added, and the reaction mixture was allowed to stand for another 96 hr at 26–28°. The mixture was poured into water and extracted three times with ether. The ethereal extracts were washed with sodium bicarbonate solution, sodium bisulfite solution, and water, dried (MgSO_4), concentrated, and distilled, giving 102 mg (80%) of lactone 24; infrared absorption (CCl_4) due to carbonyl at 5.71 μ , no OH absorption; nmr spectrum (CS_2): peak at 4.72 ppm (apparent quintet, 1 H) due to $>\text{CHOCO}$ and other peaks upfield between 1.0 and 2.9 ppm.²³

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3$: C, 72.26; H, 8.49. Found: C, 72.55; H, 8.54.

Hydrolysis and Oxidation of 24. A solution of lactone 24 (645 mg, 3.88 mmoles) and potassium hydroxide (5.67 g, 0.101 mole) in methanol (180 ml) was refluxed for 13 hr. Evaporation of most of the methanol, dilution with water, ether extraction (discarded), dropwise addition of 2 *N* sulfuric acid (99 ml, 0.198 mole) at 0°, and extraction with ether gave 688 mg (96%) of hydroxy acid, mp 90–98°, which was methylated with ethereal diazomethane (3 hr), giving 685 mg (91%) of hydroxy ester which then was oxidized by chromic acid to give 562 mg (83%) of keto ester 25, $\text{R} = \text{CH}_3$. This ester showed carbonyl absorption due to ketone and ester functions at 5.74 μ (in CCl_4), indicating that the ketone function was present in a five-membered ring. A considerable number of further transformations of this substance are given in the thesis cited in ref 22.

Transformation of the Epoxide 17 to the Tetracyclic Alcohol 18. To a stirred solution of dry, distilled diethylamine (445 mg, 6.01 mmoles) in sodium-dried benzene (2.8 ml) under nitrogen and cooled in an ice bath was added a 1.6 *M* solution of *n*-butyllithium in hexane (2.8 ml, 4.48 mmoles) by means of a syringe. The mixture was stirred for 20 min. A solution of tricyclic epoxide 17 (399 mg, 2.66 mmoles) in sodium-dried benzene (2.8 ml) was added to the lithium diethylamide mixture. The reaction mixture was stirred and refluxed for a period of 48 hr. The mixture was cooled, poured into ice-water, and extracted twice with ether. The combined ethereal extracts were washed with saturated aqueous ammonium chloride solution and water, dried (MgSO_4), concentrated, and distilled [50–60° (0.4 mm)], giving 342 mg (86%) of tetracyclic alcohol 18, mp 56–70°; near-infrared (CCl_4) absorption at 1.676 μ (ϵ 0.38); nmr (CCl_4) 1.0–2.1 (multiplet, 14 H), 3.86 (singlet, 1 H), and 4.45 ppm (singlet, 1 H). The molecular weight determined mass spectrometrically was 150.

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}$: C, 79.96; H, 9.39. Found: C, 79.96; H, 9.32.

The tetracyclic alcohol 18 (50.3 mg, 0.335 mmole) was acetylated using acetic anhydride–pyridine giving 63.4 mg (98%) of the corresponding acetate, infrared absorption at 5.73 μ ; nmr (CDCl_3) 1.1–2.2 (multiplet, 15 H) and 4.72 ppm (multiplet, 1 H). The molecular weight determined mass spectrometrically was 192.1138 (calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$: 192.1150).

Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.97; H, 8.39. Found: C, 74.81; H, 8.42.

From the tetracyclic alcohol 18 (30.4 mg, 0.203 mmole) a tosylate was prepared using *p*-toluenesulfonyl chloride (38.1 mg, 0.200 mmole) in sodium-dried ether (0.5 ml) and powdered potassium hydroxide (30.2 mg, 0.539 mmole) added portionwise at –10°. The mixture was stirred at 0–5° for a period of 12 hr, poured into water, and extracted with ether. The ethereal extract was dried (MgSO_4) and concentrated, giving 54.0 mg (88%) of a colorless solid. Two recrystallizations from *n*-pentane gave colorless crystals of tosylate 18, mp 66.5–69°; $\lambda_{\text{max}}^{\text{OH, 0.01M NaOH}}$ 262.0 $m\mu$ (ϵ 486), 267.4 $m\mu$ (ϵ 423), and 273.0 $m\mu$ (ϵ 350). The molecular weight determined mass spectrometrically was 304.1137 (calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{S}$: 304.1133).

Reaction of *p*-Toluenesulfonate of 18 with Sodium Borohydride in Aqueous Diglyme. A solution of the *p*-toluenesulfonate of 18 (88.8 mg, 0.292 mmole), sodium borohydride (94.7 mg, 2.51 mmoles), and sodium hydroxide (24.5 mg, 0.613 mmole) in 65 vol. % aqueous diglyme (0.6 ml) was stirred for 16 hr at room temperature. The solution was poured into water and extracted twice with trichlorofluoromethane (Freon 11). The extracts were washed with water, dried (MgSO_4), and concentrated, giving a mixture of products. The mixture was analyzed by vpc and found to consist of tetracyclic alcohol 18 (75%) and a 9:1 mixture of hydrocarbons (25%). The minor hydrocarbon had the same retention time on a 200-ft tricyanoethoxypropane capillary (0.011 in.) column as tricyclic olefin 10, and the major hydrocarbon was 1,2-trimethylenenorbornene, which was obtained pure by preparative vpc; nmr (CS_2) 0.9–2.2 ppm (multiplet). The molecular weight determined mass spectrometrically was 134.1094 (calcd for $\text{C}_{10}\text{H}_{14}$: 134.1095).

4,5-Trimethylenenorbornanone (26). The alcohol 18 (197 mg) was oxidized as described for the oxidation of 11, $\text{R} = \text{H}$, to 15, giving 132 mg (70%) of tetracyclic ketone 26, $\lambda_{\text{max}}^{\text{KOH}}$ 271 μ (ϵ 46); infrared (CCl_4)²² carbonyl absorption 5.67 and 5.72 μ ; nmr (CCl_4) 1.2–2.2 ppm (multiplet). The molecular weight determined mass spectrometrically was 148.

Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}$: C, 81.04; H, 8.16. Found: C, 81.34; H, 8.23.

Tetracyclic ketone 26 was not reduced by zinc in acetic acid at reflux nor by hydrogen and 10% palladium on charcoal in acetic acid at room temperature at 1 atm.

5-Bromo-4,5-trimethylenenorbornanone (27) and Its Reduction. A 0.36 *M* solution of anhydrous hydrobromic acid (38 ml, 13.7 mmoles) in methylene chloride was added to tetracyclic ketone 26 (1.19 g, 8.04 mmoles). After standing at room temperature for a period of 17 hr, the solution was concentrated, giving 1.65 g (90%) of a brown semisolid. Sublimation gave colorless crystals of bromo ketone 27, mp 146–148°; infrared absorption (CCl_4) 5.70 μ ; nmr (CCl_4) 1.5–2.7 ppm (multiplet). The mass spectrum showed two peaks of equal intensity at 228 and 230.

Reduction of 27 with the following reagents gave tricyclic ketone 15: zinc in acetic acid, di-*n*-butyltin dihydride in tetrahydrofuran, and hydrogen and 10% palladium on charcoal in 95% ethanol. The products were analyzed by infrared absorption and vpc with a 12-ft 5% Carbowax 20M column.

Acetolysis Products from 4,5-*exo*-Trimethylene-2-*exo*-norbornyl *p*-Toluenesulfonate (11, $\text{R} = \text{Ts}$). A solution of the *exo-p*-toluenesulfonate 11, $\text{R} = \text{Ts}$ (102.3 mg, 0.334 mmole), in 0.010 *M* sodium acetate in anhydrous acetic acid solution (60 ml) was stirred and maintained at 81–83° for 5 hr (*ca.* ten half-lives). The cooled solution was diluted with water, neutralized with sodium carbonate, and repeatedly extracted with ether. The combined ether extracts were washed with water, saturated aqueous sodium bicarbonate solution, and water, dried (MgSO_4), concentrated, analyzed by vpc, and distilled, giving 55.4 mg (85%) of tricyclic *exo* acetate 11, $\text{R} = \text{CH}_3\text{CO}$. This product had the same vpc retention time, the same infrared spectrum, and the same nmr spectrum as the *exo*

acetate 11, $\text{R} = \text{CH}_3\text{CO}$, prepared by acetylation of 11, $\text{R} = \text{H}$. A considerable study was made of various columns for vpc analysis of mixtures of 11, $\text{R} = \text{H}$, and 16, $\text{R} = \text{H}$, and also of mixture of the corresponding acetates; this analysis was not possible using long 0.25- or 0.125-in. columns with a large variety of stationary phases (both polar and nonpolar), since the chromatographic behavior of the *exo*, *endo* isomers was essentially identical. Slight separation was noted using tricyanoethoxypropane as stationary phase with the acetates 11, $\text{R} = \text{CH}_3\text{CO}$, and 16, $\text{R} = \text{CH}_3\text{CO}$, and it proved possible to achieve acceptable resolution using this stationary phase in a 200-ft, 0.11 in. capillary column at 100°. The total mixture obtained from the above experiment before distillation was analyzed in this way. Peaks were observed at the following retention times (min): 5.3 (3.5%), 5.5 (*sh.*, *ca.* 1%), 37–39.5 (4%, broad, includes two or more unresolved), 41.3 (91.5%, corresponds to 11, $\text{R} = \text{CH}_3\text{CO}$, the major product). It seems likely, though by no means certain, that the broad peak at 37–39 min contains the *endo* acetate 16, $\text{R} = \text{CH}_3\text{CO}$, as a component, since the latter exhibits a peak at 39 min under the conditions of this analysis. The tricyclic olefin 10 under these conditions exhibits a retention time of 5.3 min.

Acetolysis of 4,5-*exo*-Trimethylene-2-*endo*-norbornyl *p*-Toluenesulfonate (16, $\text{R} = \text{Ts}$). A solution of the *p*-toluenesulfonate 16, $\text{R} = \text{Ts}$ (99.0 mg, 0.324 mmole), in 0.010 *M* sodium acetate in anhydrous acetic acid solution (60 ml) was stirred and maintained at 100–103° for 5 hr (*ca.* ten half-lives). After neutralization and ether work-up, the product was analyzed by vpc and distilled, giving 55.2 mg (88%) of tricyclic *exo* acetate 11, $\text{R} = \text{CH}_3\text{CO}$. This product had the same retention time on vpc, the same infrared spectrum, and the same nmr spectrum as prepared by acetylation of 11, $\text{R} = \text{H}$. The vpc analysis of the total product before distillation was performed on the 200-ft capillary tricyanoethoxypropane column at 100° under the same conditions as used for the previously described analysis. The vpc product analysis, which was very similar to that for the acetolysis of 11, $\text{R} = \text{Ts}$, revealed components at the following retention times (min): 5.3 (2.5%), 5.5 (1.5%), 37–39.5 (4%, broad), and 42.2 (92%), the last of which corresponds to 11, $\text{R} = \text{CH}_3\text{CO}$.

Kinetic Data. The method of Swain and Morgan²⁶ was used with a Cary Model 14 spectrophotometer equipped with a thermostated cell compartment. Acetolyses were conducted in quartz cells sealed with tightly fitting Teflon stoppers. The *p*-toluenesulfonate was dissolved in *ca.* 10 ml of anhydrous acetic acid (dried with molecular sieves and distilled) containing fused sodium acetate at a concentration of 0.01 *M*. Excellent first-order rate constants were obtained (for tables of original data see thesis cited in ref 22). Measurements of the rate constants for acetolysis of *exo*- and *endo*-norbornyl *p*-toluenesulfonates gave results in excellent agreement with values previously obtained by titrimetric analysis.²⁷

Acknowledgment. This work was generously supported by the National Science Foundation and the National Institutes of Health.

Syntheses and Reactions of 3-Substituted Tricyclo[3.3.0.0^{2,6}]octanes and of Tricyclo[3.3.0.0^{2,6}]oct-3-ene¹

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Ithaca, New York 14850. Received December 8, 1966

Abstract: Photochlorination of tricyclo[3.3.0.0^{2,6}]octane (2) leads to 3-chlorotricyclo[3.3.0.0^{2,6}]octane (9), resulting from preferential attack at the secondary positions. Similarly, chromyl acetate oxidation of 2 gives tricyclo[3.3.0.0^{2,6}]octan-3-one (10) as the chief product, accompanied by a smaller amount of tricyclo[3.3.0.0^{2,6}]oct-3-yl acetate (11). The acetolysis of the corresponding tosylate (13) was found to proceed at a rate about 180 times that of bicyclo[2.1.1]hex-2-yl tosylate (18), producing a mixture of unrearranged and rearranged products (11, 14, and 15). These observations are accommodated by consideration of the difference in degree of substitution and in steric hindrance between the tricyclic and bicyclic esters. Finally, tricyclo[3.3.0.0^{2,6}]oct-3-ene (4) was obtained *via* tricyclo[3.3.0.0^{2,6}]oct-3-ylamine (30) using a Hofmann elimination sequence. Some unexpected features of the nmr and ultraviolet spectra of this strained olefin are described.

63 Srinivasan reported that the gas-phase, mercury-sensitized photoisomerization of *cis,cis*-octadiene (1) gives tricyclo[3.3.0.0^{2,6}]octane (2) in 10% yield.² Shortly thereafter,^{3,4} he was able to develop a solution photolysis technique which gave a yield of 2. These developments, along with our continuing interest in the highly strained bicyclo[2.1.1]hex-2-yl system (3), prompted an investigation of the



syntheses and reactions of functionalized tricyclo[3.3.0.0^{2,6}]octanes. Some of our specific goals were the introduction of substituents at C₃ of 2, to permit free radical ion studies analogous to those already carried out on bicyclo[2.1.1]hexanes.⁵⁻⁹ Another objective was to use such functionalized derivatives as intermediates for a synthesis of tricyclo[3.3.0.0^{2,6}]oct-3-ene analogous to the as yet unknown bicyclo[2.1.1]hex-2-ene.



We wish now to present our results in these

Experimental

To obtain tricyclo[3.3.0.0^{2,6}]octane for extensive study, the irradiation of 1,5-cyclooctadiene was carried out under conditions slightly different from those previously described.² By increasing the concentration of 1,5-cyclooctadiene about fourfold and by allowing the

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Srinivasan, *J. Am. Chem. Soc.*, **85**, 819 (1963).
Srinivasan, *ibid.*, **85**, 3048 (1963).
Srinivasan, *ibid.*, **86**, 3318 (1964).
Meinwald and P. G. Gassman, *ibid.*, **85**, 57 (1963).
Meinwald, P. G. Gassman, and J. J. Hurst, *ibid.*, **84**, 3722 (1962).

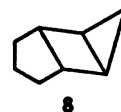
B. Wiberg and R. Fenoglio, *Tetrahedron Letters*, 1273 (1963).
B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Am. Chem. Soc.*, **83**, 151 (1961).
B. Wiberg and B. R. Lowry, *ibid.*, **85**, 3188 (1963).

conversion to proceed almost to completion, yields of ca. 50% and absolute amounts of 15–50 g of 2 could be realized in a single experiment.

Srinivasan found in this initial study that 2 was not the only product of the irradiation of 1,5-cyclooctadiene in solution. Thus, when the reaction was carried out in ether with cuprous chloride or rhodium chloride as catalyst, four products were identified: the tricyclo[3.3.0.0^{2,6}]octane 2, 1,3-cyclooctadiene (5), 1,4-cyclooctadiene (6), and bicyclo[4.2.0]octene-7 (7).



We have found that one previously undetected product consistently comprised about 10% of the reaction mixture. An elemental analysis indicated that this component was another C₈H₁₂ isomer. Its nmr spectrum showed no absorption in the olefinic region, but upfield absorption attributable to a cyclopropane grouping was apparent. A comparison of the nmr and infrared spectra of this compound with those of an authentic sample of *cis,anti,cis*-tricyclo[3.3.0.0^{2,6}]octane (8) showed two compounds to be identical.^{10,11} Although the formation of 8 might be rationalized by a small variation of the free radical chain mechanism proposed recently to account for the formation of 2 from 1,^{12a} it now appears more correct to view this



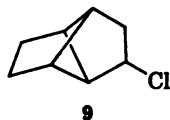
as an independent side reaction rather than as one based upon a common intermediate.^{12b}

With 2 readily available we examined methods to functionalize the hydrocarbon skeleton. Since free radical reactions generally occur without structural rearrangement, even in highly strained systems, this was the first type of reaction to be tried. Two free

(10) J. Zirner and S. Winstein, *Proc. Chem. Soc.*, 235 (1964).
(11) Private communication, Professor S. Winstein.
(12) (a) J. E. Baldwin and R. H. Greeley, *J. Am. Chem. Soc.*, **87**, 4514 (1965); (b) I. Haller and R. Srinivasan, *ibid.*, **88**, 5084 (1966).

radical substitutions which proved useful were chlorination and chromyl acetate oxidation.

In the chlorination of acyclic hydrocarbons it has been found that the order of reactivity of aliphatic carbon-hydrogen bonds toward chlorine is tertiary > secondary > primary.¹³ In alicyclic compounds, however, this order is not necessarily the same. Thus, in the chlorination of bicyclo[2.2.1]heptane only two products have been isolated, both of which involve attack at the C₂ position.¹⁴ The liquid-phase photochlorination of **2** led to analogous results; the only product detected, isolable in 50% yield, was 3-chlorotricyclooctane (**9**). The glpc of this product on several analytical columns indicated the presence of only one component. Its

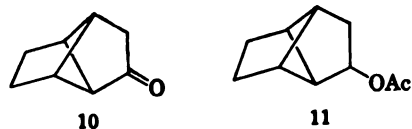


elemental analysis was compatible with the molecular formula C₈H₁₁Cl. The nmr spectrum showed a complex doublet centered at τ 5.46 (1 proton, assignable to that at C₃), and a complex series of peaks, subsequently found to be characteristic of 3-substituted derivatives of **2**, from τ 7.3 to 8.2 (10 protons).

The liquid-phase bromination of **2** was also carried out, but was unexpectedly complex. The reaction may have followed a carbonium ion pathway rather than a free radical pathway. (An example of a hydrocarbon bromination which apparently utilizes a carbonium ion mechanism is provided by the conversion of adamantane to 1-bromoadamantane.¹⁵) The product, which appeared to contain two bromine atoms, was not fully characterized.

The oxidation of hydrocarbons by chromic acid, chromyl acetate, or chromyl chloride is also reported to be a free radical substitution reaction.¹⁶ The relative rates of attack on aliphatic carbon-hydrogen bonds are typical of rates of free radical reactions, that is, tertiary > secondary > primary.¹⁷ The alcohols formed initially in these reactions are often further oxidized to ketones. This technique provides a useful ketone synthesis when the product is not readily degraded by enolization and subsequent oxidation.^{8, 18, 19}

Chromyl acetate oxidation of **2** gave tricyclo[3.3.0.0^{2,6}]octan-3-one (**10**) and tricyclo[3.3.0.0^{2,6}]oct-3-yl acetate (**11**), characterized as described below. They were formed in a ratio of 9:1, as determined by glpc, in an over-all yield of ca. 60% based on the tri-



(13) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 8.

(14) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958).

(15) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).

(16) K. B. Wiberg and R. Eisenthal, *Tetrahedron*, **20**, 1151 (1964).

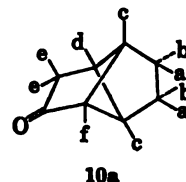
(17) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1964, pp 50-55.

(18) K. B. Wiberg in "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter 3.

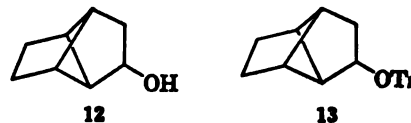
(19) P. von R. Schleyer and R. D. Nicholson, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 750.

cyclooctane consumed. The structure of **10** follows from its elemental analysis, from its mass spectrum, which showed a parent peak at m/e 122, from its infrared absorption maximum at 5.68 μ (carbonyl stretching), and from a series of reactions, described later, which relate ketone **10** to **2**. The acetate **11** could be separated from the crude ketone by a zone freezing technique, and was shown to be identical with authentic **11**, prepared, as described below, from alcohol **12**.

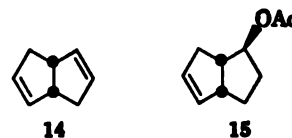
The nmr spectrum of **10** is simplified by a coincidence of chemical shift values. While there are six different types of carbon-hydrogen bonds in the molecule, the spectrum shows only four sharp bands at τ 7.40 (2), 7.78 (2), 7.86 (2), and 8.13 (4). This pattern of absorption can be explained by assuming that all four hydrogens at C₇ and C₈ (a and b, formula **10a**) have the same chemical shift, and that those at C₂ and C₁ (f and d) are also equivalent.



Reduction of **10** with lithium aluminum hydride gave the alcohol **12** in 80% yield. The corresponding tosylate **13** was prepared in 90% yield by the treatment of **12** with *p*-toluenesulfonyl chloride in pyridine. The elemental analyses of **12** and **13** and their infrared and nmr spectra were consistent with the assigned structures.



The rate of acetolysis of **13** was determined titrimetrically, at 35.0 and 50.0°, by standard methods.^{20, 21} Excellent first-order kinetics were observed over several half-lives. Three products were characterized from this acetolysis. The first (20%) was identified as bicyclo[3.3.0]octa-2,6-diene (**14**) by comparison with an authentic sample.²² Unrearranged acetate **11** was formed in 40% yield, and the ring-opened acetate **15** in 17% yield. The acetates were reduced with lithium



aluminum hydride, and the resulting alcohols were separated by preparative glpc. The alcohol from the reduction of **11** was identical in every respect with the previously characterized tricyclic alcohol **12**. The alcohol from the reduction of acetate **15** was hydrogenated over Adam's catalyst. A phenylurethan of this alcohol had the same melting point as that reported for the phenylurethan of **16**.²³ The hydrogenated alcohol was oxidized with N-bromosuccinimide, following a procedure

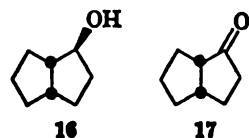
(20) S. Winstein, E. Grunwald, and L. I. Ingraham, *J. Am. Chem. Soc.*, **70**, 821 (1948).

(21) S. Winstein, C. Hanson, and E. Grunwald, *ibid.*, **70**, 812 (1948).

(22) W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

(23) A. C. Cope, H. E. Petree, and M. Brown, *J. Am. Chem. Soc.*, **80**, 2852 (1958).

of Cope,²² to give a ketone, the 2,4-dinitrophenylhydrazones of which had the same (broad) melting point as that of the known derivative of ketone 17.²⁴ Thus

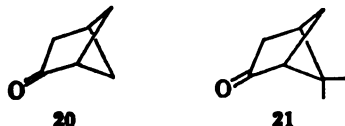


the *cis* fusion of the rings and the position of the oxygen is certain, as is the *exo* configuration of the alcohol, although a small amount of the *endo* alcohol might have gone unobserved. The position of the double bond of 15 is assigned on mechanistic grounds and on the basis of the great similarity of the nmr spectra of 14 and 15 in the olefinic proton region.

To rationalize both the rate of solvolysis of 13 and the products formed, we may compare these results with those obtained for carbonium reactions at C₂ in the bicyclo[2.1.1]hexane series. The relative rates for the acetolysis of bicyclo[2.1.1]hexyl 2-tosylate (18), 5,5-dimethylbicyclo[2.1.1]hexyl 2 α -tosylate (19), and



tosylate 13 (extrapolated to 75°) are 1:36:180.^{5,25} A major factor influencing the rate of ionization is the internal angle at the carbon atom where the ionization occurs.²⁶⁻²⁸ Although knowledge of the pertinent molecular geometry from direct physical measurement is often lacking, estimates are available from a correlation of carbonyl stretching frequencies with included angle.²⁸ The carbonyl stretching band of both 20 and 21 is found at 1764 cm⁻¹, while that of 13 is at 1758 cm⁻¹. These frequencies lead to calculated angles of 95.5° for 20 and 21, and 98.5° for 10. If the internal

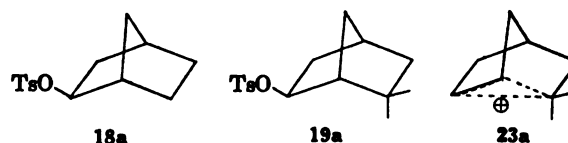


angles were the only determining factor in the rates of acetolysis, then one would expect 18 and 19 to have the same solvolysis rate, and 13 to have a rate *ca.* 15 times faster. A possible explanation for the difference in rate between 18 and 19 may be found in the hypothesis that these esters yield bridged, delocalized ions in which positive charge is distributed over three positions.^{5,25} The bridged carbonium ion 22, derived from 18, would spread its charge to a primary carbon in one of its contributing forms, whereas the bridged carbonium ion 23, derived from 19, has two additional methyl groups providing a tertiary site in place of the primary site in 22 to help stabilize the positive charge. If a similar type of bridged ion were formed in the solvolysis of 13, a reasonable model for comparison would be the presently unknown ester 24, with one methyl substituent to aid the leaving of the tosylate group. In both the

hypothetical bridged carbonium ion which would be formed from 24 and that expected from 13, the electron deficiency would be shared by a secondary carbon. To predict the rate of acetolysis of 24 relative to the rate of 18 and 19, we will simply choose the average of that for 18 and 19, which is 18. This would make the relative rates of 24:13 18:180, or 1:10. Correcting for the difference in angle at C₂ of the bicyclo[2.1.1]hexane nucleus and C₃ of the tricyclo[3.3.0.0^{2,6}]octane nucleus,^{26,28} the expected relative rates for the hypothetical model and 13 become 1.4:1. On the basis of these crude estimates, the acetolysis rate of 13 agrees well with expectations.



It should be noted that this type of argument, which appears plausible for the cases just discussed, cannot be applied successfully to the bicyclo[2.2.1]heptyl analogs of 18 and 19, 18a and 19a.²⁹ Thus, in the



bicyclo[2.2.1]heptyl series, Schleyer, *et al.*, found that 6,6-dimethyl-2-*exo*-bicyclo[2.2.1]heptyl tosylate (19a) was *less* reactive than 2-*exo*-bicyclo[2.2.1]heptyl tosylate (18a) by a factor of *ca.* 14 at 75°. These results are contrary to those which might have been expected if a bridged ion (23a) with significant contribution from the resonance form with positive charge on the tertiary site (C₆) were produced. Schleyer, *et al.*,²⁹ have rationalized the deactivation of 19a by assuming that the *endo*-6-methyl substituent suffers unfavorable steric interactions in going to a bridged transition state (23a). Since the geometric situation is quite different in 19 and 23, however, this steric effect may well not be felt. In fact, the C₁-C₅ bond loosening implied in structure 23, which corresponds to partial opening of a cyclobutane ring, with concomitant strain relief, could be a factor operating in the opposite direction, encouraging contribution from the resonance form with positive charge at C₅ in the bicyclo[2.1.1]hexyl series.

The acetolysis product obtained from 18, after reduction with lithium aluminum hydride, is bicyclo[2.1.1]hexan-2-ol (26), whereas the product of the acetolysis of 19, after reduction, is the ring-opened tertiary alcohol, 27. The formation of 26 and 27 is consistent with the bridged carbonium ion hypothesis. Acetic acid could be expected to attack ions 22 and 23 at the positions of greatest positive charge density.³⁰ Attacked in this way, 22 would yield the acetate of 26. In the case of 23, bonding of a solvent molecule to the position of greatest positive charge density (tertiary) would give the acetate of 27. Similarly, ion 28 formed from the solvolysis of 13 has no obvious position of "greatest" charge density, since all relevant positions are secondary.

(24) A. C. Cope and W. R. Schmitz, *J. Am. Chem. Soc.*, **72**, 3056 (1950).

(25) Doctoral dissertation submitted to Cornell University, J. K. Crandall, 1963.

(26) P. von R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1854 (1964).

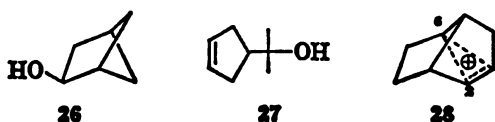
(27) J. A. Halford, *J. Chem. Phys.*, **24**, 830 (1950).

(28) C. S. Foote, *J. Am. Chem. Soc.*, **86**, 1853 (1964).

(29) P. von R. Schleyer, M. M. Donaldson, and W. E. Watts, *ibid.*, **87**, 375 (1965).

(30) J. A. Berson, *Tetrahedron Letters*, **16**, 17 (1960).

On this basis, solvent attack at both C₂ and C₆ with concomitant ring opening appears reasonable.

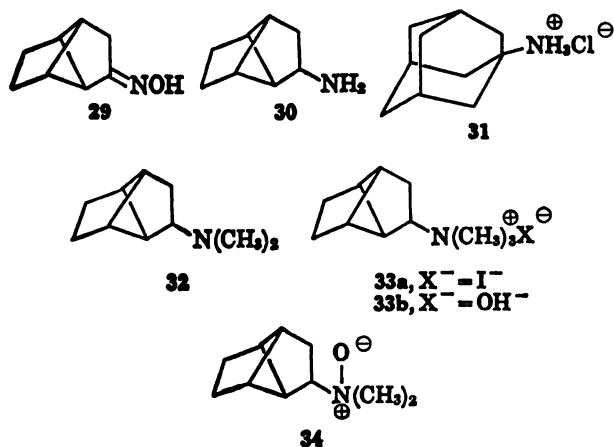


Another very significant experimental difference between the bicyclo[2.2.1]heptyl and bicyclo[2.1.1]hexyl series is that 19a suffers acetolysis, giving exclusively the *unrearranged* 6,6-dimethyl-2-*exo*-bicyclo[2.2.1]heptyl acetate,²⁹ while 19 yields *ring-opened* acetate as at least 98% of the acetate produced.²⁵ Thus, the differences between the effects of *gem*-dimethyl substitution in 19 and 19a are apparent from both the kinetic results and the products obtained.

The introduction of a double bond into the tricyclo[3.3.0.0^{2,6}]octane nucleus was another objective of this study. One of the reasons for our interest in this olefin is that all attempts to synthesize the closely related bicyclo[2.1.1]hexenes have as yet been unsuccessful.³¹ A series of reactions which led to the successful preparation of 4 are described below.

Ketone 10 reacted with hydroxylamine to give oxime 29 in 95% yield. This oxime was reduced with lithium aluminum hydride in tetrahydrofuran to give amine 30 in 80% yield. (It has been shown that adamantylamine hydrochloride (31) has both *in vitro* and *in vivo* antiviral activity.³² It will be of interest to see whether the somewhat related hydrochloride of 30 is associated with similar biological activity.)

Amine 30 was converted to the dimethylamine 32 in 80% yield by the Escheweiler-Clarke technique.³³ Methyl iodide in ether converted 32 to the trimethylammonium iodide 33a, which was then treated with a suspension of silver oxide to form the trimethylammonium hydroxide 33b. This product decomposed in a nitrogen atmosphere at *ca.* 100° (12 mm) to give 4 in 29% yield, accompanied by 53% of recovered 32.

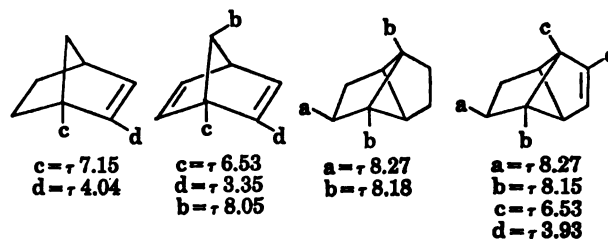


(The formation of 32 corresponds to a common side reaction in many Hofmann elimination reactions.³⁴) In an attempt to obtain better yields of 4, the amine oxide 34 was prepared from 32 and 30% hydrogen per-

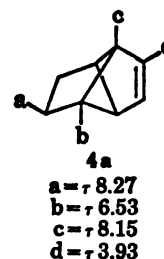
oxide. Disappointingly, the decomposition of 32 required unusually high temperatures (180–210°), and gave as its main product not 4, but an unidentified product which seemed to be aromatic. This study of 34 was not carried further.

The olefinic product obtained from 33b had the expected elemental analysis, and its molecular formula was confirmed by its mass spectrum, which showed a parent peak at *m/e* 106. A small sample of 4 was hydrogenated over Adams' catalyst, and the product was found to be identical with the parent tricyclooctane 2, as shown by nmr and infrared spectra, and by glpc comparisons. This reaction proved that the basic tricyclic nucleus had remained unchanged throughout the series of reactions which culminated in the formation of 4.

The nmr spectrum of 4 shows four groups of absorption bands centered at τ 3.93 (2 protons), 6.53 (2 protons), 8.15 (2 protons), and 8.27 (4 protons). A tentative assignment of these absorption bands, based upon the chemical shifts of closely related absorption bands in bicyclo[2.2.1]heptene,³⁵ bicyclo[2.2.1]heptadiene,³⁶ and tricyclooctane, is given below. The spin-spin couplings are described in the Experimental Section. Although the coupling pattern appears to be rationalized, it should be noted that this spin-spin coupling may be



“deceptively simple.”³⁶ One interesting aspect of the nmr spectrum of 4, assuming the above assignment of the absorption bands, is the long-range coupling ($J = ca. 2$ cps) between the olefinic ($\tau 3.93$) and homoallylic ($\tau 8.15$) protons, d and b. These protons do not have the “W” geometry usually associated with four-bond proton-proton coupling.³⁷ The alternate explanation that the coupling of the olefinic protons is actually with the adjacent allylic rather than with the homoallylic protons would appear at first to require quite unusual chemical shift assignments, as shown in formula 4a. Interesting precedent for these unexpected assignments, however, is provided by the nmr spectrum



of benzvalene (35), which has recently been synthesized, and which appears to have its allylic proton resonance

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(32) W. L. Davis, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. P. Shock, J. C. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffmann, *Science*, **144**, 862 (1964).

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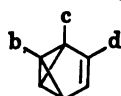
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(37) A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Letters*, 233 (1964).

ppm upfield from that of the homoallylic proton. The problem of distinguishing between these



35
b = τ 6.47
c = τ 8.16
d = τ 4.05

possible rationalizations of the nmr spectrum of 4, but one, and clarification of the assignment of 8.15 and 6.53 bands will have to await further investigation.

The nmr spectrum of 4 affords an opportunity to estimate the degree of s character in the vinyl carbon-hydrogen bonds on the basis of the corresponding H- ^{13}C coupling constant.³⁹ The coupling constant $J_{\text{H-C}}$ is upon the bond order, and varies from $J = 125$ cps for an sp^3 bond to $J = 250$ cps for an sp bond.³⁹ Carbon-hydrogen spin-spin coupling constants of 4 are closely related to those of 4, itself are collected in Table I.⁴⁰ It would appear from these data that 4 has more s character in its vinyl carbon-hydrogen bonds than does bicyclo[2.2.1]heptene, and less than bicyclo[2.2.1]heptadiene.

Compd	$J_{\text{H-C}}$, cps	$J_{\text{H-C-H}}$, cps
cyclopentene	160.5	5.8
cyclopentadiene	170	...
thylene	156.8	11.4
bicyclo[2.2.1]heptene	165.5	6.0
bicyclo[2.2.1]heptadiene	172.5	5.2
tricyclo[3.3.0.0 ^{1,4}]octane	167 \pm 1	5.1

The ultraviolet absorption spectrum of 4 appears of particular interest. Its longest wavelength band is at $\text{ca. } 251 \text{ m}\mu$, whereas the comparable absorption starts at $\text{ca. } 208 \text{ m}\mu$ in cyclopentene, at $\text{ca. } 213 \text{ m}\mu$ in bicyclo[2.2.1]heptene, and at $\text{ca. } 221 \text{ m}\mu$ in bicyclo[2.2.1]heptadiene.^{41,42} This ultraviolet spectrum is receiving more careful examination, and will be discussed elsewhere.⁴³

In summary, tricyclooctane 2 has been functionalized and the acetolysis of the corresponding 3-tosyloxy derivative has been studied. In addition, tricyclooctane has been synthesized for the first time. This synthesis shows several unexpected spectral properties and provides the first example of a simple bicyclohexene.

Experimental Section

Boiling points and melting points are uncorrected. Column chromatography was carried out on Woelm neutral alumina.

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2. J. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31**, 768, 1471 (1959).

3. C. Tori, R. Muneyuki, and H. Tanida, *Can. J. Chem.*, **41**, 3142 (1963).

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5. B. Robin and N. A. Kuebler, *ibid.*, **44**, 2664 (1966). For a discussion of the relationship between C=C stretching frequencies and bond angles, see C. F. Wilcox and R. R. Craig, *J. Am. Chem. Soc.*, **83**, 3866 (1961).

Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and by the Galbraith Laboratories, Knoxville, Tenn.

Gas-Liquid Partition Chromatography (Glpc). Analytical determinations were carried out on Aerograph Models 600 Hy-Fi and 660 Hy-Fi. Columns of the following liquid phases on Firebrick were used: 30% Ucon oil nonpolar; BDS (15% butanediol succinate); 30% Carbowax 20M; TCEP (20% 1,2,3-tris(2-cyanoethoxy)propane).

A Beckman GC-2 gas chromatograph was used for preparative glpc. The following columns were used: Carbowax, 10 ft of 30% Carbowax 20M; TCEP, 12 ft of 20% 1,2,3-tris(2-cyanoethoxy)propane.

Infrared Spectra. Most infrared spectra were run on a Perkin-Elmer Infracord Model 137 B. The carbonyl stretching frequencies of ketones 10 and 20 were measured on a Perkin-Elmer Model 521.

Nuclear Magnetic Resonance Spectra. Nmr spectra were taken on a Varian A-60 spectrometer, in carbon tetrachloride, unless otherwise noted.

Mass Spectra. All mass spectra were run on a CEC 21-103A spectrometer. Each spectrum was calibrated with a compound of known mass.

Ultraviolet Spectra. All ultraviolet spectra were taken on a Cary Model 14 spectrophotometer in the specified solvent.

Tricyclo[3.3.0.0^{1,4}]octane (2). A solution of 1,5-cyclooctadiene (25.3 g, 0.234 mole) and cuprous chloride (0.1 g) in ether (1.8 l.) was irradiated in a 2-l. Vycor flask (equipped with a condenser and drying tube) by a bank of 16 GE 68T5 lamps placed around the flask. After 1 day a green precipitate had formed. The reaction mixture was filtered and the flask washed with nitric acid. The filtrate was returned to the flask and irradiated for an additional 4 days. By the end of this period, a black, finely divided precipitate had formed and coated the walls of the flask. The reaction mixture was again filtered and returned to the cleaned flask. This procedure was repeated again after the tenth day, and fresh cuprous chloride (50 mg) was added. After 15 days of irradiation, the ratio of 2 to 1,5-cyclooctadiene was estimated to be 15:1 by glpc (30% Ucon oil nonpolar at 80°) and irradiation was stopped. The reaction mixture was distilled through a 60-cm spinning-band column and gave five fractions: (1) 0.7 g, bp 65–117°; (2) 0.5 g, bp 117–120°; (3) 4.6 g, bp 120–125°; (4) 10.2 g, bp 125–126°; (5) 3.1 g, bp 126–140°. Fractions 3 and 4 were estimated to be $\text{ca. } 90\%$ 2. Fraction 5 contained $\text{ca. } 50\%$ 2 and 50% of other C_8H_{14} isomers. The undistilled material (7.3 g) was discarded. The product could be further purified by refluxing with a solution of potassium permanganate (20 g) in 200 ml of water for 1 hr. Hydrocarbon 2 was recovered by steam distillation from the permanganate solution. Extraction of the water layer with *n*-pentane, followed by distillation, yielded 11.5 g (45%) of $\text{ca. } 98\%$ pure 2. The infrared and nmr spectra agreed with the published data.¹

cis,anti,cis-Tricyclo[3.3.0.0^{1,4}]octane (8). From several preparations of 2, fractions equivalent to fraction 5 were collected and redistilled through a spinning-band column. A sample, bp 133–135°, was collected which was estimated to be 60% 8 by glpc (Ucon oil nonpolar). This fraction was further purified by preparative glpc (20% TCEP), yielding a sample of 8 $\text{ca. } 95\%$ pure. An nmr spectrum of 8 showed absorption bands centered at τ 7.9, 8.5, 8.98, and 9.45. A sample collected from the preparative glpc was analyzed.

Anal. Calcd for C_8H_{14} : C, 88.82; H, 11.18. Found: C, 88.72; H, 11.27.

A comparison of the nmr and infrared spectra of 8 with those of an authentic sample of *cis,anti,cis*-tricyclo[3.3.0.0^{1,4}]octane,^{10,11} obtained directly from Professor S. Winstein, showed the two compounds to be identical.

Tricyclo[3.3.0.0^{1,4}]octan-3-one (10). Acetic acid (200 ml) and acetic anhydride (200 ml) were added to a 2-l. three-necked flask which was equipped with a Teflon stirrer and a thermometer. Chromium trioxide (40 g) was added to the solution with stirring, to prevent the formation of a solid mass. Heat was evolved as the chromium trioxide reacted with the acetic anhydride to form chromyl acetate. After being stirred for 1 hr, the reaction mixture was cooled to 0° and hydrocarbon 2 (27.8 g, 0.228 mole) of $\text{ca. } 98\%$ purity was added dropwise at such a rate that the temperature remained below 3°. After being stirred for 15 hr at 0–3°, the reaction mixture was warmed slowly to 15° and then heated to 75°. Water (200 ml) was added to the reaction mixture and heating was continued at 100° for 2 hr. The reaction mixture was cooled and a solution of sodium hydroxide (360 g) in 500 ml of water (enough base to neutralize 90% of the acetic acid) was carefully added, with

cooling. The reaction mixture was diluted with water and extracted with ether six times. The ethereal solution was washed with saturated sodium bicarbonate solution until the washings remained basic, then with saturated sodium chloride solution, and was finally dried over sodium sulfate. The dried ethereal solution was distilled through a Podbielniak-type column to remove solvent, and the undistilled residue was redried over magnesium sulfate and finally distilled to yield ketone 10 and acetate 11 [bp 90° (32 mm)] in a 9:1 ratio as estimated by glpc (15% BDS at 120°). The yield of the ketone-acetate mixture was ca. 60% based on the amount of hydrocarbon consumed. A small sample of the product mixture was purified by zone freezing, and the ketone, whose melting point was slightly below room temperature, was analyzed. The infrared spectrum (neat) of 10 showed absorption maxima at 3.4, 5.69, 7.05, 7.80, 8.08, 8.30, 8.65, 9.00, 9.9, 11.20, 12.1, and 12.3 μ . The nmr spectrum exhibited singlets at τ 7.40 (2), 7.78 (2), 7.85 (2), and 8.13 (4). *Anal.* Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.75; H, 8.21.

A semicarbazone, mp 199–200°, was prepared from 10 and recrystallized for analysis from absolute ethanol.

Anal. Calcd for $C_8H_{11}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.45; H, 7.32; N, 23.50.

A 2,4-dinitrophenylhydrazone, mp 206–207°, was prepared from 10 and recrystallized for analysis from ethyl acetate.

Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.67; N, 18.54. Found: C, 55.85; H, 4.85; N, 18.68.

Tricyclo[3.3.0.0^{3,4}]octan-3-ol (12). Ketone 10 (885 mg, 7.25 mmoles) in anhydrous ether (10 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (200 mg) in ether (25 ml). The reaction mixture was refluxed for 15 min, then cooled. Water (1 ml) was cautiously added. After being stirred for a further 30 min, the reaction mixture was filtered, and the precipitated salts were washed three times with ether. The ethereal solution was dried (magnesium sulfate) and filtered and the ether removed to yield a colorless oil (750 mg) which crystallized on standing. When the reaction product was sublimed, it yielded alcohol 12 (700 mg, 78%), mp 33–34°. The infrared spectrum (neat melt) showed absorption maxima at 3.0, 3.38, 3.47, 7.4, 7.8, 8.73, 9.10, 9.5, 9.7, 9.85, and 11.8 μ . The nmr spectrum showed a one-proton doublet ($J = 7$ cps) at τ 5.58 (HCO), a singlet at τ 5.96, and a complex series of peaks from τ 7.45 to 8.6 (10 protons).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.47; H, 9.79.

3-Acetoxytricyclo[3.3.0.0^{3,4}]octane (11). Alcohol 12 was acetylated in the usual way, by treatment with acetic anhydride and pyridine. After the usual work-up, the product was distilled through a Podbielniak-type column to yield 11, bp 65° (2.5 mm) (5.6 g, 75%). An infrared spectrum showed acetate absorption maxima at 5.67 and 8.00 μ .

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.53.

Tricyclo[3.3.0.0^{3,4}]octan-3-ol *p*-Toluenesulfonate (13). Alcohol 12 (1.07 g, 0.0086 mole) and *p*-toluenesulfonyl chloride (1.82 g, 0.01 mole) were dissolved in pyridine (5 ml) at 0°. To the reaction mixture, after standing for 18 hr at 5°, was added a small piece of ice to destroy any remaining tosyl chloride. After remaining 30 min more at 5°, the reaction mixture was poured into ice. A white precipitate quickly formed. The white solid was filtered, washed with water, and dried to yield crude 13 (2.19 g). The crude 13 was recrystallized from 2-methylbutane (175 ml) by cooling the solution to –40°, which yielded the tosylate 13 as a white crystalline solid (2.03 g), mp 65–66°. A second crop of crystals (0.08 g), mp 64–65°, was obtained by removal of two-thirds of the solvent and cooling to –78°. The total yield of 13 was 2.11 g (88%). An infrared spectrum ($CHCl_3$) showed bands at 6.22, 7.3–7.4, 8.52, and 10.3 μ , which correspond to a *p*-toluenesulfonate ester. A sample of 13, mp 65–66°, was recrystallized from 2-methylbutane for analysis.

Anal. Calcd for $C_{16}H_{18}SO_2$: C, 64.73; H, 6.52; S, 11.50. Found: C, 64.58; H, 6.62; S, 11.61.

Kinetic Measurements of Acetolysis of 13. The solvolysis reactions were run in anhydrous acetic acid solution that was 0.0549 *N* in sodium acetate. In both runs a specified amount of 13 was dissolved in 25.00 ml of the solvent, and samples were withdrawn from the reaction flask with a 1.00-ml pipet. The samples were titrated with 0.0328 *N* perchloric acid in acetic acid using bromophenol blue as indicator. The buret used had a 2-ml capacity with a micrometer drive that could be read to the nearest 0.001 ml; at 35.0°, $k = 4.08 \times 10^{-4} \text{ sec}^{-1}$; at 50.0°, $k = 2.52 \times 10^{-4} \text{ sec}^{-1}$.

Characterization of Acetolysis Products Derived from 13. Tosylate 13 (5.6 g) was dissolved in a solution of glacial acetic acid (100 ml) which contained acetic anhydride (6 ml) and was 0.5 *N* in sodium acetate. The solution was heated at 95° for 0.5 hr; water (5 ml) was added, and heating was continued for 0.5 hr at 95°. The reaction mixture was cooled and poured into a separatory funnel, and water and ether were added. The aqueous layer was extracted four times with ether. The ethereal solution was washed with a saturated sodium carbonate solution until the washings remained basic, then with saturated sodium chloride solution. It was finally dried over magnesium sulfate. The ether was removed by distillation and the residue distilled, yielding three fractions: (1) 0.40 g, bp 41° (32 mm); (2) 1.82 g, bp 73° (5 mm); (3) 0.09 g, bp 73° (5 mm). Fraction 1 (20% yield over-all) was shown to be identical with bicyclo[3.3.0]octadiene-2,6 by infrared and nmr spectral comparison.²¹ Fractions 2 and 3 (57% over-all) were shown to be acetates by their infrared spectra. They were reduced by lithium aluminum hydride in the usual fashion. The alcohols (ca. 1 g of the mixture) were separated by preparative glpc (30% Carbowax at 160°). The major product (70% of the alcohols; 40% over-all) was shown to be tricyclooctan-3-ol 12 by infrared comparison with an authentic sample. The minor alcohol (30% of the alcohols; 17% over-all) showed infrared absorption at 3.0 and 3.28 μ . The nmr spectrum showed bands centered at τ 4.67 (2), 6.25 (1), 6.66 (1), and a complex series of bands from τ 7.3 to 8.95. A glpc purified sample was analyzed.

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.14; H, 9.72.

A sample of the unknown alcohol was hydrogenated over pre-reduced Adams' catalyst in methanol. The reaction mixture was poured into a separatory funnel and water and pentane were added. The aqueous layer was extracted twice with pentane. The pentane layer was dried over sodium sulfate and filtered, and the pentane removed, leaving an alcohol with infrared absorption maxima at 2.95, 6.87, 7.42, 9.0, 9.3–9.4, 9.83, 10.02, 10.2, and 10.67 μ . A phenylurethan was prepared from this alcohol and appeared as a white, crystalline solid, mp 71–76°. The white solid was recrystallized once from pentane, yielding a phenylurethan, mp 73–76° (lit.²² *exo*-bicyclo[3.3.0]octan-2-ol phenylurethan, mp 75–76°). About 100 mg of the hydrogenated alcohol was oxidized in acetone by *N*-bromosuccinimide, according to the procedure of Cope.²³ A 2,4-dinitrophenylhydrazone was prepared from the crude ketone. This derivative was chromatographed over activity 1 alumina, using benzene as the eluent. The first 8 fractions were combined, the solvent was removed, and the somewhat purified product was re-chromatographed on a silica gel thin layer plate, using pentane-ethyl acetate (95:5) as the eluent. The orange band, which had separated from a colorless band, was removed from the plate and the product extracted from the silica gel with chloroform. The chloroform was removed and the derivative crystallized upon standing. It was recrystallized once from ethanol to give a sample with mp 111–120°. The 2,4-dinitrophenylhydrazone of bicyclo[3.3.0]octan-2-one is reported to have a similar melting point range, 110–114.5°, attributed to a mixture of the *syn* and *anti* isomers.^{23,24}

3-Chlorotricyclo[3.3.0.0^{3,4}]octane (9). Tricyclooctane 2 (9.74 g, 0.090 mole) was added, in the dark, to a flask which contained a solution of benzene (107 g) and chlorine (ca. 3.5 g, 0.05 mole). The flask was then placed in a beaker of ice and set in the sunlight. After 1 min the color of the chlorine had disappeared. Nitrogen was bubbled through the reaction mixture to remove most of the hydrochloric acid. The solution was extracted once with a saturated sodium bicarbonate solution and finally dried over sodium sulfate. The reaction mixture was distilled through a spinning-band column (60 cm) and yielded hydrocarbon 2 (4.89 g) and chlorocarbon 9 (3.52 g, 55%), bp 68° (10 mm). An infrared spectrum (neat) showed absorption maxima at 3.39, 3.48, 6.91, 7.78, 7.98, 8.06, 9.15, 10.72, 10.92, 11.15, 13.8–13.9, and 14.0 μ . The nmr showed a complex one-proton doublet ($J = \text{ca. } 7$ cps) at τ 5.5 (HCCI) and a complex series of peaks from τ 7.3 to 8.6 (10 protons).

Anal. Calcd for $C_8H_{11}Cl$: C, 67.37; H, 7.78; Cl, 24.85. Found: C, 67.20; H, 7.92; Cl, 24.71.

Bromination of Tricyclo[3.3.0.0^{3,4}]octane. To a three-necked flask, equipped with stirrer, condenser, and dropping funnel, was added tricyclooctane 2 (2.9 g, 0.027 mole) and bromine (8 ml). The reaction mixture was heated, and at ca. 40° hydrogen bromide started to evolve. Heating was continued at 60° for 8 hr; the reaction mixture was diluted with carbon tetrachloride (25 ml). The reaction mixture was cooled and poured into a beaker which contained a solution of sodium sulfite. After the bromine had reacted, the reaction mixture was poured into a separatory funnel

layers were separated, and the organic layer was washed with a saturated sodium bicarbonate solution until the washings remained neutral. The reaction mixture was dried over sodium sulfate. The solution was decanted from the drying agent and the carbon tetrachloride and 2 were removed by means of a rotary evaporator. The remaining oil (4.32 g) was distilled to give a pale yellow oil, bp 71° (0.5 mm) (1.79 g). An nmr spectrum showed a complex absorption from τ 4.5 to 8.7. A sample was redistilled for analysis.

Anal. Calcd for $C_{10}H_{16}Br_2$: C, 36.12; H, 4.06; Br, 59.82. Found: C, 34.45; H, 4.36; Br, 61.08.

Tricyclo[3.3.0.0^{2,5}]octan-3-one Oxime (29). To a 50-ml flask was added ketone 10 (2.08 g, 0.017 mole), hydroxylamine hydrochloride (1.75 g, 0.019 mole), potassium hydroxide (1.8 g), water (1 ml), and methanol (5 ml). Concentrated hydrochloric acid was added to the reaction mixture, after standing at room temperature for 2 days, until the mixture became acidic. The methanol was removed by means of a rotary evaporator, and the remaining mixture of oily oxime and water was extracted twice with ether. The ether solution was washed once with saturated sodium chloride solution, dried over magnesium sulfate, and filtered. The ether was removed by means of a rotary evaporator. The remaining oil (4.6 g) was sublimed and yielded oxime 29, mp 54–57.5° (2.21 g). The infrared spectrum (CCl_4) showed absorption maxima at 3.2, 3.4, 5.88, 7.80, 8.05, 8.29, 8.97, 9.16, 10.6, 10.8, and 11.1 μ .

Anal. Calcd for $C_{10}H_{16}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.25; H, 7.98; N, 10.08.

The starting material were not pure ketone 10 but a mixture of ketone 10 and acetate 11, then the best method for the purification of the oxime was recrystallization from pentane. The impure oxime was dissolved in ca. 15 times its volume of pentane and cooled to 0°. An oil separated after 1 hr; the pentane was decanted. This oil and the pentane cooled to –40° for an additional 12 hr. The pentane was decanted from the crystalline oxime and the oxime was washed free of pentane by a stream of nitrogen. The yield was 70%.

Tricyclo[3.3.0.0^{2,5}]octylamine (30). A solution of oxime 29 (0.059 mole) in anhydrous tetrahydrofuran (100 ml) was added to a stirred suspension of lithium aluminum hydride (0.118 mole) in tetrahydrofuran (300 ml). The reaction mixture was stirred for 2 days. After cooling, the suspension was hydrolyzed by dropwise addition of water (25 ml), followed by stirring for an additional 30 min. The solution was filtered, and the precipitated inorganic salts were extracted by ether in a Soxhlet apparatus for 1 day. The combined tetrahydrofuran and ether solutions were dried over molecular sieves (Fisher Type 4A) and the solvent was distilled off through a Podbielniak-type column. The residue was distilled and yielded amine 30 (0.059 mole, 82%), bp 83° (32 mm). The infrared spectrum (neat) showed absorption maxima at 2.95, 3.0, 3.40, 3.47, 6.2, 6.81, 6.90, 7.40, 7.80, 9.13, and 11.1 μ . The nmr spectrum showed a complex series of peaks, characteristic of the 3-substituted derivatives of the tricyclooctane nucleus, from τ 7.7 to 9.0.

Benylthiourea, mp 134–143°, was prepared from 30. Repeated recrystallizations from ethanol and acetone–pentane gave a sample that was analyzed, despite its broad melting range (134–143°).

Anal. Calcd for $C_{14}H_{18}N_2S$: C, 69.74; H, 7.02. Found: C, 69.35; H, 7.12.

N-Dimethylaminotricyclo[3.3.0.0^{2,5}]octane (32). To amine 30 (0.024 mole) was added, with cooling, formic acid (5.0 g) and formaldehyde (5.5 g of a 33% solution). The reaction mixture was stirred on a steam bath for several hours, cooled, and acidified with *N* hydrochloric acid. All volatile material was removed under reduced pressure, and the remaining oil made basic with sodium hydroxide. The aqueous mixture was extracted with ether and dried over magnesium sulfate and the ether removed by a rotary evaporator. The remaining colorless oil was distilled and yielded amine 32 (3.0 g, 80%), bp 74° (15 mm). The infrared spectrum showed absorption maxima at 3.55 and 3.61 μ , characteristic of the *N,N*-dimethyl grouping.

Tricyclo[3.3.0.0^{2,5}]octane-3-one Oxime (33a). was prepared from 32 and recrystallized from ethanol.

Anal. Calcd for $C_{10}H_{16}N_2O_7$: C, 50.53; H, 5.30; N, 14.73. Found: C, 50.72; H, 5.33; N, 14.63.

Tricyclo[3.3.0.0^{2,5}]octyltrimethylammonium Iodide (33a). A. (1.08 g, 0.0071 mole) in ether (20 ml) was added methyl iodide (2 ml) and potassium carbonate (0.25 g). The reaction mixture started to turn cloudy almost immediately and was let

stand at room temperature overnight. The precipitate that had formed was filtered, washed with ether, and recrystallized from ethanol–ether, yielding 33a (2.02 g, 95%), mp 234–243°. A sample, mp 245–247° dec, was recrystallized for analysis from ethanol–ether.

Anal. Calcd for $C_{11}H_{18}NI$: C, 45.23; H, 6.85; N, 4.76; I, 43.12. Found: C, 44.99; H, 6.70; N, 4.82; I, 43.18.

B. Oxime 29 (12.0 g, 0.0879 mole) in tetrahydrofuran (100 ml) was added to a stirred slurry of lithium aluminum hydride (10 g) in tetrahydrofuran (500 ml, freshly distilled from lithium aluminum hydride). The reaction mixture was refluxed for 2 days and cooled, and water (40 ml) was carefully added. The reaction mixture, after stirring for an additional hour, was filtered, and the precipitated inorganic salts were extracted by ether in a Soxhlet apparatus for 1 day. The combined tetrahydrofuran and ether solutions were dried over molecular sieves (Fisher Type 4A). The solution was decanted from the molecular sieves, and methyl iodide (8.1 ml, 0.088 mole) was added to the solution and let stand overnight. The solvent was distilled off through a Podbielniak-type column. The residue was transferred to a small flask and methanol (100 ml), methyl iodide (35 ml), and sodium carbonate (30 g) were added; the reaction mixture was then refluxed for 2 days. The methanol and methyl iodide were removed by means of a rotary evaporator and the remaining salts extracted four times with boiling chloroform (100-ml portions). The chloroform was removed by rotary evaporation, and the residue was recrystallized from ethanol–ether, yielding crystalline 33a (22.9 g, 83%).

Tricyclo[3.3.0.0^{2,5}]octene-3 (4). Trimethylammonium iodide 33a (12.5 g, 0.040 mole) was dissolved in a solution of methanol (100 ml) and water (50 ml). To this solution was added freshly prepared silver oxide (0.050 mole), and the reaction mixture was stirred for 2 days at 35°. The reaction mixture was then filtered, and the silver salts were washed with three portions of methanol (20 ml). The combined filtrate and washings were distilled, in a nitrogen atmosphere, under reduced pressure. When the solvent had been removed, the syrupy residue was heated. Decomposition commenced at 95° (12 mm) and was complete at 120° (12 mm). To the products, which were collected in a flask cooled in a Dry Ice bath, was added pentane (5 ml). The reaction mixture was cooled in a freezer. After the water had frozen, the organic layer was decanted and the ice washed with pentane (5 ml). The combined pentane solution was dried over sodium sulfate. The solution was then distilled through an 8-in., spinning-band column and was cut into six fractions: (1) 0.0547 g, bp 63° (130 mm); (2) 0.616 g, bp 58° (110 mm); (3) 0.232 g, bp 86–108° (100 mm); (4) 1.15 g, bp 108–118° (100 mm); (5) 1.01 g, bp 118° (100 mm); (6) 0.807 g, bp 118° (100 mm). Fractions 1 and 2 were shown to be 4 (29% yield from 33a; 60% based on unrecovered amine 32) and fractions 3–6 were shown to be 32. The infrared spectrum of 4 showed absorption at 3.24, 3.37, 3.48, 6.44, 6.82, 7.65, 8.02, 8.3, 8.57, 11.15, and 14.7 μ . The infrared absorption band at 6.44 μ is tentatively assigned to the C=C stretching frequency.⁴⁴ The nmr spectrum (CCl_4) showed a two-proton triplet ($J = 2$ cps) at τ 3.93, a 2-proton pentuplet ($J = 0.7$ cps) at τ 6.53, a two-proton triplet ($J = 2$ cps) of pentuplets ($J = 0.4$ cps) at τ 8.15, and a complex four-proton band centered at τ 8.27. A sample of fraction 1 was analyzed.

Anal. Calcd for $C_{10}H_{16}$: C, 90.51; H, 9.49. Found: C, 90.35; H, 9.50.

A small sample of 4 was hydrogenated over prerduced Adams catalyst in methanol. The methanol solution was extracted with water and pentane. The pentane layer was dried over magnesium sulfate. The pentane was distilled off and the residue was separated, by preparative glpc (30% TCEP), from the remaining solvent and shown to be tricyclo[3.3.0.0^{2,5}]octane by glpc and infrared and nmr spectral comparisons.

The ultraviolet spectrum of 4 showed an absorption maximum at ca. 215 $m\mu$ (in isooctane) with an extinction coefficient of 2640; at 230 $m\mu$, the extinction coefficient was 1730; at 240 $m\mu$, it was 700; at 250 $m\mu$, it was 150. The O–O band is centered at 250 $m\mu$ in this solvent. A spectrum was also run in the vapor phase. A very small drop of 4 was spaced in a 1-cm liquid cell and a spectrum of the vapor was taken. Vibrational fine structure could be seen on the electronic absorption envelope at 251, 246, 239, 237, 232, 227, 223, 220, 219, 215, 213.5, 212.2, 211.2, and 211.0 $m\mu$. The extinction coefficients were not determined in the vapor phase spectrum.

(44) For a discussion of the relationship between C=C stretching frequencies and bond angles, see C. F. Wilcox and R. R. Craig, *J. Am. Chem. Soc.*, **83**, 3866 (1961).

The mass spectrum of 4 determined on a CEC 21-130A instrument at 70 ev showed a parent peak at m/e 106, a base peak at 78, and other intense peaks at 91, 39, and 105.

3-N,N-Dimethyltricyclo[3.3.0.0^{2,5}]octylamine Oxide (34). To a 50-ml flask was added 32 (0.718 g, 4.75 mmoles), methanol (2 ml), and hydrogen peroxide (30%, 2 ml), and the reaction mixture was let stand at room temperature for 2 days. A small amount of platinum black was added to destroy any remaining hydrogen peroxide. The solvent was removed under reduced pressure, leaving a white solid (0.86 g). The amine oxide was recrystallized

from tetrahydrofuran to yield crystalline 34 (0.76 g, 95%), mp 104–106°, no dec.

Pyrolysis of Amine Oxide 34. Pyrolysis of the amine oxide 34 was accomplished by heating in a round-bottomed flask equipped with a capillary nitrogen inlet and connected through a short column to two traps in series, cooled in Dry Ice. The nitrogen pressure was reduced to 10 mm, and most of the amine oxide decomposition took place between 180 and 210°. An nmr spectrum of the crude volatile products showed that only about 5% was the hoped for tricyclocotene 4, while the rest seemed to be aromatic.

Aromatic Azapentalenes. I. Dibenzo-1,3a,4,6a-tetraazapentalene and Dibenzo-1,3a,6,6a-tetraazapentalene.¹ New Heteroaromatic Systems

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Abstract: The new heteroaromatic compounds, dibenzo-1,3a,6,6a-tetraazapentalene (III) and -1,3a,4,6a-tetraazapentalene (II), have been prepared in good yield by the thermal and photochemical decompositions of the *o*-azido phenyl derivatives of 1H- and 2H-benzotriazoles, respectively. The physical and spectral properties of these unusually stable pentalene analogs are described, as well as their structure determination. The mode of formation of the tetraazapentalene and the role of the annular nitrogen atoms in providing a $4n + 2 \pi$ electron system are discussed.

In recent years, there has been great interest in formulating and demonstrating aromatic character for a variety of carbocyclic and heterocyclic systems.² Aromatic stability has been demonstrated in cyclopropenium, cyclopentadienide, benzene, tropylium, and cyclo-nonatetraenide, as well as in nonalternant and hetero systems, such as ferrocene, tropolone, and azulene.³ All of these compounds contain 2, 6, 10, etc., π electrons and illustrate an extension of Hückel's argument that cyclic molecules having $4n + 2 \pi$ electrons possess closed shells of electrons and large delocalization energies.⁴

The hydrocarbon pentalene, an 8 π electron system, has never been synthesized despite repeated efforts.⁵ Condensed pentalenes have been prepared and found to possess no special stability; for example, dibenzopentalene is reported to exhibit olefinic properties around the central pentalene nucleus, which undergoes polymerization, addition of bromine, etc.^{6b}

(1) These compounds may be named as 5,11-dehydro-5H,11H-benzotriazolo[2,1-*a*]- and 5,7-dehydro-5H,7H-benzotriazolo[1,2-*a*]-benzotriazole, respectively. The trivial name of azapentalenes is employed in this and subsequent papers in order to call attention to the central rings, to which these systems owe so much of their properties.

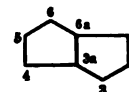
(2) Excellent reviews of these topics have appeared recently. See, for instance: (a) "Non-Benzenoid Aromatic Compounds," D. Ginsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959; (b) M. E. Vol'pin, *Russ. Chem. Rev.*, 29, 129 (1960).

(3) Leading references to recent works appear in E. A. LaLancette and R. E. Benson, *J. Am. Chem. Soc.*, 87, 1941 (1965).

(4) E. Hückel, *Z. Physik*, 70, 204 (1931).

(5) (a) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 611 (1936); (b) C. T. Blood and R. P. Linstead, *ibid.*, 2255, 2263 (1952); C. C. Chuen and S. W. Fenton, *J. Org. Chem.*, 23, 1538 (1958); (c) J. D. Roberts and W. F. Gorham, *J. Am. Chem. Soc.*, 74, 2278 (1952); (d) M. Gates and S. P. Malchick, *ibid.*, 79, 5546 (1957).

The azapentalenes are of special interest since their properties are governed to a striking extent by the orientation of the hetero atoms. Thus, azapentalenes



I

with pyridine-type nitrogens at the nonfused positions (e.g., 1–6 of compound I) in either or both rings contain 8 π electrons and are expected to be nonaromatic.

Paul and Weise found that both 2,3-benzo-1-azapentalene and 5,6-benzo-1-azapentalene are brown, unstable materials which could not be isolated pure.⁶

Kato and Ohta⁸ were unsuccessful in an attempt to prepare the 8 π electron dibenzo-1,4-diazapentalene from diindole. Treibs⁹ reported the preparation of this derivative through dehydrogenation of diindole; however, this work was recently reported¹⁰ to be erroneous.

The preparation of the highly stable, heteroaromatic compound, dibenzo-1,3a,4,6a-tetraazapentalene (II), was described earlier.^{11a} Recently, we have synthe-

(6) H. Paul and A. Weise, *Tetrahedron Letters*, 163 (1963). These authors dispute an earlier report of the synthesis of 2,3-benzo-1-azapentalene.⁷

(7) W. Treibs, *Naturwissenschaften*, 46, 170 (1959).

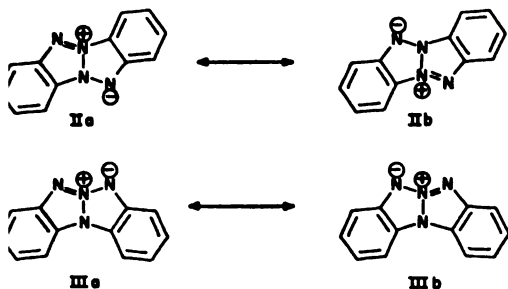
(8) H. Kato and M. Ohta, *Bull. Chem. Soc. Japan*, 34, 357 (1961).

(9) W. Treibs, *Naturwissenschaften*, 48, 130 (1961).

(10) H. Paul and A. Weise, *Z. Chem.*, 4, 147 (1964).

(11) (a) R. A. Carboni and J. E. Castle, *J. Am. Chem. Soc.*, 84, 2453 (1962). Since this report, several other examples of aromatic azapentalenes have appeared; e.g., (b) T. W. G. Solomons and F. W. Fowler, *Chem. Ind. (London)*, 1462 (1963); (c) T. W. G. Solomons, F. W. Fow-

new tetraazapentalene system, dibenzo-1,3a,6,6a-tetraazapentalene (III), which exhibits aromatic properties similar to II. Unlike azapentalenes which do not contain bridgehead nitrogen atoms, these tetra-



azapentalenes can only be represented as hybrids of a pair of charge-separated forms, e.g., IIa,b and IIIa,b. In each of these structures, two of the four nitrogen atoms, two of which occupy the bridgehead positions, contribute six electrons to the π system, and the parent structures may be considered as hybrids of their relationship with the isoelectronic pentalene and the carbocyclic analog, pentalene diene.¹² Other examples of aromatic azapentalenes with nitrogens at the bridgehead have recently been reported.^{11b-f}

This paper presents the synthesis, structure, and properties of II and III as well as a discussion of their relationship to each other.

Results and Discussion

Dibenzo-1,3a,4,6a-tetraazapentalene (II) is a yellow, crystalline solid, mp 237–238°, which exhibits yellowish fluorescence when viewed under ultraviolet light. It is weakly basic, being insoluble in dilute mineral acid but dissolves in concentrated sulfuric acid; however, it precipitates when the pale yellow acid solution is poured into water. The crystalline methiodide is formed very slowly on prolonged heating with methyl iodide, a reaction which is readily reversible at higher temperatures. Compound II has no detectable dipole moment in benzene solution.

The isomeric dibenzo-1,3a,6,6a-tetraazapentalene (III) is a colorless solid, mp 255°, which does not exhibit fluorescence in solution. Although this isomer is weakly basic, it appears to be slightly more soluble than II in mineral acids and does not form a methiodide readily. Compound III has a dipole moment in benzene of 4.36 D.

These heteroaromatic systems are little affected by heating in solvents below 300° and can be sublimed unchanged at atmospheric pressure. Both are also unchanged after treatment with warm alkali or concentrated sulfuric acid.

Calorimetric measurements for these isomeric dibenzotetraazapentalenes show that the heat of formation of III is 10 cal/mole greater than that of II.¹³

(f) I. Calderazzo, *J. Am. Chem. Soc.*, **87**, 528 (1965); (d) R. Pfeiffer, M. K. Rauer, *Ber.*, **96**, 1827 (1963) (this paper reports seven compounds which had been previously characterized^{11a} as tetraoctatetraenes); (e) R. Pfeiffer and H.-G. Hahn, *Ber.*, **90**, 2411 (1963); (f) S. Trofimenko, *J. Am. Chem. Soc.*, **87**, 4393 (1965); **88**, 666 (1966); (g) T. W. G. Solomons and C. F. Voight, *J. Am. Chem. Soc.*, **88**, 5256 (1966); **88**, 1992 (1966).

(h) T. J. Katz and M. Rosenberger, *ibid.*, **84**, 865 (1962); (b) T. M. Rosenberger, and R. K. O'Hara, *ibid.*, **86**, 249 (1964).

(i) T. Chia and H. E. Simmons, *J. Am. Chem. Soc.*, **89**, 2638 (1967).

The dibenzotetraazapentalenes exhibit an interesting variety of chemical reactions which reflect the dual pyrrole-pyridine nature of the annular nitrogen atoms. Thus, electrophilic substitution reactions were observed on both benzenoid and heterocyclic rings. These reactions and others of the tetraazapentalenes are described in separate papers.

The ultraviolet spectra of the two dibenzotetraazapentalenes show many of the characteristic similarities and differences that have been noted¹⁴ between aromatic heterocyclics and their carbocyclic analogs. Both II and III exhibit three main regions of absorption in the ultraviolet spectrum. In this respect, they resemble the annularly condensed tetracyclic hydrocarbons, e.g., the benzophenanthrenes, such as chrysene. Principal absorptions of II and III are given in Table I with those of chrysene. The major regions of absorption are separated in the table, those in each group clearly forming a vibrational subsystem.

Table I. Absorption Maxima of the Two Dibenztetraazapentalenes and Chrysene* in Ethanol

λ_{\max} , m μ	ϵ	λ_{\max} , m μ	ϵ	λ_{\max} , m μ	ϵ
402	38,300	356	39,700	360	630
382	23,300	343	32,300	352	360
364	7,740			343	630
323	4,110	280	8,250	320	14,200
				306	13,500
308	2,850	271	5,900	295	12,100
				281	12,100
255	63,300	234	25,000	268	
				257	
				241	
				220	

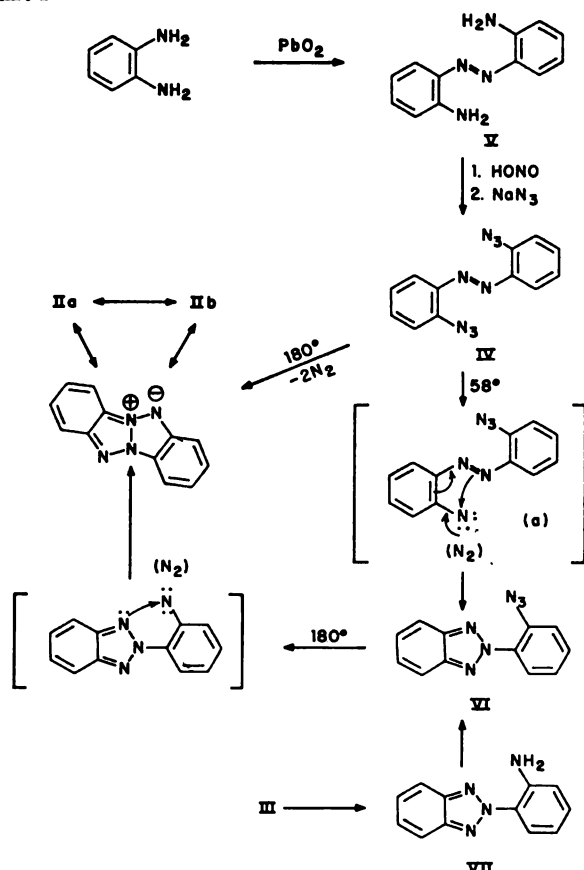
* W. V. Mayneord and E. M. F. Roe, *Proc. Roy. Soc. (London)* **A152**, 299 (1935).

The long-wavelength absorptions of the tetraazapentalenes are about 50 times more intense than the α band of chrysene. Similar comparisons have been noted by Badger and his co-workers¹⁴ for many aromatic azahydrocarbon-hydrocarbon combinations. It is noteworthy that the absorptions of 1,3a,4,6a-tetraazapentalene (II) show an appreciable shift to longer wavelengths compared to the 1,3a,6,6a isomer (III) or chrysene, particularly in the long-wavelength region. The spectrum of III also contains less fine structure than that of II.

A. Dibenzo-1,3a,4,6a-tetraazapentalene (II). This compound is prepared in excellent yield by the thermal or photochemical decomposition of *o,o'*-diazidoazobenzene (IV) (see Chart I). The yellow diazide IV, mp 116–117° dec, is formed in greater than 90% yield on treatment of tetraazotized *o,o'*-diaminoazobenzene (V) with 2 equiv of sodium azide. When a solution of IV in a high-boiling solvent, such as decahydronaphtha-

(14) G. M. Badger, R. S. Pearce, and R. Pettit, *J. Chem. Soc.*, 3199 (1951).

Chart I



lene or *o*-dichlorobenzene, is heated at 180°, 2 moles of nitrogen is smoothly evolved. From the cooled, concentrated mixture, long, yellow needles of II are precipitated.

It was found, however, that the nitrogen was liberated in two distinct stages, 1 mole at the surprisingly low temperature of 58° and the second mole at approximately 170°. Thus, when *o,o'*-diazidoazobenzene was heated in refluxing acetone or benzene for 2 hr, the orange-red color characteristic of the azo derivative disappeared. The crystalline product which was isolated in good yield still contained an azido group. The solid, mp 77–78°, was identified as 2-(*o*-azidophenyl)-2H-benzotriazole (VI).

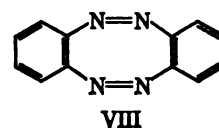
The infrared spectrum of this material was quite similar to those of a number of 2-arylbenzotriazoles. An absorption was noted at approximately 10.3 μ in each of the 2(aryl)-2H-benzotriazoles prepared in this study. The spectrum of VI also contained characteristically strong peaks at 4.75 μ for the azido function. The structure of VI was confirmed by an independent synthesis in which *o,o'*-diaminoazobenzene was oxidized with cupric sulfate¹⁵ in pyridine to form 2-(*o*-aminophenyl)-2H-benzotriazole (VII), mp 97–98°. Diazotization of VII followed by treatment with sodium azide gave a product, mp 77–78°, which was identical with VI.

When 2-(*o*-azidophenyl)-2H-benzotriazole was dissolved in decahydronaphthalene and heated to 160–170°, another mole of nitrogen was evolved and II was obtained in nearly quantitative yield. These transformations were also obtained when benzene solutions

of either the diazidoazobenzene or 2-(*o*-azidophenyl)-2H-benzotriazole were exposed to sunlight for several days.

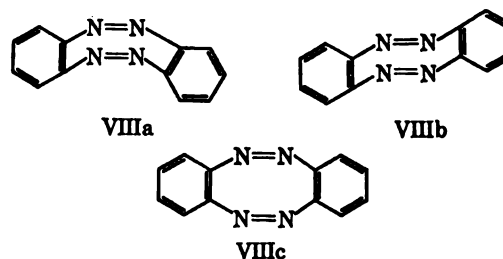
The formation of 1,3a,4,6a-tetraazapentalene II and its intermediate products may be represented by the reaction scheme shown in Chart I. The azidophenylbenzotriazole VI may form by a concerted reaction involving rupture of the N–N₂ bond of the first azide in IV by light or heat with concomitant cyclization or by formation, at least incipiently, of the neutral, electron-deficient species (a). To be specific, this chemistry will be discussed in terms of nitrene intermediates, although no compelling evidence for this interpretation is yet in hand. A cyclization can then be effected by the transfer of electrons from the neighboring, electron-rich, azo link to the developing univalent nitrogen to form 2-(*o*-azidophenyl)-2H-benzotriazole (VI). In a similar manner, the decomposition of the second azide group may be accompanied by interaction between the electrons of N-1 or N-3 and the electrophilic nitrogen of the decomposing azide. The higher temperature required for the second cyclization may reflect the decreased availability of electrons on the triazole nitrogens.

The planar tetraazapentalene structure of II has been conclusively established by X-ray,¹⁶ and all chemical evidence supports this conclusion. It is important to note that the dibenzotetraazapentalene II is a valence isomer of dibenzo-1,2,5,6-tetraazacyclooctatetraene (VIII), a structure that might have been anticipated to be capable of existence. This molecule could form on



decomposition of the azide VI by rupture of the N–N bond of the triazole followed by formation of a new bond between the azido nitrogen and the 1- or 3-nitrogen of the triazole. Compounds claimed to be derivatives of the simple tetraazacyclooctatetraene ring system have been described as high-melting, fluorescent solids of high thermal stability.^{11e,17} Some of these derivatives were shown recently to be simple tetraazapentalene systems.^{11d,18}

Of the three possible conformers of the tetraazacyclooctatetraene VIIIa–c, only *trans*-VIIIb and the planar VIIIc structures are possible in view of the



observed zero dipole moment of the molecule. The proton nmr spectrum of II in deuterochloroform revealed a complex ABCD pattern containing at least 15

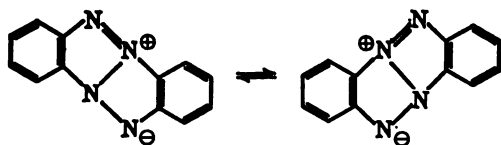
(15) E. Hoggarth in "Chemistry of Carbon Compounds," Vol. IVa, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, 1957, p 450.

(16) (a) M. B. Laing and K. N. Trueblood, in preparation; (b) M. E. Burke, R. A. Sparks, and K. N. Trueblood, *Acta Cryst.*, **16**, A64 (1963).

(17) R. Metz, *Angew. Chem.*, **68**, 580 (1956).

(18) M. Brufani, W. Fedeli, G. Giacomello and A. Vaciago, *Chem. Ber.*, **96**, 1840 (1963).

each of which possessed fine structure. The μm showed no tendency to change to a symmetrical B_2 pattern at higher temperatures (up to 225°). Tetraazacyclooctatetraene structures VIIIb and would be expected to have an A_2B_2 spectrum and resemble naphthalene. On the other hand, the tetraazapentalene structure should belong to the more complex ABCD class, provided that a valence tautomerism of the following type does not occur frequently exceeding the separation frequency of the experiment (60 cps). Since the proton spectrum is

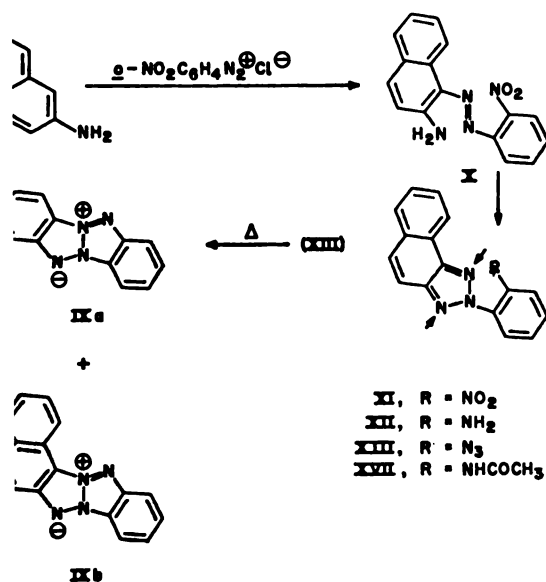


obtained over a wide temperature range, we conclude that the product is best represented by structure II and, moreover, that no exchange as represented by the tautomerism occurs.

In order to obtain further evidence for the tetraazapentalene structure and its possible valence tautomerism, an analogous compound was prepared in which the benzene rings are replaced by a naphthalene system with fusion at the α, β position.

The synthesis of the naphtho-benzo compound was carried out in a manner similar to that employed for the synthesis of II. 1-(*o*-Nitrophenylazo)-2-naphthylamine (X) was obtained by the reaction of 2-naphthylamine and *o*-nitrophenyldiazonium chloride in dilute

hydrochloric acid. This was converted *via* cupric sulfate-ammonia solution to 2-(*o*-nitrophenyl)-2H-naphtho[1,2-*d*]triazole (XI) in 83% yield. Reaction of the aminoazo compound X with thionyl chloride at 80° also gave a yield of naphthotriazole XI. Reduction to the corresponding aminophenyl-naphthotriazole XII was accomplished with iron powder and acetic acid (70% yield) and with alcoholic sodium sulfide (91% yield). Oxidation, followed by aqueous sodium azide treatment, yielded 2-(*o*-azidophenyl)-2H-naphtho[1,2-*d*]triazole (XIII) in 95% yield.



Meldola and F. Hughes, *J. Chem. Soc.*, 59, 372 (1891).

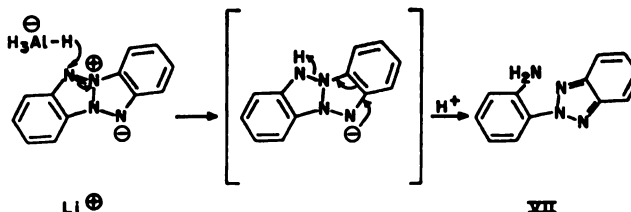
The developing nitrene intermediate derived from XIII by loss of nitrogen could now close at either of the naphthotriazole nitrogen atoms marked by arrows to give IXa and IXb. If the tetraazapentalene formulation of the nucleus is correct and if there is a large barrier for the valence tautomeric exchange, then we would expect to observe the formation of two non-superimposable isomers IXa and IXb. Formation of the naphthobenzotetraazacyclooctatetraene should give rise to but one isolable product.

Thermal decomposition of the azidophenyl-naphthotriazole in *o*-dichlorobenzene or decahydronaphthalene at 170 – 180° proceeded smoothly with evolution of 1 mole of nitrogen to yield a yellow, crystalline product, mp 190 – 200° . The solid exhibited yellow-green fluorescence under ultraviolet light, similar to that of dibenzotetraazapentalene II. Chemical analyses corresponded well for $C_{16}H_{10}N_4$ despite the wide melting-point range. This suggested a mixture of at least two products of identical empirical formula. Chromatographic separation employing mixed solvents yielded two sharp-melting products, mp 212 – 213° (faster moving) and 243 – 245° (slower moving), in addition to an intermediate fraction composed of the two unseparated components. Each of the isomers analyzed correctly, and their infrared spectra showed strong similarities. A 1:1 composite of the pure isomers accounts for all of the peaks observed in the spectrum of the original, wide-melting solid.

These results clearly support the tetraazapentalene structure in preference to the tetraazacyclooctatetraene structure. Furthermore, no evidence for the interconversion of IXa and IXb could be obtained, since both are stable at their melting points.

It was of interest to determine which of the structures IXa and IXb was associated with the higher and the lower melting isomers, respectively. One method for accomplishing this was suggested by the action of lithium aluminum hydride on the tetraazapentalene nucleus.

When a solution of the dibenzotetraazapentalene II in tetrahydrofuran was treated with an excess of lithium aluminum hydride at 60° , cleavage of a N–N bond occurred with the formation, after hydrolysis, of 2-(*o*-aminophenyl)-2H-benzotriazole (VII). It is possible to rationalize this reductive ring cleavage by attack of a hydride ion at N-1 according to the scheme shown, fol-

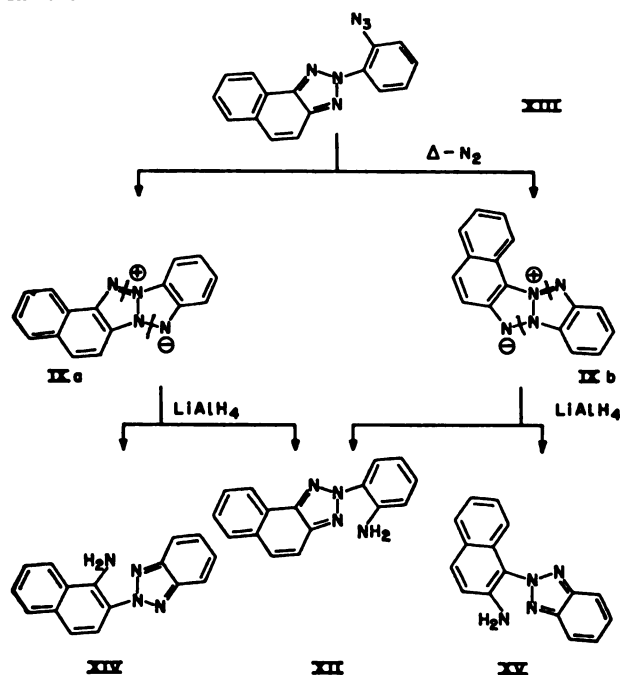


lowed by hydrolysis to yield the benzotriazole derivative VII.

Similar treatment of each of the isomeric naphthobenzotetraazapentalenes IXa and IXb might, therefore, be expected to give different mixtures of triazoles XII and XIV, and XII and XV, respectively, as shown in Chart II. Identification of either mixture of products should determine the configuration of both isomers.

Samples of each pure isomer were treated with excess lithium aluminum hydride in tetrahydrofuran at

Chart II

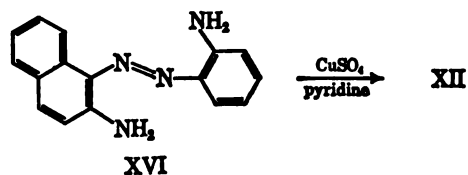


60–70° for several hours. The excess hydride was destroyed, and the reaction products were isolated in each case. Infrared spectra of the product mixtures were compared with authentic composites of XII and XV which were prepared by independent syntheses.

As expected, the similarities in spectra for the two reaction mixtures presented some difficulties. This was augmented by the formation in each case of the common product, 2-(o-aminophenyl)-2H-naphtho[1,2-d]triazole (XII), as the major component. However, the very close similarity between a 3:1 synthetic mixture of XII and XV and the products from the low-melting isomer indicated that the latter possessed structure IXb. The infrared spectrum of the higher melting isomer's reduction products, though exhibiting many similarities to the synthetic mixture, nevertheless showed several variations including significant differences in the 10.6–11.2 μ region.

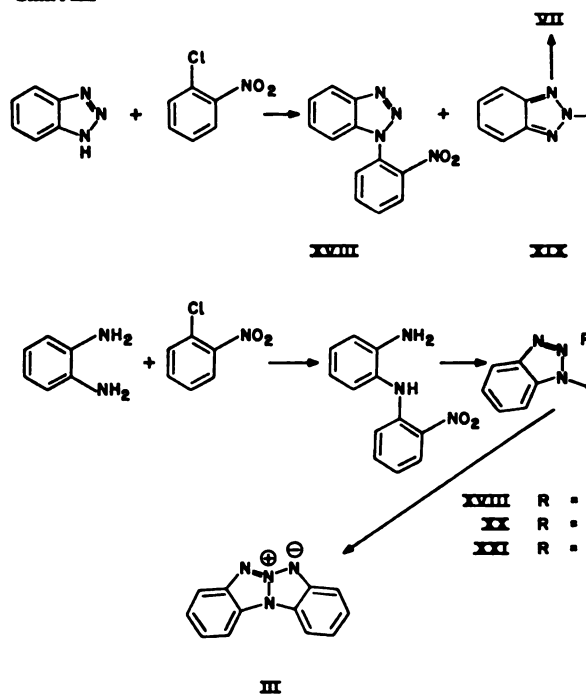
Attempted chromatographic separation of the reduction products of IXb led to the isolation of the more abundant naphthotriazole XII; however, the β -aminonaphthylbenzotriazole XV was not isolated in the pure state.

The preferential cleavage of IXa and b to give XII as the major component is not unexpected in view of its formation as the sole product from the oxidative cyclization of the diaminoazo derivative XVI with copper sulfate-pyridine.



B. Dibenzo-1,3a,6,6a-tetraazapentalene (III). This compound was prepared by the thermal decomposition of 1-(o-azidophenyl)-1H-benzotriazole (XXI) in a manner analogous to that employed for the preparation of II from VI (see Chart III). The isomeric tetraazapentalene (III) is a colorless, crystalline solid whose

Chart III



physical and chemical properties closely resemble of II. It differs from II in its spectral properties a having an appreciable dipole moment (4.36 D in zene at 25°). The large dipole moment is in a with the formulation of III as a mesoionic stru with unsymmetrically distributed charge.

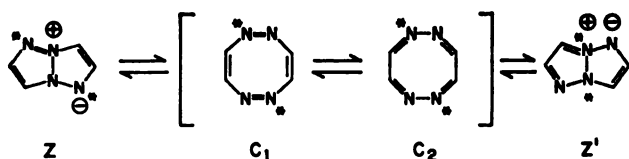
The 1-(o-azidophenyl)-1H-benzotriazole (XXI), prepared from the corresponding amine XX which turn, was obtained from the nitrophenylbenzotri XVIII. This latter compound was prepared orig by the reaction of o-chloronitrobenzene with b triazole, as described by Vystrcil, *et al.*,²⁰ We f however, that this procedure leads to a mixture o and 2H-o-nitrophenylbenzotriazoles (XVIII and in yields of 39 and 16%, respectively. The two is (XVIII and XIX) were separated by column matography. The structure of isomer XIX was fied by catalytic reduction to 2-(o-aminophenyl) benzotriazole (VII). A more satisfactory synthe XVIII was achieved by diazotization of o-ami nitrodiphenylamine, in turn conveniently ava from o-phenylenediamine by a modification c procedure of Kehrmann and Steiner.²¹

Structure of Tetraazapentalenes. The elect structure and spectra of the tetraazapentalenes v discussed in more detail in a later paper.¹⁸ Perha most striking aspect of II and III is their pron aromatic character as revealed in their thermody stability, chemical reactivity, and electronic sp Closely related to their stability is the question c ence isomerization with a tetraazacyclooctatetrae illustrated for the unsubstituted nucleus wher asterisks label the course of isomerization.

The azapentalenes Z and Z' are clearly equi when unlabeled and could be interconverted b opening to C₁ and/or C₂. Experimentally, this not occur for the dibenzo derivatives and mean a large energy barrier separates Z and C₁ or C₂.

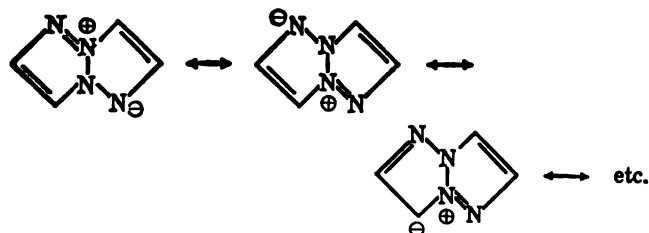
(20) B. Starkova, A. Vystrcil, and L. Starka, *Collection Czech Commun.*, 22, 1019 (1957).

(21) F. Kehrmann and G. Steiner, *Ber.*, 34, 3089 (1901).



all attempts in this laboratory and elsewhere^{11d,e} to prepare tetraazacyclooctatetraenes have given tetraazapentalenes instead, it seems very likely that the latter structure is the more thermodynamically stable. In fact, the evidence thus far suggests that a tetraazacyclooctatetraene would go over exothermically and spontaneously to the corresponding tetraazapentalene.

In Z two nitrogens are pyridine-like and two pyrrole-like, so that the system contains 10 π electrons. In molecular orbital language, the aromaticity of Z results from a closed decet of π electrons in a cyclic molecule which obeys Hückel's $4n + 2$ rule. Alternatively, in valence-bond language, a high resonance energy is expected based on the observation that 12 *nonexcited* structures in the Pauling sense can be written along with a very large number of mono- and higher excited structures. The resonance should be particularly important, since many of the nonexcited structures, such as



are of comparable energy. The fact that only charge-separated structures can be written for the tetraazapentalenes seems to be intimately related to large resonance energies and aromaticity. In fact, calculations suggest that 10 π electron azapentalenes which can be written without forced charge separation are less stable than corresponding isomers which require charge-separated structures.¹³

The relative stabilities of the 8 π electron cyclooctatetraene structures and 10 π electron pentalene structures can be deduced by considering the delocalization energy of planar cyclooctatetraene and of pentalene dianion. Hückel theory predicts delocalization energies of 1.66β and 2.46β , respectively, where β is the usual resonance integral for an ethylenic double bond. Even with the assumption of a fictitious planar cyclooctatetraene whose degenerate ground state has been neglected, the stabilization energy per π electron is larger in the 10 π system (0.25β /electron) than in the 8 π system (0.21β /electron).

Precisely the same relative stability is found in the nitrogen analogs. Hückel calculations were carried out for Z, C₁, and C₂ employing reasonable parameters,^{13,22} and it could be shown that delocalization is even more important in stabilizing the tetraazapentalenes than the carbon analog. It was also shown that the chemical reaction C₁ (or C₂) \rightarrow Z is expected to be exothermic by a substantial degree, although accurate predictions cannot be made.

(22) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 135.

Explicit calculations also reveal that the molecular orbitals of the 1,3a,4,6a- and 1,3a,6,6a-tetraazapentalene systems are remarkably similar, and we conclude that the precise location of the nitrogen atoms in charge-separated tetraazapentalenes has only a minor effect on stability. These conclusions and those given above serve to support the view that tetraazapentalenes must be considered truly aromatic molecules.

Experimental Section²³

o,o'-Diaminoazobenzene (V). To a stirred mixture of 45 g (0.5 mole) of *o*-phenylenediamine and 2 l. of benzene was added 239 g (1.0 mole) of lead dioxide. After 1 hr the mixture was brought to reflux and maintained thus for 3 hr. The insoluble lead salts were removed by filtration and the deep orange filtrate was cooled. Concentrated hydrochloric acid (150 ml) was added to the latter with stirring, and the solid which precipitated was collected by filtration. The solid, suspended in cold water (300–400 ml), was treated with sodium hydroxide solution to a pH of approximately 9. The alkaline mixture was extracted with methylene chloride, and the extract was dried over magnesium sulfate, then evaporated to dryness. Recrystallization of the residue from benzene gave two crops of orange crystals, mp 133–134° (lit.²⁴ 133–134°). The yield was 20 g.

o,o'-Diazidoazobenzene (IV). A solution of 7 g (0.1 mole) of sodium nitrite in 40 ml of water was added dropwise to a stirred mixture of 8.6 g (0.04 mole) of *o,o'*-diaminoazobenzene, 60 ml of concentrated hydrochloric acid, and 80 ml of water at 0–2°. The temperature was maintained below 10° during the addition. Stirring was continued for an additional hour after the nitrite addition. Sodium azide (6.5 g, 0.1 mole) in 40 ml of water was slowly added to the diazonium solution at 5° with continued stirring. Nitrogen evolved, and the yellow diazide precipitated during the addition. The mixture was stirred for an additional 2 hr, then filtered to obtain the diazidoazobenzene (9.8 g, 93% yield), mp 110–111° dec.

Anal. Calcd for C₁₂H₈N₆: C, 54.54; H, 3.05; N, 42.41. Found: C, 54.75; H, 3.31; N, 42.37.

2-(*o*-Aminophenyl)-2H-benzotriazole (VII). *o,o'*-Diaminoazobenzene (4.4 g, 0.02 mole) was dissolved in 50 ml of pyridine and treated with 12.8 g (0.08 mole) of copper sulfate added in portions with stirring. After 30 min at room temperature, the reaction mixture was heated at reflux for 2 hr, cooled, and poured into 4–5 volumes of cold water with stirring. The dark solid which separated was collected by filtration and washed with water. Two recrystallizations from ethanol and one from hexane with concomitant treatment with activated carbon yielded well-defined, yellow crystals of VII, mp 97–98°; yield, 65%.

Anal. Calcd for C₁₂H₁₀N₄: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.55; H, 4.98; N, 26.56.

The infrared spectrum contains a peak at 10.3 μ , which was found in all 2-aryl-2H-benzotriazoles examined in this investigation. The ultraviolet spectrum in ethyl alcohol exhibits absorption maxima at 357 m μ (ϵ 9700), 296 (12,000), 268 (6400), and 229 (20,000).

2-(*o*-Azidophenyl)-2H-benzotriazole (VI). A solution of *o,o'*-diazidoazobenzene (5 g) in acetone or benzene was heated at reflux for 2 hr. One mole of nitrogen evolved, and the orange color was discharged. The solvent was removed by distillation, and the crystalline residue was recrystallized from petroleum ether or aqueous acetone (70% yield). The light yellow needles melted at 78–79°.

Anal. Calcd for C₁₂H₈N₄: C, 61.01; H, 3.41; N, 35.58. Found: C, 61.04; H, 3.65; N, 35.94.

When a benzene solution of the diazidoazobenzene was exposed to sunlight for 3 days, a crystalline product was isolated, mp 76–77°, whose infrared spectrum was identical with that of the product

(23) All melting points are corrected. Nmr spectra were obtained with Varian HR-60 and A-60 spectrometers. Saturated deuteriochloroform solutions with tetramethylsilane as an internal standard were used unless otherwise noted. Infrared spectra in potassium bromide wafers were determined with a Perkin-Elmer 21 spectrometer. Ultraviolet spectra were determined in ethanol. Dipole moments were determined by Mr. C. Wortz in benzene solution at 25° using a Type DM-01 Dipolmeter (Wissenschaftlich-Technische Werkstätten Weilheim O.B., Germany).

(24) R. Willstätter and A. Pfannenstiel, *Ber.*, 38, 2348 (1905).

described above. The presence of an azido group was clearly indicated by the strong absorption at 4.75μ in the infrared spectrum; a band at 10.3μ is associated with the 2H-triazole structure.

Dibenzo-1,3a,4,6a-tetraazapentalene (II). (A) From *o,o'*-Diazidoazobenzene (IV). The diazide (8.2 g, 0.031 mole) in 700 ml of decalin was gradually heated to 175° with stirring. Nitrogen evolution occurred at approximately 60° with discharge of the orange azo color. At 170° , nitrogen was again evolved. The temperature was maintained at 175 – 185° for 2–3 hr, and the solution was concentrated to approximately 100 ml. The dibenzotetraazapentalene II separated as long, yellow needles (6.0 g, 93% yield) which melted at 237 – 238° ; ν_{\max} 3070, 1615, 1580 (w), 1490, 1435, 1390, 1330, 1253, 1248, 1237, 1004, 997, 943, 937, 838 (w), 832 (w), 812, 747, and 731 cm^{-1} .

Anal. Calcd for $\text{C}_{12}\text{H}_8\text{N}_4$: C, 69.22; H, 3.87; N, 26.91; mol wt, 208. Found: C, 69.06; H, 3.99; N, 26.92; mol wt, 221.

(B) From 2-(*o*-Azidophenyl)-2H-benzotriazole (VI). The benzotriazole derivative VI in decalin was heated at 175 – 185° for 2–3 hr in the manner described above. Compound II was obtained in 95% yield.

When a benzene solution of VI was exposed to sunlight for 10 days, a yellow, crystalline product precipitated, mp 236 – 237° , whose infrared spectrum was identical with that of II from the thermal method.

Lithium Aluminum Hydride Reduction of Dibenzo-1,3a,4,6a-tetraazapentalene (II). A solution of 2.0 g of II in 200 ml of tetrahydrofuran was added slowly to a suspension of 5 g of lithium aluminum hydride in 75 ml of tetrahydrofuran. The mixture was stirred at 25° for 1 hr and was heated at reflux for 4 hr. The cooled mixture was carefully poured into cold water, and the organic products were extracted with methylene chloride. Evaporation of the solvent yielded 2-(*o*-aminophenyl)-2H-benzotriazole (VII), identical in chemical and spectral properties with the material described above.

1-(*o*-Nitrophenylazo)-2-naphthylamine (X). Compound X was prepared by the method of Meldola and Hughes¹⁹ by diazotizing reprecipitated *o*-nitroaniline (27.6 g, 0.2 mole) with 13.0 g (0.2 mole) of sodium nitrite, filtering, and adding the diazonium solution to a cold, stirred solution of 2-naphthylamine (25 g, 0.18 mole) in dilute hydrochloric acid. The mixture was stirred for 1 hr and filtered to collect the dark solid (yield, 48 g). Recrystallization from acetic acid yielded lustrous, bronze-like crystals, mp 202 – 202.7° (lit.¹⁹ 198°).

2-(*o*-Nitrophenyl)-2H-naphtho[1,2-*d*]triazole (XI). Method I. A mixture of 7.5 g of azo derivative X in 75 ml of pyridine and 20 g of anhydrous CuSO_4 was refluxed with rapid stirring for 4 hr. The cooled reaction mixture was poured into four volumes of water and filtered to obtain a reddish solid (7.2 g). Recrystallization from 225 ml of ethanol yielded a crop of yellowish crystals (5.5 g). An additional 0.75 g was obtained on dilution of the mother liquor with water (total yield 83%). The product melted at 121 – 122° .

Method II. To a mixture of the azo compound X (5 g) in 50 ml of benzene was added 3.0 g of thionyl chloride. The mixture was heated at reflux with stirring for 18 hr. The brown-yellow mixture was evaporated to dryness, and the solid residue was recrystallized from 100 ml of ethanol to yield 3.5 g (70%) of pale yellow solid. An additional alcohol recrystallization yielded almost colorless, transparent plates, mp 121.8 – 122.2° . The infrared and ultraviolet spectra of this product were identical with the product obtained in method I.

Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}_2$: C, 66.20; H, 3.48; N, 19.30. Found: C, 66.03; H, 3.33; N, 19.58.

1-(*o*-Aminophenylazo)-2-naphthylamine (XVI). An attempt to form the 2-(2'-amino-1'-naphthyl)-2,1,3-benzotriazole (XV) by reductive cyclization of 1-(*o*-nitrophenylazo)-2-naphthylamine (X) gave, instead, the diaminoazo derivative XVI by simple reduction.

To a warm, stirred mixture of 7 g (0.024 mole) of X in 210 ml of ethanol was added a solution of 24 g (0.1 mole) of sodium sulfide nonahydrate. The mixture was heated at reflux for 3 hr. An additional 12 g of the sodium sulfide was added after the first hour. The cooled mixture was filtered to collect the reddish crystals (3.5 g). Dilution of the filtrate with 500 ml of water yielded an additional 2 g of product (total yield 87%). A sharp melting point was not achieved despite several recrystallizations from various solvents. However, the structure of the product was ascertained by spectra and by chemical reactions described below.

2-(*o*-Aminophenyl)-2H-naphtho[1,2-*d*]triazole (XII). The amino derivative XII was prepared by treating the corresponding nitro compound XI with iron powder in acetic acid (yield, 70%) and by

reduction with sodium sulfide (yield 91%). After recrystallization from ethanol, XII melted at 126 – 127° .

Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_4$: C, 73.82; H, 4.64; N, 21.53. Found: C, 74.09; H, 4.65; N, 21.72.

Compound XII shows a marked blue fluorescence when viewed under ultraviolet illumination, both in solution and in the solid state. The *N*-acetyl derivative XVII was prepared in 86% yield by heating with acetic anhydride. After recrystallization from ethanol, the melting point was 159.2 – 160.6° .

Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}$: C, 71.50; H, 4.67; N, 18.53. Found: C, 71.29; H, 5.27; N, 18.35.

2-(*o*-Azidophenyl)-2H-naphtho[1,2-*d*]triazole (XIII). The 2-(*o*-aminophenyl)-2H-naphtho[1,2-*d*]triazole (XII) (13 g, 0.05 mole) was diazotized with a solution of 4.5 g (0.065 mole) of sodium nitrite in 30 ml of water. The mixture was stirred for 1 hr, during which a yellow solid separated. An aqueous solution of 4.5 g (0.07 mole) of sodium azide was added dropwise at 5° with continued stirring. No immediate evolution of gas was apparent. However, after 10 min gas evolution became quite evident with accompanying foam formation. After 1.5 hr, the bright yellow color was discharged. The cream-colored, solid azide was collected by filtration and recrystallized from 600 ml of ethanol, mp 124.2 – 124.8° dec, yield, 13.6 g (95%).

Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{N}_6$: C, 67.12; H, 3.52; N, 29.36. Found: C, 67.42; H, 3.72; N, 29.14.

α,β -Naphthobenzotetraazapentalenes (IXa,b). The azido compound XIII (5.8 g, 0.02 mole) was heated in 200 ml of decalin at 180° for 2 hr with stirring. The color deepened to a brownish yellow during this period. The hot solution was treated with activated carbon, filtered, and allowed to cool slowly. A total of 3.4 g (65%) of IXa,b was obtained in two crops, mp 192 – 220° .

Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{N}_4$: C, 74.40; H, 3.90; N, 21.70. Found: C, 74.14; H, 4.08; N, 22.13.

This mixture was subjected to chromatography through neutral Woelm alumina, using chloroform and eventually chloroform-methylene chloride as the developing solvents. The faster moving fraction was predominantly the lower melting isomer IXb, the intermediate fractions were mixtures, and the later fractions contained primarily the high-melting isomer IXa. Recrystallization of the lower and higher melting fractions gave yellow crystals, mp 211.5 – 212.5 and 244.5 – 245° , respectively.

Anal. Found (lower melting isomer): C, 73.90; H, 4.14; (higher melting isomer) C, 74.26; H, 4.03.

Comparison of the infrared spectra of the two isomers showed several differences in the fingerprint region. However, all of the peaks encountered in the spectrum of the original isomer mixture are accounted for by the spectra of the pure isomers.

Lithium Aluminum Hydride Reduction of the Low-Melting Isomer (IXb). A mixture of 0.300 g of the low-melting naphthobenzotetraazapentalene isomer in 25 ml of tetrahydrofuran was treated with a filtered solution of lithium aluminum hydride (excess) in tetrahydrofuran. The mixture was stirred at 25° for 30 min, at reflux for 1 hr, then overnight at room temperature (in a second run, the reaction mixture was refluxed for 5 hr with similar results). The now deeply colored mixture was treated with ethyl acetate, then with water to destroy excess hydride. The mixture was made acid with hydrochloric acid, poured into water, then again made alkaline. The mixture was extracted twice with ether and the latter dried over sodium sulfate, then evaporated to dryness, yielding an oily residue. Comparison of the infrared spectrum of this product with that of a 3:1 synthetic mixture of XII and XV showed that they were almost identical.

Chromatographic separations on Woelm neutral alumina employing ether, ether-methylene chloride, methylene chloride, and methylene chloride-ethyl acetate yielded 2-(*o*-acetamidophenyl)-2H-naphtho[1,2-*d*]triazole (XVII) as a crystalline solid which was identical with an authentic sample. Attempts to isolate the expected minor component XV were not successful.

Note! Acetylation of the amine apparently occurred during chromatographic development with ethyl acetate. In one run, a fast-moving component was isolated from a methylene chloride-ethyl acetate fraction and appeared to have a nonamidic N-H group. This material, which may have been the product of incomplete reduction, did not appear to be either of the expected products.

Lithium Aluminum Hydride Reduction of the High-Melting Isomer IXa. This reduction was carried out as described for the low-melting isomer (above). The oily residue isolated from this reaction showed some significant differences from the authentic composite in infrared spectrum.

Nitrophenyl)-1H-benzotriazole (XVIII). (A) From Benzotriazole. In this modification of the procedure of Vystřil, *et al.*,²⁰ 119.1 g of 1H-benzotriazole, 125 g of powdered sodium and 0.5 g of cupric acetate was placed in a 500-ml three-necked flask immersed in an oil bath held at 220–230°. The flask was equipped with a magnetic stirrer and a short distilling column. After a period of 40 hr, 27 ml of acetic acid was collected. The product was subjected to steam distillation to remove excess nitrobenzene. The viscous, black residue was rinsed with benzene and extracted with a mixture of benzene and methylene chloride. The extract was filtered and dried over magnesium sulfate. The methylene chloride was removed under reduced pressure, the benzene solution remaining was eluted with benzene through a column of chromatographic grade silicic acid contained in a 125-mm diameter, sintered-glass funnel. After a forerun containing *o*-nitrobenzene, a fraction containing 37.5 g (16%) of 2-(*o*-nitrophenyl)-2H-benzotriazole (XIX) was collected (ca. 1500 ml of solvent was required; see below). The column was then eluted with 1 l. of methylene chloride; this yielded 95 g (39%) of 1-(*o*-nitrophenyl)-1H-benzotriazole (XVIII), mp 118.9–120° (lit. mp 118°²⁴).

From *o*-Amino-*o*'-nitrodiphenylamine. A mixture of 250 g of *o*-nitroaniline, 500 g of *o*-chloronitrobenzene, and 2 l. of absolute alcohol was mechanically stirred and heated to reflux in a steam bath for 3 days. The mixture was then subjected to distillation, and the nonvolatile residue was extracted with a 4 l. of chloroform. The extract was filtered, washed, and dried over magnesium sulfate. Solvent was removed under reduced pressure, and the residue was recrystallized from about 100 ml of alcohol to yield 305 g (58%) of *o*-amino-*o*'-nitrodiphenylamine in two crops, mp 106–107° (lit.²¹ mp 103°). A solution of 236 g of this product in 240 ml of acetic acid, 100 ml of water, and 1 l. of alcohol was poured onto 1500 g of crushed ice. A solution of 100 g of sodium nitrite in 200 ml of water was added at once while stirring. The mixture was stirred overnight. The solid was separated by filtration, washed with water, suction dried, and recrystallized to yield 223 g (90%) of 1-(*o*-nitrophenyl)-1H-benzotriazole, whose infrared spectrum was identical with that of the product obtained by method A.

Nitrophenyl)-2H-benzotriazole (XIX). The crude chromatographic product described above was eluted with methylene chloride through a column of Woelm neutral alumina and recrystallized from ethanol to yield white crystals melting at 132.8–133.8°; λ_{max} 290 m μ (ϵ 14,710), 290 (13,830), and 222 (25,000).

Calcd for $\text{C}_{13}\text{H}_8\text{N}_4\text{O}_2$: C, 60.00; H, 3.36; N, 23.33. Found: C, 59.70; H, 3.46; N, 23.03.

Structure XIX was verified by reduction to the corresponding amine using hot, aqueous, ethanolic sodium sulfide solution. The amine (mp 93.5–94°) was identical (mixture melting point, infrared spectrum) with the 2-(*o*-aminophenyl)-2H-benzotriazole described above.

Aminophenyl)-1H-benzotriazole (XX). A solution of 25.7 g of II in 400 ml of ethanol was hydrogenated at 3 atm using 0.2 g of tin(IV) oxide catalyst. The solution was filtered and evaporated

to dryness to yield a tan solid, which was recrystallized from 180 ml of 95% alcohol to yield 16 g of 1-(*o*-aminophenyl)-1H-benzotriazole. A second crop of 2.9 g was obtained by evaporation of the solvent to a final volume of 50 ml. A portion recrystallized from ethanol melted at 132–132.4°; λ_{max} 287 m μ (ϵ 5780) and 242 (15,700); ν_{max} 3410, 3320, 3200, 1622, 1570, 1465, 1452, 1314, 1290, 1268, 1243, 1182, 1160, 1122, 1080, 1040, 948, 853, 785, 762, and 692 cm^{-1} .

Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_4$: C, 68.55; H, 4.79; N, 26.61. Found: C, 68.64; H, 4.85; N, 26.75, 26.95.

1-(*o*-Azidophenyl)-1H-benzotriazole (XXI). A solution of 11.6 g of XX in 40 ml of hydrochloric acid was placed in a beaker equipped with a stirrer and immersed in an ice bath, and 60 g of crushed ice was added, followed by the dropwise addition of a solution of 3.9 g of sodium nitrite in 25 ml of water at 0–3°. After addition was complete, the solution was filtered into an ice-cooled flask, and a solution of 3.8 g of sodium azide in 25 ml of water was added dropwise while the reaction temperature was maintained at 0–5°. (Some ether was added to suppress foaming.) The reaction mixture was stirred overnight, and the solid product was collected by suction filtration and water washed. The crude 1-(*o*-azidophenyl)-1H-benzotriazole weighed 12.4 g (99%) and was used in the next step without further purification. A portion recrystallized from hexane melted at 84.6–85°; λ_{max} 254 m μ (ϵ 18,600), 235 (14,300), and 285 (sh) (680).

Anal. Calcd for $\text{C}_{12}\text{H}_8\text{N}_6$: C, 61.01; H, 3.42; N, 35.58. Found: C, 61.52; H, 3.66; N, 36.07.

Dibenzo-1,3a,6,6a-tetraazapentalene (III). A solution of 12.4 g of XXI in 30 ml of *o*-dichlorobenzene was added dropwise to 20 ml of refluxing *o*-dichlorobenzene heated with an oil bath. The solution was heated at reflux for 3 hr after addition was complete. Activated charcoal was added, and the mixture was filtered hot. On cooling, it deposited 8.13 g (74%) of crude III as grayish white needles. The product was purified by continuous elution with methylene chloride through a bed of Woelm neutral activated alumina. A heavy-solvent liquid-liquid extractor was found to be convenient for this purification. A layer of ca. 30 g of alumina was placed on top of a layer of glass wool in the bottom of the apparatus. The crude azapentalene was placed on top of the alumina and was slowly eluted through the alumina by the condensed vapors of refluxing methylene chloride. A portion of the product recrystallized from ethanol melted at 254.8–255.2°.

Anal. Calcd for $\text{C}_{12}\text{H}_8\text{N}_4$: C, 69.22; H, 3.88; N, 26.91. Found: C, 69.30; H, 3.88; N, 26.97; dipole moment: 4.36 D (0.002 M in benzene at 25°).

Three crystalline forms of the product could be obtained which differed somewhat in infrared spectrum. These were converted to the same form by melting and cooling; ν_{max} 3070, 1515, 1490, 1460, 1450, 1430, 1390, 1325, 1310 (w), 1290, 1253, 1155, 1148, 1121 (w), 1090 (w), 1030, 1005 (w), 963, 930, 898 (w), 870 (w), 842 (w), 745, 730, and 724 (sh) cm^{-1} .

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J. Dal Monte, A. Mangini, R. Passerini, and C. Zauli, *Gazz. chim. Ital.*, **88**, 977 (1958).

Aromatic Azapentalenes. II. Reactions of Monobenzo- and Dibenzo-1,3a,4,6a-tetraazapentalenes¹

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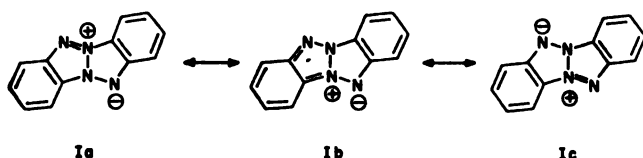
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Abstract: The reactions of dibenzo-1,3a,4,6a-tetraazapentalene (I) with a variety of reagents are described. The directive influence of the tetraazapentalene nucleus on electrophilic substitution reactions at the benzene rings is discussed. Ring-opening reactions of I with peracetic acid, lithium aluminum hydride, and cuprous cyanide give 2-phenylbenzotriazole derivatives. Monobenzo-1,3a,4,6a-tetraazapentalenes have been prepared, and the physical and chemical properties of these compounds are described.

The nitrogen-containing analogs of pentalene, the azapentalenes, are represented by replacement of the ring carbon atoms (with any associated hydrogen atoms) by nitrogen atoms. Placement of the annular nitrogens at nonfused positions gives azapentalenes containing 8 π electrons. However, when both fused positions are occupied by nitrogen, the molecules possess electronic configurations similar to those of pentalene dianion or naphthalene. The preparation of dibenzo-1,3a,4,6a-tetraazapentalene (I) as well as the isomeric 1,3a,6,6a-tetraazapentalene was described previously.^{2,3}

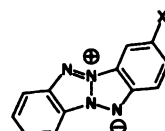
The heteroaromatic molecule I may be formally represented by a series of charge-separated structures Ia–c.



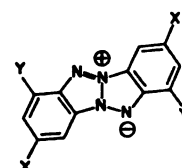
The chemical and physical properties of the dipolar tetraazapentalene might be expected to reflect a structure which lies between neutral naphthalene and pentalene dianion.⁴ This paper describes some of the chemical and physical properties of I as well as those of monobenzo-1,3a,4,6a-tetraazapentalene.

Electrophilic Substitution. Dibenzo-1,3a,4,6a-tetraazapentalene (I) undergoes a number of facile electrophilic substitution reactions with and without disruption of the tetraazapentalene nucleus.

Treatment of I with chlorine or bromine in acetic acid or chloroform readily gave the dihalogenated derivatives IIIa,b in good yields. When I was treated with N-bromosuccinimide in acetonitrile, the monobromo



- II a, X = Cl
b, X = Br
c, X = NO₂
d, X = NH₂



- III a, X = Cl, Y = H
b, X = Br, Y = H
c, X = NO₂, Y = H
d, X = NH₂, Y = H
e, X, Y = NO₂
f, X = SOCl₂, Y = H

compound IIb was produced in 70% yield, together with a small quantity (5–10%) of dibromo derivative. Chromatography on alumina gave no evidence of tional monobromo isomers. Further bromination of this product with bromine in chloroform gave a similar treatment of I with N-chlorosuccinimide in acetonitrile was less successful, yielding a mixture of monochloride IIa, dichloride IIIa, and some unre-

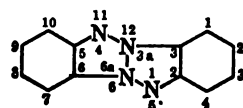
I. Nitration at 5° with 70% nitric acid gave a mixture of dinitro derivatives, from which the predominant dinitro derivative, IIIc, mp 352°, was isolated. These nitro products exhibit strong yellow-green fluorescence in solution. When I was treated with 90% nitric acid, the tetranitro derivative IIIe (mp 410° dec) was obtained in excellent yield. Surprisingly, the tetranitro product was also formed when I was heated with aqueous nitric acid at 60°. The latter is normally employed as an oxidizing rather than a nitrating mixture. When I was treated at 0° with 25% aqueous nitric acid, a mononitro product formed. Evidence for only one mononitro isomer in the crude product was found.

Treatment of I with chlorosulfonic acid at 90° produced the bis(sulfonyl chloride) IIIf in 50% yield. The compound was relatively resistant to water but reacted with amines and ammonia to give the expected sulfonamides.

Stannous chloride reduction of the mono- and dibenzotetraazapentalenes gave incomplete conversion to the corresponding amines Id and IId, respectively, thus rendering difficult the purification of the products. However, catalytic hydrogenation of methylformamide with 10% palladium on carbon gave the desired amines which were more readily purified.

Position of Electrophilic Substitution. The halogenation of I occurs to a very large extent at the 2

(1) These compounds may be named 1,5-dehydrotriazolo[2,1-a]benzotriazole and 5,11-dehydrobenzotriazolo[2,1-a]benzotriazole, respectively. The tetraazapentalene nomenclature is employed in this and subsequent papers to emphasize the role of the annular nitrogens of the central rings in providing the unusual properties of this novel system. The following numbering system has been adopted in this paper.

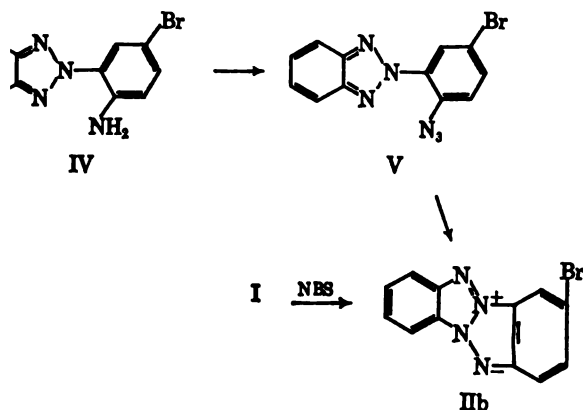


(2) R. A. Carboni and J. E. Castle, *J. Am. Chem. Soc.*, **84**, 2453 (1962).

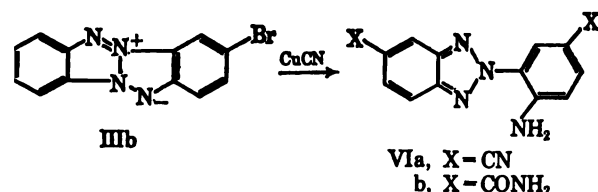
(3) R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *ibid.*, **89**, 2618 (1967).

(4) (a) T. J. Katz and M. Rosenberger, *ibid.*, **84**, 865 (1962); T. J. Katz, M. Rosenberger, and R. K. O'Hara, *ibid.*, **86**, 249 (1964); (b) D. Peters, *J. Chem. Soc.*, 1274 (1960).

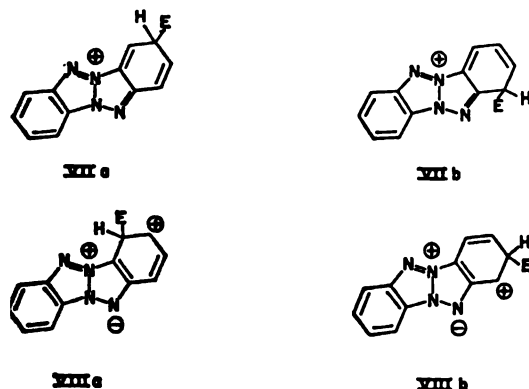
ion(s) in the benzene rings, *i.e.*, *para* to the non-nitrogens. The position of the bromine atom in I was established through conversion of 2-(5'-bromophenyl)-2H-benzotriazole (V) to the corresponding tetraazapentalene derivative which was identical with IIb. The location of the two bromo groups at 1 and 8 positions in IIIb was established by con-



on of the latter with cuprous cyanide to 2-(2'-ophenyl)-5,5'-dicyano-2H-benzotriazole (VIa) and



to the diamide VIb, which was identical with a molecule prepared by an independent route. This reaction is discussed later. If the quasiquinoid intermediates VIIa and VIIb are accepted as models for the



transition states during electrophilic attack, these transition states should be more stable than those for substitution at the 1,3 (7,9) positions (VIIIa,b). In the latter only limited charge delocalization is possible. Substitution of I would similarly be expected to occur at the 2, 4, 8, and 10 positions. It is unlikely that the substitution reactions would be complicated by migration of the ring nitrogens in view of their weakly nucleophilic character and the mild conditions employed (*e.g.*, aqueous nitric acid).

The preferential substitutions at the 2, 4, 8, and 10 positions are also in accord with an approximate charge distribution calculated by molecular orbital methods.⁶

Y. T. Chia and H. E. Simmons, *J. Am. Chem. Soc.*, **89**, 2638 (1967).

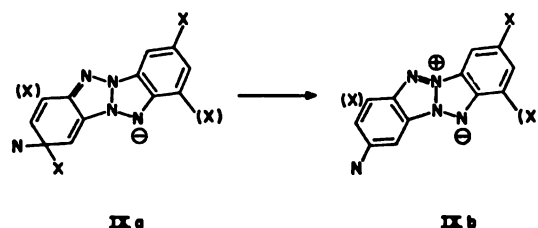
The apparent absence of isomers in the monobromination and -nitration is surprising since the calculated charge densities at C-2 and C-4 are close, and the localization energies associated with attack at either position might be expected to be comparable.

Tetracyanoethylene (TCNE), a weak electrophile which is capable of undergoing substitution reactions with reactive aromatic systems,⁶ such as dimethylaniline, phenol, etc., did not give the tetracyanoethyl or tricyanovinyl derivative of I. Rather, an acetonitrile solution containing I and TCNE gave a deep color associated with formation of a π complex (see below).

Nucleophilic Displacement Reactions on Substituted Tetraazapentalenes. When a solution of tetranitrodibenzotetraazapentalene (IIIe) in dimethylformamide was treated with azide ion, a diazidodinitro derivative was produced. Milder conditions yielded the 2- (or 4-) monoazidotrinitro derivative.

The dinitrodibenzotetraazapentalene (IIIc) also was attacked by azide ion; however, the reaction proceeded more slowly.

As in the case of electrophilic attack, nucleophilic substitution might be expected to occur with relative ease at the 2,4 or 8,10 positions in tetraazapentalenes. Attack at these positions probably involves anionic intermediates which may serve as models for the rate-determining transition state. One important contributing resonance structure for such anions may be formulated as IXa. Corresponding stabilization of the transition state for substitution at the 1,3 or 7,9 positions is not possible.

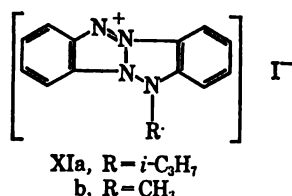


Reaction with *n*-Butyllithium. Compound I undergoes a metalation reaction with *n*-butyllithium. Thus, when I was treated with *n*-butyllithium, followed by methyl iodide, a bright yellow crystalline product was obtained which analyzed correctly for the monomethyl derivative despite a broad melting point range. The strong resemblance of the infrared and ultraviolet spectra of the methyl derivative to those of the parent compound indicated little alteration in the electronic system, *i.e.*, the methyl group is attached to the benzene ring rather than to a nitrogen. When the crude product was chromatographed on nonalkaline Woelm alumina, a sharp-melting (200–201°) solid, characterized as the monomethyl derivative X, was isolated from the early eluates. The position of substitution has not yet been proved. However, the 4 (10) position (*i.e.*, “*ortho*” to nonfused N) should be favored by the ability of the metal to coordinate with an electron pair on the nitrogen while the hydrogen in the adjacent position is removed by attack from the protophilic butyl anion.⁷

(6) (a) B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and G. F. Mower, *ibid.*, **80**, 2783 (1958); (b) J. R. Roland and B. C. McKusick, *ibid.*, **83**, 1652 (1961).

(7) H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 261 (1954).

Reactions at the Nitrogen Atoms. When propylene was passed into a solution of I in concentrated sulfuric acid under the normal Friedel-Crafts conditions, little, if any, C-alkylated product was obtained; rather, a high yield of N-isopropyltetraazapentalenium hydrogen sulfate formed. The latter was isolated as the iodide XIa by neutralization of the reaction mixture and treatment with sodium iodide.



The N-methyl derivative XIb was prepared by prolonged treatment of I with methyl iodide, and more readily with methyl sulfate at 150°, followed by treatment of the resulting water-soluble methosulfate with aqueous sodium iodide.

The cationic derivatives are light-sensitive, crystalline solids. The yellow iodide XIb, when heated at reduced pressure, reverted to methyl iodide and I. The ultraviolet spectra of I, XIa, and XIb are shown in Table I.

Table I. Ultraviolet Absorption Maxima for Dibenzotetraazapentalene I and Its N-alkylated Derivatives XIa,b

I		XIa		XIb	
λ_{\max} , m μ	ϵ_{\max}	λ_{\max} , m μ	ϵ_{\max}	λ_{\max} , m μ	ϵ_{\max}
402	38,300	378	19,700	377	20,000
382	23,300	362	19,200	361	19,900
364	7,740	323	10,100	323	10,400
323	4,110				
308	2,850				
255	63,300	241	32,900	239	35,000

The ultraviolet spectrum of the N-isopropyl cation XIa is almost identical with that of the N-methyl derivative XIb. The spectra of XIa and XIb are equally shifted toward shorter wavelengths with respect to the corresponding peaks in the spectrum of I.

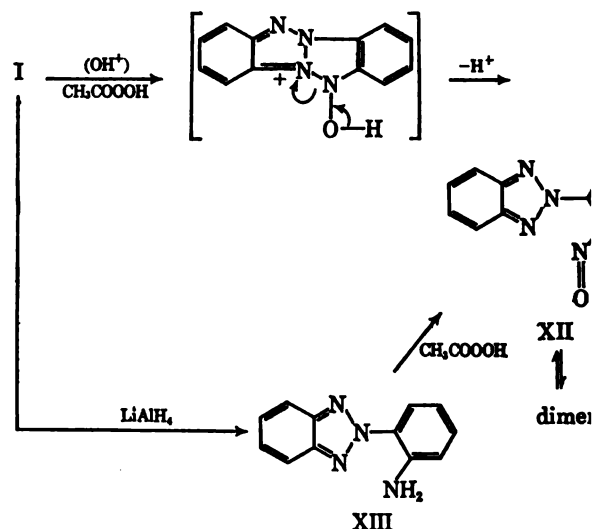
Complex Formation. Dibenzotetraazapentalene functions as a moderately weak π base in the presence of strong π acids such as tetracyanoethylene and 7,7,8,8-tetracyanoquinodimethane (TCNQ).⁸ The latter appears to form a more stable complex with I than does tetracyanoethylene. Treatment of TCNQ with compound I in warm acetonitrile gave dark green crystals of the 1:1 π complex. The complex is diamagnetic and exhibits a resistivity of 4.6×10^8 ohm cm. The solid gives green solutions when cold; however, the color is discharged on heating, indicating thermal dissociation. The complex is also dissociated in chloroform by differential solubility of its two components; the insoluble TCNQ separates, leaving the soluble compound I behind. Compound I thus appears to be only a moderately strong π base, which is not surprising in view of the presence of the four electronegative ring nitrogen atoms.

(8) (a) R. E. Merrifield and W. D. Phillips, *J. Am. Chem. Soc.*, **80**, 2778 (1958); (b) L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *ibid.*, **84**, 3374 (1962).

Silver salts and salts of copper(I) also react with compound I to form 2:1 complexes. The silver complex was unaffected by recrystallization from methylformamide, while the cuprous cyanide complex was broken into its components on warming in acetonitrile.

Reactions with Ring Opening. Although an aqueous solution of I is stable to potassium permanganate, the molecule is readily attacked by peracetic acid under relatively mild conditions with cleavage of a N-N bond. When a chloroform solution of I was treated with peracetic acid, an oxidative cleavage occurred with the formation of 2-(*o*-nitrosophenyl)-2H-benzotriazole (XII). This cream-colored solid, mp 185–185.5° solves in organic solvents to yield green solutions, characteristic of nitroso compounds. The physical and spectral data suggest that the nitroso compound probably exists as the dimer in the solid state.

The structure of the product was substantiated by independent synthesis through peracetic acid oxidation of 2-(*o*-aminophenyl)-2H-benzotriazole (XIII).



A nonfused nitrogen with its relatively high electron density would be a favorable site of attack for electrophilic peracid. The accompanying electron shift leads directly to the corresponding nitrosophenylbenzotriazole XII.

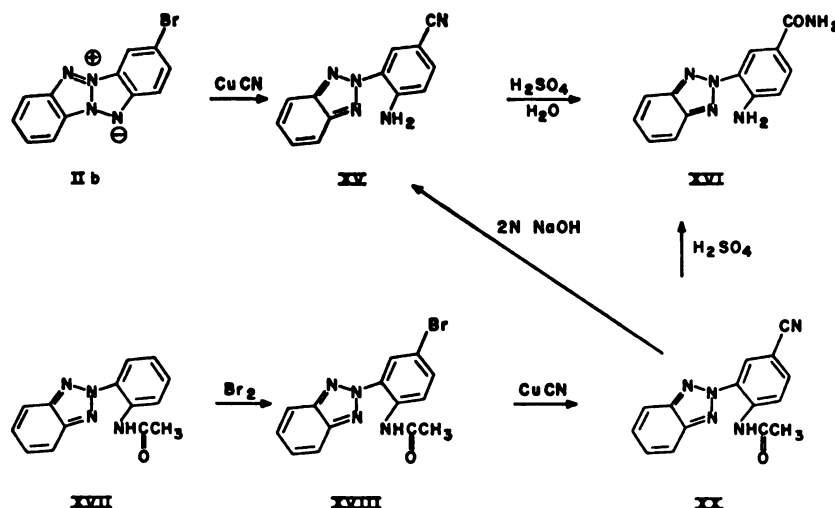
Similarly, lithium aluminum hydride converted dibenzotetraazapentalene to 2-(*o*-aminophenyl)-2H-benzotriazole (XIII).^{3b}

When the tetraaza derivative I was hydrogenated in acetic acid at 125° with 5% palladium on carbon, a colorless solid, mp 121–122°, which was identified as 2-(*o*-acetamidophenyl)-2H-4,5,6,7-tetrahydrobenzotriazole (XIV), was isolated. The identical substance was obtained from the catalytic hydrogenation⁹ of I followed by acetylation.

An attempt to replace the halogen atom in the 2-bromodibenzotetraazapentalene IIb with a methyl group by reaction with cuprous cyanide in refluxing N-methylpyrrolidone¹⁰ resulted in N-N cleavage to give cyano-2-(*o*-aminophenyl)-2H-benzotriazole (XV) in 60% yield. XV was converted to the corresponding

(9) K. Fries, W. Franke, and W. Burns [*Ann.* **511**, 241 (1934)] reported that hydrogenation of 2-phenyl-2H-benzotriazole with BaSO₄ in acetic acid gave reduction of the fused six-membered ring leaving the 2-aryl group intact.

(10) M. Newman and H. Boden, *J. Org. Chem.*, **26**, 2525 (1961).



amido derivative XVI by hydrolysis with sulfuric

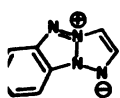
acid. The conversion of XV and XVI as 5'-cyano- and 5'-carbamoyl-2'-aminophenyl-2H-benzotriazoles, respectively, was established through independent syn-

thesis. 2-(*o*-Acetamidophenyl)-2H-benzotriazole (XVII) was brominated in acetic acid to obtain the 5-bromo derivative XVIII. The position of the bromine at the *para* to the acetamido group was confirmed by the proton nmr spectrum. Replacement of the halogen by cyano with cuprous cyanide by hydrolysis with dilute alkali or concentrated sulfuric acid gave the same cyano and carbamoyl derivatives, XV and XVI, respectively, as did the reaction described above.

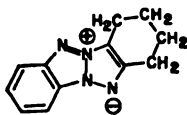
Comparison of derivatives from both routes confirms: (a) the preferred position for halogenation (and subsequent nitration) in dibenzo-1,3a,4,6a-tetraazapentalene is at the 2 (or 8) position, *i.e.*, *para* to a non-nitrogen; (b) that the ring-opening reaction occurs *via* cleavage of the N-N bond in which the nitrogen is attached to the negatively substituted benzene ring.

In a similar manner, treatment of the dibromide IIb with cuprous cyanide produced the corresponding 5,5'-bis(2'-aminophenyl)-2H-benzotriazole (VIa), the mononitrotetraazapentalene IIc yielded the 5'-nitro-5'-nitrophenyl-2H-benzotriazole (XIX). The substituted pentalene I also underwent cleavage, at an appreciably slower rate, to form compound III. This ring-opening reaction did not occur with cuprous cyanide.

Monobenzo-1,3a,4,6a-tetraazapentalenes. It was of interest to determine the physical and chemical consequences of removing one of the benzo moieties from the hetero system. Two routes were found which lead to monobenzo-1,3a,4,6a-tetraazapentalene (XXI) and tetramethylene-2,3-benzo derivative XXII, respectively.



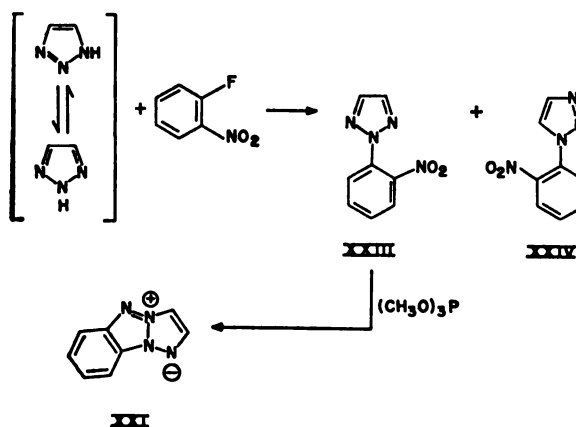
XXI



XXII

Monobenzo-1,3a,4,6a-tetraazapentalene XXI was prepared by cyclization of 2-(*o*-nitrophenyl)-2H-triazole

(XXIII) with trimethyl phosphite.¹¹ Compound XXIII was prepared by treatment of 1,2,3-triazole with *o*-fluoronitrobenzene.



The resulting mixture of 1- and 2-arylated triazoles could be separated by distillation. The 1 isomer XXIV was identified by comparison with an authentic sample prepared by the addition of acetylene to *o*-nitrophenyl azide.¹¹

Purification of the monobenzo-1,3a,4,6a-tetraazapentalene by vacuum distillation and recrystallization from ethanol gave colorless crystals, mp 108.8–109.7°, whose analysis was in agreement with the structure XXI (C₈H₄N₄). The compound possessed a distinct quinoline-like odor.

A similar deoxygenative cyclization with *o*-nitrophenyl-1H-triazole (XXIV) gave the isomeric 2,3-benzo-1,3a,4,6a-tetraazapentalene.¹¹

5,6-Tetramethylene-2,3-benzo-1,3a,4,6a-tetraazapentalene (XXII) was prepared by conversion of 2-(*o*-aminophenyl)-2H-tetrahydrobenzotriazole (XXV) to the corresponding azide XXVI followed by thermal decomposition, in a manner similar to that employed in the preparation of I.³ From the concentrated reaction mixture was obtained the tetraazapentalene XXII as an almost colorless solid, mp 131.5–133°.

A comparison of the ultraviolet absorption spectra of the two monobenzo-1,3a,4,6a-tetraazapentalenes in Table II reveals their similarity.

The nonfluorescent XXI and XXII exhibit a pronounced hypsochromic shift in the ultraviolet spectra,

(11) J. C. Kauer and R. A. Carboni, *J. Am. Chem. Soc.*, **89**, 2633 (1967).

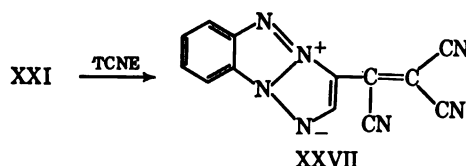
Table II. Ultraviolet Absorption Spectra of Monobenzotetraazapentalenes^a XXI and XXII

XXI		XXII	
λ_{\max} , m μ	ϵ_{\max}	λ_{\max} , m μ	ϵ_{\max}
343	21,800	351	28,200
278	3,040	278	2,850
236	27,700	242	25,900

^a Measured in ethyl alcohol.

compared to the dibenzo analog I. The long-wavelength region is without the prominent fine structure which characterizes compound I and its benzo-naphtho analogs.³

Both of the benzotetraazapentalenes XXI and XXII reacted with tetracyanoethylene (TCNE) in tetrahydrofuran solution to form a deep blue complex. In the case of XXI, however, the solution liberated hydrogen cyanide slowly, and the blue color was replaced with a deep reddish purple. These transformations were much more rapid in *N,N*-dimethylformamide. The deeply colored tricyanovinyl derivative XXVII precipitated on dilution of the solution with water.



The monobenzotetraazapentalene reacted much more rapidly with methyl iodide than did the dibenzo derivative I. The resulting stable methiodide XXVIII exhibited an ultraviolet spectrum in water solution very similar to that of the pentalene XXI in hydrochloric acid, suggesting that the positions of methylation and alkylation are the same.

Experimental Section

Monobromodibenzotetraazapentalene (IIb). a. **From Bromination of I.** A solution of 20.8 g (0.10 mole) of dibenzo-1,3a,4,6a-tetraazapentalene (I) in 2 l. of refluxing acetonitrile was stirred vigorously while 17.8 g (0.10 mole) of *N*-bromosuccinimide in 250 ml of acetonitrile was added dropwise over a period of 20 min. The clear yellow solution was refluxed for 2.5 hr, during which time a yellow solid (dibromo derivative) precipitated. The latter was removed from the hot mixture by filtration. The filtrate was concentrated to two-thirds of its original volume, then filtered while hot to remove a small quantity of solid. The acetonitrile solution was cooled to 5° to give 20 g (70%) of product, mp 196–198°. Successive recrystallizations from benzene and hexane gave an analytical sample, mp 201.0–202.5°.

Anal. Calcd for $C_{12}H_7N_4Br$: C, 50.19; H, 2.46; N, 19.51; Br, 27.83. Found: C, 50.26; H, 2.47; N, 19.39; Br, 27.66.

b. **From Thermolysis of 2-(5'-Bromo-2'-azidophenyl)-2H-benzotriazole (V).** A solution of 3.4 g of V in 30 ml of *o*-dichlorobenzene was heated at 180° for 1 hr, during which time nitrogen evolved and the solution turned yellow-brown. The solution was concentrated to one-third volume and cooled. The yellow crystalline solid (2.4 g) was collected by filtration, washed with fresh solvent, and dried, mp 205–206°. The infrared spectrum of this material was identical with that of the product from method a.

Dibromodibenzotetraazapentalene (IIb). a. A warm, stirred mixture of I (1.0 g, 0.005 mole) and 85 ml of glacial acetic acid (50°) was treated with 2 g (0.0125 mole) of bromine in acetic acid. A bright yellow precipitate formed almost immediately. The mixture was heated at 70° for 15 min, cooled to 50°, and filtered. The first crop of crystals (1.4 g) was recrystallized from *o*-dichlorobenzene to obtain bright yellow crystals, mp 295–297°.

Anal. Calcd for $C_{12}H_6Br_2N_4$: C, 39.38; H, 1.65; N, 15.31; Br, 43.67. Found: C, 39.15; H, 1.60; N, 15.15; Br, 43.20.

The ultraviolet spectrum (in chloroform) exhibited the characteristic three areas of absorption, the strongest peaks in each group being 424 m μ (ϵ 52,000), 314 (3660), and 268 (75,760).

b. **Bromination of IIb.** A solution of 2.87 g (0.01 mole) of IIb in chloroform was treated with 1.6 g (0.01 mole) of bromine in chloroform, giving an immediate yellow product (3.2 g) which exhibited the same infrared spectrum and melting point as the dibromo derivative above.

Dichlorodibenzotetraazapentalene (IIIa). Compound I (1.0 g, 0.005 mole) was added to a stirred solution of 0.8 g (0.11 mole) of chlorine in 34 ml of glacial acetic acid. The mixture was gradually heated to reflux, and approximately half of the solvent was removed by distillation. The cooled concentrate was diluted with three volumes of water, and the insoluble precipitate was collected by filtration (1.0 g). Two recrystallizations of the dried solid from *o*-dichlorobenzene gave yellow, fanlike crystals, mp 303–304°.

Anal. Calcd for $C_{12}H_6N_4Cl_2$: C, 52.01; H, 2.19; Cl, 25.59. Found: C, 51.85; H, 2.48; Cl, 25.65.

Nitration of Dibenzo-1,3a,4,6a-tetraazapentalene. Mononitration (IIc). To 700 ml of cold (10°) 25% nitric acid was added with stirring 50 g of I. The yellow suspension was stirred vigorously while warming to room temperature during 1.5 hr. After standing overnight at 25°, an orange solid was collected by filtration, washed with water, and dried. The crude mononitro derivative (11 g, 91%) was purified by chloroform extraction, mp 301–303°.

Anal. Calcd for $C_{12}H_7N_5O_2$: C, 56.91; H, 2.79; N, 27.66. Found: C, 57.21; H, 3.00; N, 27.92.

Dinitration (IIIc). Compound I (1.0 g) was added in small portions to 15 ml of concentrated nitric acid at 5° with stirring. The mixture was stirred for an additional 30 min, then poured into ice-water. A quantitative yield of the yellow-orange dinitro compound, mp 340° dec, was obtained. *Anal.* Calcd for $C_{12}H_5N_6O_4$: C, 48.33; H, 2.03; N, 28.18. Found: C, 48.21; H, 2.25; N, 28.08.

Tetranitration (IIIe). To a stirred solution of 1 g of I in concentrated H_2SO_4 was added an excess (20 ml) of fuming red nitric acid with slight cooling. After 15 min, the mixture was heated to 60° and maintained at this temperature for an additional 15 min. The orange mixture was cooled somewhat and poured into five volumes of ice-water. The orange tetranitro derivative was collected by filtration (1.55 g). Recrystallization from dimethylformamide yielded an orange-red solid, mp 410° dec, which contained one solvent molecule of crystallization.

Anal. Calcd for $C_{12}H_3N_8O_8$: C, 39.05; H, 2.40; N, 27.33. Found: C, 39.47; H, 1.65; N, 27.82.

Dilute solutions of each of the nitro compounds in organic solvents such as acetone, tetrahydrofuran, or dimethylformamide exhibited a strong greenish fluorescence.

Monoaminodibenzotetraazapentalene (IId). A slurry of 10 g of the nitro compound IIc and 10% palladium-on-carbon catalyst (0.5 g) in 150 ml of *N,N*-dimethylformamide was hydrogenated at 30–40 psi of hydrogen for 1 hr. Most of the hydrogen was absorbed during the first 10 min. The yellow-green slurry was heated to boiling and filtered under nitrogen. On cooling, a crop (5.4 g) of coppery crystals separated. An additional 2.3 g of product was obtained from the concentrated filtrate. The crude product was purified by continuous extraction with chloroform. An analytical sample was prepared by sublimation at 250° (1 mm). The light yellow needles darkened in air at 240° and melted slowly when placed in a bath at 318°.

Anal. Calcd for $C_{12}H_8N_4$: C, 64.56; H, 4.07; N, 31.38. Found: C, 64.35; H, 3.89; N, 31.13.

Acetamide derivative, recrystallized from acetonitrile, had mp 334°, λ_{\max}^{EtOH} 420 m μ (ϵ 42,800), 397 (24,700), 378 (8650), 324 (2100), 311 (4200), and 264 (55,600).

Anal. Calcd for $C_{14}H_{11}ON_4$: C, 63.39; H, 4.18; N, 26.40. Found: C, 63.78; H, 4.45; N, 26.37.

Benzamide derivative, yellow needles from acetonitrile, had mp 278–280°.

Anal. Calcd for $C_{13}H_{11}ON_4$: C, 69.73; H, 4.01; N, 21.40. Found: C, 69.97; H, 4.17; N, 21.03.

Diaminodibenzotetraazapentalene (IIId). The dinitro derivative (5.0 g, IIc) was hydrogenated as described above. The solid (2.8 g) which separated from the dimethylformamide solution was purified by successive extractions with 20 ml of hot *N,N*-dimethylformamide and four 25-ml portions of dimethyl sulfoxide. Dilution of the combined extracts with methanol gave 1.6 g (40%) of the diamino derivative. An additional 1.1 g of crude product was recovered from the original reaction solution by dilu-

water. An analytical sample was prepared by recrystallization from dimethyl sulfoxide. The maroon needles melted at ca. 265°.

Calcd for $C_{12}H_{10}N_4$: C, 60.49; H, 4.24; N, 35.28. Found: C, 60.24; H, 4.24; N, 35.00.

Amide derivative, maroon crystals, had mp 380° dec.

Calcd for $C_{20}H_{18}O_2N_4$: C, 69.94; H, 4.08; N, 18.82. Found: C, 69.57; H, 3.96; N, 18.92.

benzo-1,3a,4,6a-tetraazapentalene-2',8'-disulfonyl Chloride
A solution of 25 g of dibenzo-1,3a,4,6a-tetraazapentalene in of chlorosulfonic acid was stirred, and the temperature raised to 90° over a period of 3 hr. The solution was heated for 10°. It was then cautiously poured onto ice (behind shields in hood). The solid was separated by filtration and was lightly washed with water and then air-dried. The crude yellow solid weighed 49 g. A 36-g portion was extracted with of boiling ethyl acetate. After cooling, the undissolved sulfonyl chloride (13.8 g) was separated by filtration. The acetate was evaporated, and the residue was extracted with of ethyl acetate at room temperature. The undissolved sulfonyl chloride (3.9 g) was combined with the 13.8-g residue and recrystallized from methylene chloride-hexane to yellow platelets melting at 268–269.5° dec; λ_{max} (ε 45,700), 350 (2140), 333 (2350), 283 (54,600), and 238

Calcd for $C_{12}H_8N_4S_2O_4Cl_2$: C, 35.58; H, 1.49; N, 13.83; Cl, 17.05. Found: C, 36.06; H, 1.58; N, 13.64; Cl, 17.05.

processing the residues, an over-all yield of 51% of this sulfonyl chloride could be obtained. The disulfonyl chloride is resistant to hydrolysis in neutral solution (e.g., boiling acetone) but reacted with ammonia and amines to form amides.

N,N',N''-Tetramethyldibenzo-1,3a,4,6a-tetraazapentalenedi-imide, from dimethylamine and IIIc in methylene chloride, as yellow crystals, mp 318–320°, when recrystallized from methylene chloride-hexane.

Calcd for $C_{14}H_{12}N_4O_2S_2$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.45; H, 4.40; N, 19.60.

azido-1,3a,4,6a-tetraazapentalene. To a hot solution (135°) of tetranitrodibenzo-1,3a,4,6a-tetraazapentalene (10 g) in 400 ml of dimethylformamide was added 10 g of sodium azide in 80 ml of dimethylformamide. The mixture was stirred for 2 hr. The reaction mixture was kept at 80–85°, then cooled in an ice bath. The yellow-orange crystals separated were collected by filtration and washed with ethyl ether. The yield was 8.4 g. A sample melted with decomposition when placed in a bath at 200°. Anal. Calcd for $C_{12}H_8N_8O_4$: C, 37.90; H, 1.06; N, 44.21. Found: C, 37.90; H, 1.06; N, 44.00.

Infrared absorption of the compound exhibited the characteristic azide band at 4.75 μ and the nitro bands in the 6.5–7.5- μ

-Nitrosophenyl)-2H-benzotriazole (XII). a. From I and c. Acid. A mixture of 8.3 g (0.04 mole) of the tetraazapentalene I in 120 ml of chloroform and 20 ml of 40% peracetic acid was stirred for 2 hr. The mixture was cooled and poured into a cold solution of 50 g of sodium hydroxide. The organic layer was dried and evaporated to dryness. The solid residue was removed from chloroform to yield crystals melting at 191–192°. The total yield was 7.2 g (75%). The infrared spectrum of I showed a strong band at 7.87 μ characteristic of nitroso

The ultraviolet spectrum in ethanol showed a weak maximum at 740 m μ (ε 45) as well as strong absorption at 284 m μ (ε 22,600) and 227 m μ (ε 22,600).

From 2-(o-Aminophenyl)-2H-benzotriazole (XIII) and Peracetic Acid. 2-(o-Aminophenyl)-2,1,3-benzotriazole (XIII) (8.3 g, 0.04 mole) in 100 ml of chloroform was treated with 12 ml of 40% peracetic acid in a manner similar to that described above. There was obtained a total of 7.3 g of pale yellow product, mp 185–186°. The infrared spectrum was identical with that of the nitroso XII obtained from the tetraazapentalene I.

Calcd for $C_{12}H_8N_4O$: C, 64.28; H, 3.60; N, 24.99; (monomer), 224. Found: C, 63.96; H, 3.72; N, 24.56; (in ethylene chloride), 229.

Complex Formation with Dibenzo-1,3a,4,6a-tetraazapentalene (I). a. With Ethyl Acetate. To a solution of 1.0 g of I in 75 ml of warm tetrahydrofuran was added a solution of silver nitrate (2 g) in acetone. A yellow solid formed immediately. The mixture was stirred for 3 hr, filtered, and washed with fresh acetonitrile and

chloroform (1.7 g). Recrystallization from dimethylformamide yielded a crop of yellow crystals, mp >300°.

Anal. Calcd for $[C_{12}H_8N_4 \cdot 2AgNO_3]$: C, 26.30; H, 1.47; N, 15.34. Found: C, 26.66; H, 1.44; N, 15.62.

b. With Tetracyanoquinodimethane (TCNQ). A solution of 0.4 g (0.02 mole) of TCNQ in hot acetonitrile (25 ml) was mixed with 0.41 g (0.02 mole) of the tetraazapentalene I in 25 ml of hot acetonitrile. The resulting yellow-green solution was heated at reflux for 5 min and allowed to cool slowly. A crop of dark green crystals (0.52 g) separated. Anal. Calcd for $C_{24}H_{16}N_8$ (1:1 complex): C, 69.89; H, 2.94; N, 27.17. Found: C, 69.90; H, 3.51; N, 27.80.

The complex is diamagnetic and exhibits a resistivity of 4.6×10^8 ohm cm. The product is decomposed to starting materials by differential solubility (in chloroform).

c. With Cuprous Cyanide. Compound I (2.08 g, 0.01 mole) and cuprous cyanide (0.89 g, 0.005 mole—as $[CuCN]_2$) were each dissolved in 25 ml of warm N-methylpyrrolidone, mixed, and heated on a steam bath for 30 min. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was triturated in benzene, collected by filtration, and then dried. The light yellow-green solid (1.72 g, 89% yield) melted at 277–278° dec.

Anal. Calcd for $C_{14}H_{10}N_4Cu_2$ (1:1 complex): C, 43.42; H, 2.09; N, 21.70. Found: C, 41.14; H, 2.22; N, 20.88.

The infrared spectrum showed an absorption band at 4.65 μ ($CuCN$) and all the bands of I except that at 8.0 μ .

Reaction with n-Butyllithium. Compound I (6.5 g, 0.025 mole) in 250 ml of benzene was treated with a hexane solution of n-butyllithium (0.06 mole) at room temperature with stirring for 1 hr. The mixture was refluxed for 2 hr and treated with 0.07 mole of methyl iodide. After an additional hour of heating, the mixture was cooled and treated with water. The dried benzene layer was evaporated to dryness to yield a yellow solid residue (5.4 g). Portions of the product were recrystallized from various solvents including ethanol, benzene, and cyclohexane. The bright yellow crystals analyzed correctly for a monomethyl derivative X despite a broad melting point range, suggesting an isomeric mixture. Anal. Calcd for $C_{13}H_{11}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.26; H, 4.91; N, 24.99.

The infrared and ultraviolet spectra of the methyl derivative are very similar to those of the parent compound, indicating that the electronic system has been little altered, i.e., the methyl group is attached to the benzene ring rather than to a nitrogen. The solid was chromatographed on nonalkaline Woelm alumina with benzene, benzene-methylene chloride, and finally ethyl acetate. A small quantity of sharp-melting (200–201°) product (X) was isolated from the initial eluates; λ_{max} 405 m μ (ε 44,400), 385 (24,400) 367 (7810), 324 (4620) sh 313 (2640), 310 (2975), 303 (2264), 296 (2240), and 259 (60,825).

N-Alkylations of I. a. **Dibenzo-1-isopropyl-1,3a,4,6a-tetraazapentalenium Iodide (XIa)**. A solution of I (10 g, 0.048 mole) in 50 ml of concentrated sulfuric acid was stirred while propylene was passed in during a 20-min period. The reaction mixture was cooled with an ice bath during this period, and the reaction flask was provided with a Dry Ice-acetone condenser to prevent loss of propylene. The mixture was allowed to come to room temperature slowly, and the mixture was poured onto 800 g of ice. After a small amount of waxy material was removed by filtration, the pH of the mixture was adjusted to 8 with sodium carbonate, and the clear yellow solution was allowed to stand at room temperature for 3 days. Excess saturated aqueous sodium iodide solution was added, giving an immediate bright-yellow precipitate. The latter was collected by filtration, washed with water, and dried *in vacuo* at room temperature. The product XIa (16 g, 88%) melted with decomposition at 140° after recrystallization from methylene chloride. Anal. Calcd for $C_{14}H_{11}N_4I$: C, 47.63; H, 4.00; N, 14.81; I, 33.55. Found: C, 47.92; H, 4.16; N, 14.93; I, 34.22.

b. **Dibenzo-1-methyl-1,3a,4,6a-tetraazapentalenium Iodide (XIb)**. A mixture of 5 g (0.0024 mole) of I and 200 ml of methyl iodide was heated at reflux for 1 week. The orange crystals (2 g, 24%) which separated were collected by filtration and air dried, mp 191° dec (to blue melt).

Anal. Calcd for $C_{13}H_{11}N_4I$: C, 44.59; H, 3.17; N, 16.00; I, 36.24. Found: C, 45.00; H, 3.53; N, 15.60; I, 36.01.

c. **Dibenzo-1-methyl-1,3a,4,6a-tetraazapentalenium Methanesulfate**. A mixture of 15 g (0.072 mole) of I and 140 ml of freshly distilled dimethyl sulfate was heated at 150° for 45 min, cooled, and treated with 1 l. of ether containing 80 ml of methylene chloride. The ether solution was separated by decantation, and the insoluble oil was further extracted with a mixture comprising 400 ml of

methylene chloride and 400 ml of acetone, whereupon the oil changed to a light-tan solid (18.3 g). The latter was recrystallized from a methanol-acetone-ether mixture, yielding nearly colorless crystals of the methosulfate, mp 199° dec.

Anal. Calcd for $C_{11}H_{11}N_4O_4S$: N, 16.76; S, 9.59. Found: N, 16.51; S, 9.71.

2-(*o*-Aminophenyl)-2H-4,5,6,7-tetrahydrobenzotriazole (XXV). A solution of 1.3 g of 2-(*o*-aminophenyl)-2H-benzotriazole (XIII) in 25 ml of acetic acid was hydrogenated at 40 psi using 100 mg of 10% palladium-on-charcoal catalyst. The solution was filtered, and solvent was removed under vacuum. An ethereal solution of the residue was washed with dilute sodium carbonate solution. Evaporation of the organic layer yielded colorless crystals of the tetrahydro derivative (XXV) (85% yield) which, after recrystallization from petroleum ether, melted at 78–80°; $\lambda_{\text{max}}^{\text{EtOH}}$ 320 m μ (ϵ 7200), 269 (9610), and 238 (20,500).

Anal. Calcd for $C_{12}H_{11}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.43; H, 6.51; N, 26.06.

N-Acetyl derivative XIV, mp 121–122°, was identical with the product formed when the tetraazapentalene I was hydrogenated in acetic acid at 125° with 5% palladium-on-carbon and a hydrogen pressure of 1000 psi.

2-(*o*-Azidophenyl)-5,6,7,8-tetrahydrobenzotriazole (XXVI). Compound XXV (10.3 g, 0.05 mole) in 40 ml of concentrated hydrochloric acid and 50 ml of water was diazotized at 5° with a solution of sodium nitrite (3.7 g, 0.05 mole) which was added dropwise. The mixture was stirred for an additional 90 min and filtered to remove a small amount of undissolved solid. The cold, stirred filtrate was treated dropwise with an aqueous solution of sodium azide (3.3 g, 0.05 mole). A gummy solid separated, and nitrogen was evolved. The reaction mixture was stirred rapidly at 5° for 90 min, during which time the product was transformed to a grainy, light yellow solid (6.3 g). The azide melted at 48.5–49.6° after recrystallization from pentane.

Anal. Calcd for $C_{12}H_{11}N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 60.49; H, 4.96; N, 35.27.

5,6-Tetramethylene-2,3-benzo-1,3a,4,6a-tetraazapentalene (XXII). A solution of 10.3 g of crude azide XXVI in 200 ml of decalin was heated at reflux for 1 hr, during which time 1 mole of nitrogen was evolved. Most of the decalin was removed by distillation at atmospheric pressure. On cooling, the concentrated solution set to a brownish yellow crystalline mass. The solid was collected by filtration and recrystallized from hexane. A crop of yellow non-fluorescent crystals (mp 131.5–133°, 4.35 g) was obtained. An additional 0.9 g of product was isolated from the concentrated mother liquor; $\lambda_{\text{max}}^{\text{EtOH}}$ 351 m μ (ϵ 28,200), 278 (2850), and 242 (25,900).

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.32; H, 5.94; N, 26.25.

2-(*o*-Nitrophenyl)-2H-triazole (XXIII). A mixture of 6.9 g of 1,2,3-triazole, 14.1 g of *o*-fluoronitrobenzene, and 10.6 g of sodium carbonate (anhydrous) in 45 ml of *N,N*-dimethylformamide was heated to reflux for 65 hr. The product was poured onto ice and extracted with ether. The ether extract was dried with magnesium sulfate, and solvent was removed under reduced pressure. The residue was distilled (oil bath) through a Vigreux column to yield 11.6 g (62%) of 2-(*o*-nitrophenyl)-2H-triazole, bp 97–99° (40 μ). The pot residue was nearly pure 1-(*o*-nitrophenyl)-1H-triazole (XXIV, 20%) which was also prepared by the reaction of acetylene with *o*-nitrophenyl azide.¹¹ The 2H-triazole XXIII was recrystallized from pentane-benzene (5:3) at –20° to obtain colorless crystals, mp 27.0–27.5°.

Anal. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.47. Found: C, 50.87; H, 3.30; N, 29.66.

2,3-Benzo-1,3a,4,6a-tetraazapentalene (XXI). A solution of 10.5 g (0.05 mole) of 2-(*o*-nitrophenyl)-2H-triazole (XXIII) and 25 g of triethyl phosphite in 25 ml of xylene was heated for 6 hr in an oil bath maintained at 150°. The product was vacuum distilled, and 6.81 g of crude 2,3-benzo-1,3a,4,6a-tetraazapentalene (XXI) was collected at 100° (50 μ). The distillate solidified and was recrystallized from ethanol to yield 5.5 g (70%) of colorless crystals which melted at 107–108°. A sample recrystallized three times from ethanol melted at 108.8–109.7°; ν_{max} (KBr) 3150 m, 3110 m, 1515, 1472 m, 1460, 1370 vs, 1349, 1270, 1210, 1168, 1097, 995 m, 920 vs, 890 m, 792 m, 746 vs, 731 vs, 703 m, and 688 vs cm^{-1} ; $\lambda_{\text{max}}^{\text{EtOH}}$ 311 m μ (ϵ 14000), 267 (5450), 238 (9390), and 222 (14970).

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 60.67; H, 4.22; N, 35.19.

6-(α,β -Tricyanovinyl)-2,3-benzo-1,3a,4,6a-tetraazapentalene (XXVII). A solution of 0.84 g of XXI (0.0053 mole) in 5 ml of *N,N*-dimethylformamide (DMF) was treated with a solution of 0.70

g of tetracyanoethylene in 10 ml of DMF. The initial green of the solution gradually turned to deep red. The solution warmed on the steam bath for 30 min and was poured over of ice. The solid product was separated by filtration, water washed, and dried under a nitrogen stream (0.85 g). The deep red crystals of tricyanovinyl derivative XXVII melted at 264–266° after recrystallization (with some difficulty) from a mixture of benzene and 100 ml of hexane; $\lambda_{\text{max}}^{\text{EtOH}}$ 505 m μ (ϵ 2383 (6300), 322 (12,100), 308 (9750), and 231 (16,620).

Anal. Calcd for $C_{12}H_5N_7$: C, 60.23; H, 1.94. Found: 61.00; H, 2.06.

N-Methyl-2,3-benzo-1,3a,4,6a-tetraazapentalenium (XXVIII). A solution of 0.30 g of 2,3-benzo-1,3a,4,6a-tetralene in 10 ml of methyl iodide was sealed in a glass tube heated at 100° for 20 hr. The tube was cooled and opened, the solid product was separated by filtration and washed with carbon tetrachloride. The yellow, crystalline, water-soluble product XXVIII melted at 193.6–194° dec; $\lambda_{\text{max}}^{\text{EtOH}}$ 318 m μ (ϵ 1268 (4560), and 225 (33,300).

Anal. Calcd for $C_9H_9N_4I$: C, 36.02; H, 3.02; N, 18.90. Found: C, 36.04; H, 3.02; N, 18.90.

Reactions of Dibenzotetraazapentalene Derivatives with Cyanide. a. **2-(2'-Amino-5'-nitrophenyl)-2H-benzotriazole from IIc.** A mixture of IIc (5.0 g, 0.02 mole), 1.8 g (0.02 mole) of cuprous cyanide, and 20 ml of *N*-methylpyrrolidone was under reflux for 2 hr and poured into a mixture of 10 ml of ethylamine and 50 ml of water. The solid was collected by filtration, washed with water, then methanol, and finally dried (6.4 g). The solid was continuously extracted with benzene in a Soxhlet apparatus for 12 hr. From the evaporated benzene extract the obtained 2.3 g (46%) of XIX. An analytical sample, purified by benzene recrystallization and sublimation, melted at 251°; $\lambda_{\text{max}}^{\text{EtOH}}$ 350 m μ (ϵ 20,900), 295 (19,100), and 235 (16,600).

Anal. Calcd for $C_{12}H_9N_5O_2$: C, 56.47; H, 3.55; N, 39.98. Found: C, 55.61; H, 3.58; N, 39.72.

b. **2-(2'-Amino-5'-cyanophenyl)-2H-benzotriazole (XV) from IIb.** A mixture of 2.87 g (0.01 mole) of IIb, 1.6 g (0.009 mole) of cuprous cyanide, and 20 ml of *N*-methylpyrrolidone was heated at reflux for 4 hr and poured into a dilute hydrochloric acid solution containing 5 g of ferric chloride. The mixture was warmed on a steam bath for 15 min and then cooled, and the solid was collected by filtration. The solid was washed with methanol and dried (1.5 g). The solid was continuously extracted with benzene in a Soxhlet apparatus for 12 hr. From the latter, 1.5 g (63%) of solid, whose infrared spectrum was consistent with the structure of XV, was isolated. Two benzene recrystallizations yielded crystals of XV, mp 232–234°; $\lambda_{\text{max}}^{\text{EtOH}}$ 362 m μ (ϵ 13,500), 300 (12,760), and 233 (28,300).

Anal. Calcd for $C_{11}H_9N_5$: C, 66.37; H, 3.86; N, 29.77. Found: C, 66.78; H, 3.91; N, 30.39.

Compound XV was prepared by an independent route by refluxing a mixture of 2-(2'-acetamido-5'-bromophenyl)-2H-triazole (2.5 g) (XVIII) (see below) with cuprous cyanide (2.0 g) in 20 ml of *N*-methylpyrrolidone. The reaction mixture was poured into an ethylenediamine-water mixture (10:100, v/v). The solid (1.42 g) was collected by filtration and recrystallized from methanol to give 1.2 g of XV, mp 210–213°.

Hydrolysis of the 2-(2'-acetamido-5'-cyanophenyl)-2H-triazole (XX) with 1 equiv of sodium hydroxide (2 *N* solution) in the amine XV, which was identical with the product obtained from IIb.

c. **2-(2'-Amino-5'-carboxamidophenyl)-2H-benzotriazole (VIa) from IIb.** A mixture of XV or XX with sulfuric acid was heated at 100° for 30 min, then poured onto ice; mp 282–284.5° from an ethanol.

Anal. Calcd for $C_{12}H_{11}ON_5$: C, 61.65; H, 4.38; N, 33.97. Found: C, 61.85; H, 4.20; N, 33.60.

d. **2-(2'-Aminophenyl)-5,5'-(or 4,4')-dicyano-2H-benzotriazole (VIa) from IIb.** A mixture of IIb (3.7 g, 0.01 mole), 2.7 g (0.02 mole) of cuprous cyanide, and 20 ml of *N*-methylpyrrolidone was under reflux for 2 hr, then poured into a mixture of 50 g of ethylenediamine and 300 ml of water. The solid was collected by filtration, washed thoroughly with water, then extracted repeatedly with hot benzene. Evaporation yielded 1.2 g (45%) of product. Two recrystallizations from toluene-hexane yielded a yellow crystalline solid VIa, mp 244–246°; $\lambda_{\text{max}}^{\text{EtOH}}$ 381 m μ (ϵ 13,600), 280 (24,247) and 247 (28,100).

Anal. Calcd for $C_{11}H_9N_5$: C, 64.61; H, 3.09; N, 32.30. Found: C, 64.64; H, 3.00; N, 31.95.

2-(2'-Acetamido-5'-bromophenyl)-2H-benzotriazole (XVIII) was prepared by stirring a solution of 84 g (0.357 mole) of 2-(*o*-acetamidophenyl)-

ole (XVII) in 1.2 l. of glacial acetic acid containing 2 iv of fused sodium acetate was added 112 g (0.70 mole) e. The mixture was stirred at 50° for 3 hr, cooled, and th water. Crude XVIII was obtained in 90% yield. stallizations from methanol yielded a colorless product,

mp 179.5–180°; $\lambda_{\text{max}}^{\text{EtOH}}$ 320 (sh) $m\mu$ (ϵ 11,100), 299 (16,450), 265 (17,800), 257 (sh) (16,200), and 299 (29,000).

Anal. Calcd for $C_{14}H_{11}BrN_3O$: C, 50.78; H, 3.35; N, 16.92: Found: C, 50.64; H, 3.39; N, 17.21.

The proton nmr spectrum is in accord with structure XVIII.

Aromatic Azapentalenes. III. 1,3a,6,6a-Tetraazapentalenes

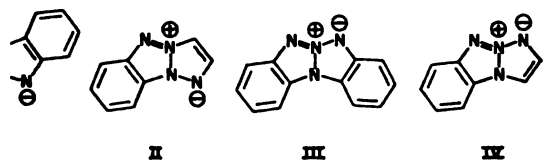
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Abstract: Syntheses of mono- and dibenzo-1,3a,6,6a-tetraazapentalene derivatives are described. A new ring-closure reaction leading to these as well as to the isomeric 1,3a,4,6a-tetraazapentalenes is based on the trialkyl phosphite deoxygenation of *o*-nitrophenyltriazole derivatives.

ous papers in this series have described the aration of several new aromatic azapenta-; systems: dibenzo-1,3a,4,6a-tetraazapentalene ; 3-benzo-1,3a,4,6a-tetraazapentalene (II),² and 1,3a,6,6a-tetraazapentalene (III).³ This paper ; the preparation and chemical properties of and dibenzo-1,3a,6,6a-tetraazapentalenes and ivatives.



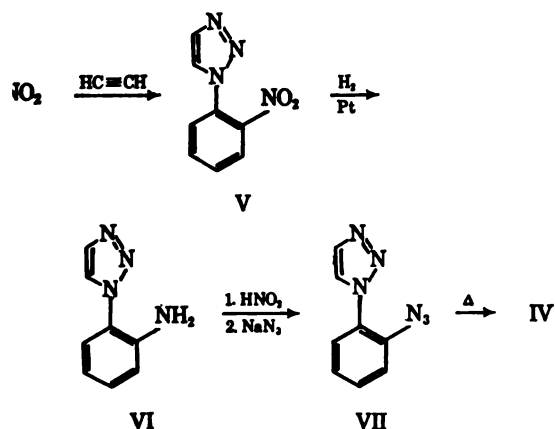
etic Routes to 1,3a,6,6a-Tetraazapentalenes. hesis of III by the pyrolysis of 1-(*o*-azidophenyl)-otriazole has been previously reported.³ s of 1-(*o*-azidophenyl)-1H-triazole in a similar led to the monobenzo-1,3a,6,6a-tetraazapenta- in 44% yield. The cyclization is probably ef- y interaction of the 2p electrons of the center of the triazole ring with the developing nitrene

during pyrolysis. The precursory nitrophenyltriazole V was prepared *via* reaction of *o*-azidonitrobenzene with acetylene. Catalytic reduction of V gave the corresponding amine VI, which was converted to azide VII by diazotization and treatment with azide ion.

Benzo-1,3a,6,6a-tetraazapentalene (IV) is a colorless, nearly odorless solid with a dipole moment of 4.73 D. at 25° in benzene. Like the dibenzo derivative III, IV exhibits three main regions of absorption in the ultraviolet (Table I).

Table I. Ultraviolet Absorption Maxima for 1,3a,6,6a-Tetraazapentalenes

III		IV		II		XVII	
λ_{max} , $m\mu$	ϵ_{max}	λ_{max} , $m\mu$	ϵ_{max}	λ_{max} , $m\mu$	ϵ_{max}	λ_{max} , $m\mu$	ϵ_{max}
356	39,800	335	16,100	343	21,800	343	16,400
343	32,500	326	15,200			335	16,600
280	8,250	293	4,110	278	3,040	299	4,080
271	5,900	285	3,760			290	3,440
234	35,000	232	28,600	236	27,700	236	29,800



The ultraviolet absorption peaks of the isomeric benzo-1,3a,4,6a-tetraazapentalene II are included in the table for comparison.³ It will be noted that the long-wavelength absorption of II is more intense and is hypsochromically shifted with respect to the corresponding absorption in IV. A similar effect has been noted in the dibenzo analogs I and III. The origins of these differences will be discussed in a subsequent communication.⁴

Several alternative procedures for generating these tetraazapentalenes directly from the more accessible nitro compounds were examined. An unsuccessful attempt was made to effect a deoxygenative ring closure of 1-(*o*-nitrophenyl)-1H-benzotriazole (VIII) to III by pyrolysis with ferric oxalate.^{5,6} However, deoxygena-

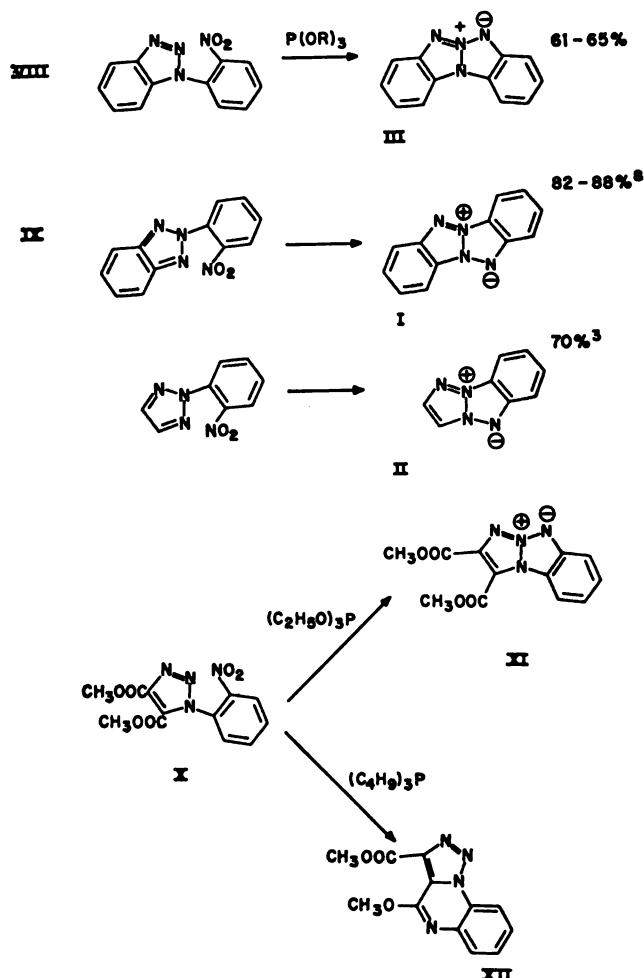
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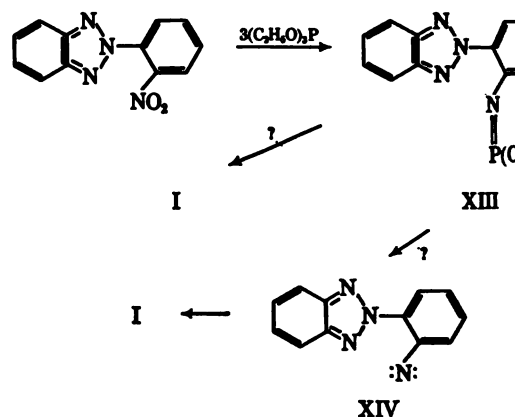
tive cyclization of this triazole with phosphites and phosphines proceeded smoothly.⁷ When VIII was heated with excess triethyl phosphite in xylene, tetraazapentalene III was isolated from the cooled solution in good yield and high purity. The by-products appeared to be very soluble in aromatic hydrocarbon solvents, facilitating the isolation of III. The *o*-nitrophenyltriazoles IX and X likewise gave the corresponding tetraazapentalenes in fair to good yields.



This reaction is importantly affected by the nature of the phosphorus compound. For instance, the reaction of VIII or IX with tributylphosphine is more rapid than with the less nucleophilic triethyl phosphite. The yields and product purities are much higher with the latter reagent, however. When the phosphine was employed with the ester X, attack at both the carbonyl oxygen atom and the nitro group occurred. The resulting product has been tentatively assigned the triazoloquinoxaline structure XII.

Several intermediates are possible for these reactions. A univalent nitrogen species XIV may form by removal of oxygen atoms from the nitro groups. A prior for-

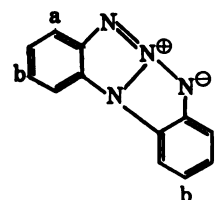
mation of phosphinimine (e.g., XIII) with subsequent elimination of triethyl phosphite may likewise lead to the nitrene XIV. Finally, intramolecular displacement of the phosphite group in XIII by a triazole ring may lead directly to the azapentalene.



The last two sequences were shown to be highly likely when the phosphinimine XIII (prepared from the corresponding azide and triethyl phosphite) was heated to yield I on pyrolysis in refluxing xylene.

Chemical Properties. The chemical reactivity of dibenzotetraazapentalene III (e.g., in electrophilic substitution reactions) parallels closely that reported for isomeric 1,3a,4,6a system I.³

Mononitration occurred in 25% nitric acid at room temperature. Dinitro and tetranitro derivatives at 0-5° in 70 and 90% nitric acid, respectively. Reaction of III with chlorine or chlorosulfonic acid gave the corresponding dichloro and bis(chlorosulfonate) derivatives, respectively. Although the positions of substitution in these electrophilic reactions have not been rigorously proved, charge density and localization considerations similar to those employed for the 6a isomer I^{2,4} favor positions a and b as sites for



The tri- and tetranitro derivatives of I and positive Janovski reactions,⁹ while the mononitro derivatives did not. Two nitro groups in a tetranitro derivative were readily replaced by a diazo group in a manner similar to that of the 1,3a,4,6a system I, yielding the corresponding dinitro diazide.

III reacted slowly with methyl iodide at 100° to form an unstable adduct which could be isolated in pure state. On the other hand, treatment of III in concentrated sulfuric acid with reflux led smoothly to an N-isopropyl methosulfate derivative, which was converted to the iodide for characterization.

Catalytic hydrogenation of III (palladium on carbon, 125°) resulted in a rupture of the pentalene moiety.

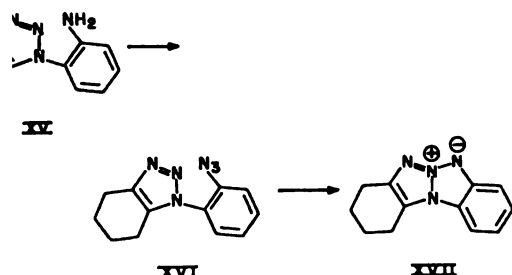
(9) Aromatic systems with two or more *meta*-positioned nitro groups generally react at the doubly activated position (*ortho* to one nitro group and *para* to the other) with alkaline acetone to form an intensely colored azide. See, for instance, R. Foster and R. K. Mackie, *Tetrahedron* (1962); 19, 691 (1963).

(7) The generation of nitrene-like intermediates in the phosphite deoxygenation of nitro compounds has been discovered independently in other laboratories: (a) J. I. G. Cadogan and M. Cameron-Wood, *Proc. Chem. Soc.*, 361 (1962); (b) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 4831 (1965); (c) B. M. Lynch and Y.-Y. Hung, *J. Heterocyclic Chem.*, 2, 218 (1965); (d) R. J. Sundberg, *Tetrahedron Letters*, 477 (1966).

(8) Studies in these and in other laboratories^{7b} indicate that I can be obtained in good yield by the reaction of *o,o'*-dinitroazobenzene with trialkyl phosphites. The nitrophenyltriazole IX may be an intermediate in this reaction.

hydrogenation of the benzo ring. The re-aminophenyl)-4,5,6,7-tetrahydro-1H-benzo-) was then reconverted in the usual manner (XVI) to a new tetraazapentalene derivative.

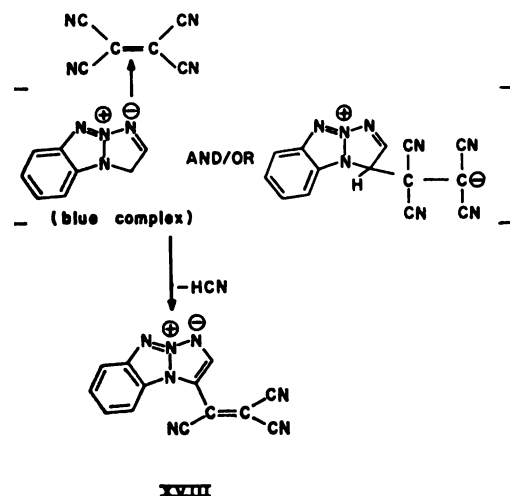
Compound XVII exhibits an ultraviolet spectrum similar to that of the monobenzo derivative (Table I).



Substituted monobenzopentalene IV exhibits greater reactivity toward electrophiles than the dibenzo analog. Nitration leads rapidly to a trinitro compound, whereas the monobenzo derivative, under slightly more vigorous conditions, gives a positive Janovski reaction. Nitro introduction does not.⁹ This suggests that the first group enters the tetraazapentalene ring and the second, respectively. More vigorous conditions are required for the introduction of a second nitro group in the monobenzo derivative.

Nmr studies have verified these conclusions. Like its dibenzo analog, IV reacts readily with iodine to form a stable N-methyl derivative. The ultraviolet spectrum of the latter in water is very different from that of the benzotetraazapentalene IV in acetic acid, indicating that the sites of protonation and ethylation are the same. Insoluble metal complexes were formed with a wide variety of heavy

metals. In contrast to the dibenzo derivatives I and III, the tetraazapentalene IV reacts readily with the electrophile tetracyanoethylene (TCNE) in dimethylformamide (DMF). A deep blue complex is formed in concentrated solution, followed by loss of hydrogen cyanide and the development of a red color. The loss of hydrogen cyanide is much slower



metals. In contrast to the dibenzo derivatives such as phenols, N,N-dimethylaniline, and benzene derivatives, it is reported to form tricyanovinyl derivatives under similar conditions, for instance, J. R. Roland and B. C. McKusick, *J. Am. Chem. Soc.*, **83**, 1652 (1961).

in tetrahydrofuran solution, and the blue color of the complex persists for many hours in solution. The following reaction sequence is suggested.

Electrophilic attack by tetracyanoethylene on IV undoubtedly occurs at the pentalene ring rather than on the benzo substituent. This conclusion is supported by the nonoccurrence of a similar reaction with either of the dibenzo analogs I and III or with the substituted monobenzotetraazapentalene XVII. The latter compound forms a similar (isolable) blue complex; however, lack of an available position on the pentalene ring precludes the subsequent collapse of the complex to the corresponding tricyanovinyl derivative.

Experimental Section

All melting points are corrected. Nmr spectra were obtained with a Varian A-60 spectrometer. Saturated deuteriochloroform solutions with tetramethylsilane as an internal standard were used unless otherwise noted. Peak center positions are reported as $\tau = 10 - \delta_H$ ppm; number of protons (by integration) is given in parentheses.

Infrared spectra were determined in potassium bromide wafers with a Perkin-Elmer 21 spectrophotometer unless otherwise noted. Peak positions are reported in wavenumbers; m and w indicate medium and weak intensities, respectively. Ultraviolet spectra were determined in ethanol. Dipole moments were determined in benzene solution at 25°.

o-Azidonitrobenzene. The following modification of the procedure of Noelting and Michel¹¹ was used.

A solution of 48.4 g of *o*-nitroaniline in 500 ml of hot 19% hydrochloric acid was poured while stirring onto 500 g of ice contained in a 4-l. beaker immersed in a methanol-ice bath. The resulting slurry was diazotized by the slow addition of an aqueous solution of 26 g of sodium nitrite while the temperature was maintained at 0–5°. The solution was stirred for 1 hr at this temperature, ice was added, and the solution was filtered quickly and returned to the 4-l. beaker. A solution of 24.5 g of sodium azide in 75 ml of water was added dropwise at 0–7°. A layer of ether on the solution minimized frothing. The solution was stirred for 2 hr, and ether was added to dissolve the solid. The ether layer was separated, washed with water, and dried over magnesium sulfate. Solvent was removed under reduced pressure to a final volume of 150 ml, and a total of 100 ml of warm pentane was added slowly to the warm ether solution with stirring. A total of 53 g (98%) of *o*-azidonitrobenzene (mp 51–52°) was obtained in two crops.

1-(*o*-Nitrophenyl)-1H-triazole (V). A solution of 50 g of *o*-azidonitrobenzene in 300 ml of acetone in a 1-l. autoclave was heated with acetylene gas under a pressure of ca. 10 atm at 50° for 6 hr, at 60° for 6 hr, and at 70° for 6 hr. The autoclave was cooled and vented between cycles to remove accumulated nitrogen. Solvent was removed under reduced pressure, and the product was crystallized from a mixture of 150 ml of benzene and 50 ml of hexane to yield 34 g (59%) of V in two crops. The major by-product was benzofuroxan, which can optionally be distilled from the crude reaction mixture (oil bath at 135° (1 mm)). A portion of V recrystallized from benzene-hexane melted at 94.3–95.1°; λ 290 (sh) $m\mu$ (ϵ 1650) and 223 (sh) (13,800); ν_{max} 3180 w, 3130 w, 1620 m, 1595 m, 1535, 1517 m, 1458 w, 1360, 1327, 1308, 1234, 1202 w, 1130 w, 1105 w, 1086 m, 1045, 1026, 988 m, 958 w, 948 m, 885 m, 854, 795, 784, 748, 714 m, 704 m, and 698 cm^{-1} .

Anal. Calcd for $C_8H_6N_4O$: C, 50.53; H, 3.18. Found: C, 50.61; H, 3.18.

1-(*o*-Aminophenyl)-1H-triazole (VI). A solution of 25 g of V in 150 ml of *n*-propyl alcohol was hydrogenated at 40 psig with 0.2 g of platinum oxide. The product was flash distilled (oil bath; bp 135° (0.2 mm)) to yield 18.4 g (87%) of VI, mp 38.7–39.3°, ν_{max} (neat) 3420, 3310, 3200 m, 3120 m, 1620, 1512, 1478 m, 1460, 1430 w, 1320, 1272 m, 1225, 1195 m, 1158 m, 1120 w, 1090 m, 1040, 1025, 980, 788 m, 750, 718, and 670 cm^{-1} .

Anal. Calcd for $C_8H_6N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.96; H, 5.21; N, 35.25.

1-(*o*-Azidophenyl)-1H-triazole (VII). A solution of 37.3 g of VI in 250 ml of concentrated hydrochloric acid was poured onto 750 g of ice contained in a 2-l. beaker cooled to –30° with a Dry Ice-

(11) E. Noelting and O. Michel, *Ber.*, **26**, 86 (1893).

carbon tetrachloride-chloroform bath. A solution of 18 g of sodium nitrite in 50 ml of water was added dropwise at -20 to -22° . The solution was stirred for 2 hr, and a solution of 18 g of sodium azide in 50 ml of water was added dropwise at -20 to -22° . Ether was added to minimize frothing. After being stirred for 3 hr, the solution was warmed to room temperature, neutralized with sodium hydroxide solution, and extracted with ether. The ether layer was dried over magnesium sulfate, and solvent was removed under vacuum to a volume of 300 ml. Hexane (250 ml) was added, and 22.2 g (51%) of white crystals of VII was collected. A portion recrystallized from ether melted at $70.3-71.2^{\circ}$; λ 335 (sh) μ (ϵ 82), λ_{\max} 254 μ (ϵ 12,100), λ 235 (sh) μ (ϵ 11,700); ν_{\max} 3120, 2250, 2220, 1600 m, 1510 m, 1480 m, 1470 m, 1318, 1270 w, 1236, 1195 m, 1160 m, 1133 w, 1108 m, 1090 m, 1042, 1032 m, 986 m, 955 w, 945 w, 810, 758, 735 w, 710 m, and 700 cm^{-1} .

Anal. Calcd for $\text{C}_6\text{H}_4\text{N}_4$: C, 51.61; H, 3.25; N, 45.15. Found: C, 51.91; H, 3.40; N, 44.88.

Benzo-1,3a,6,6a-tetraazapentalene (IV). A solution of 25.4 g (0.136 mole) of the azide VII in 75 ml of *o*-dichlorobenzene was heated in an oil bath at $175-200^{\circ}$. When gas evolution (0.14 mole total) had ceased, the solvent was removed under reduced pressure (2.0 mm) at 80° in a rotary film evaporator. The residue in methylene chloride was eluted continuously through a column of 400 ml of Woelm neutral alumina. (A heavy-liquid continuous extraction apparatus can be conveniently adapted for this purpose.) Solvent was distilled from the eluate to yield 11.24 g of IV. Recrystallization from ethanol yielded 9.45 g (44%) in two crops, mp $121.6-122.2^{\circ}$, λ_{\max} (concentrated hydrochloric acid) 311 μ (ϵ 14,100), 267 (5450), 238 (9390), and 222 (14,970) (see Table I for ethanol solvent); ν_{\max} 3150 m, 1620 m, 1582 w, 1512 m, 1478, 1440 w, 1375, 1340, 1330 m, 1305 m, 1280 m, 1196 w, 1186 w, 1157, 1137, 1110 w, 1080 m, 1007, 983 w, 978 m, 863 m, 810, 747, 734, 727, and 700 cm^{-1} .

Anal. Calcd for $\text{C}_6\text{H}_4\text{N}_4$: C, 60.75; H, 3.82; N, 35.43. Found: C, 60.97; H, 3.38; N, 35.71, 35.76.

This compound could also be prepared in 36% yield by heating to reflux overnight a solution of 1.14 g of V and 4.0 g of trimethyl phosphite in 10 ml of xylene.

Silver nitrate complex was formed in 89% yield from acetonitrile solutions of IV and silver nitrate; white crystals, mp 200° dec.

Anal. Calcd for $\text{C}_6\text{H}_4\text{N}_4 \cdot \text{AgNO}_3$: C, 29.29; H, 1.84; N, 21.35. Found: C, 29.29, 29.19; H, 2.45, 2.10; N, 21.44.

Cupric chloride complex was prepared in 95% yield by the addition of 1.0 g of cupric chloride dihydrate to a solution of 0.50 g of IV in 50 ml of warm ethanol; blue-black crystals, mp $179-182^{\circ}$.

Anal. Calcd for $\text{C}_{12}\text{H}_8\text{N}_4 \cdot \text{CuCl}_2$: C, 32.84; H, 2.07; N, 19.15; Cu, 21.72. Found: C, 33.73; H, 2.14; N, 19.16; Cu, 21.04.

Mercuric chloride complex was formed in 27% yield from 0.6 g of mercuric chloride and a solution of 0.2 g of IV in 5 ml of ethanol; white crystals, mp $170-172^{\circ}$.

Anal. Calcd for $\text{C}_6\text{H}_4\text{N}_4 \cdot \text{HgCl}_2$: C, 22.36; H, 1.41; N, 13.04. Found: C, 22.63; H, 1.84; N, 13.18.

Manganese chloride complex was prepared in 20% yield from 1.97 g of manganese chloride tetrahydrate and 1.58 g of IV in 150 ml of warm ethanol; yellow, water-sensitive crystals, mp $310-315^{\circ}$.

Anal. Calcd for $\text{C}_6\text{H}_4\text{N}_4 \cdot \text{MnCl}_2$: C, 33.83; H, 2.13; Mn, 19.34. Found: C, 33.98; H, 2.26; Mn, 19.25.

Dimethyl 1-(*o*-Nitrophenyl)-1H-triazole-4,5-dicarboxylate (X). A solution of 41 g of *o*-azidonitrobenzene and 40 g of dimethyl acetylenedicarboxylate in 25 ml of chloroform was held at 30° for 15 days. The crystalline adduct (35.7 g) was separated by filtration and washed with 1:3 chloroform-hexane. The combined filtrates and washings were warmed to 70° for 2 hr, and volatile products were removed under reduced pressure (100° (0.5 mm)). The residue was recrystallized from 80% methanol to yield an additional 23.8 g of adduct. A portion recrystallized successively from methanol-water and from benzene-hexane melted at $87.5-88^{\circ}$; ν_{\max} 1730, 1610 m, 1590 w, 1535, 1505 m, 1452 m, 1440 m, 1378 m, 1348, 1305, 1258, 1220, 1208, 1168 w, 1107, 1080 w, 1008, 962 m, 937 m, 853, 830 m, 810 m, 788, 748, 728 w, and 695 cm^{-1} .

Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_6$: C, 47.06; H, 3.29; N, 18.30. Found: C, 47.20; H, 3.44; N, 18.36.

Dimethyl 4,5-Benzo-1,3a,6,6a-tetraazapentalene-2,3-dicarboxylate (XI). Under nitrogen a solution of 7.0 g of triethyl phosphite in 50 ml of toluene was added over 24 hr to a refluxing solution of 6.12 g of X in 100 ml of toluene. The solution was heated to reflux for 6 hr, and solvent and volatile products were removed under reduced pressure. The resulting oil crystallized partially. The white crystals (1.35 g) were dried on a clay plate, and after successive

recrystallization from methanol and benzene-hexane melt $127.0-128.4^{\circ}$; λ_{\max} 353 μ (ϵ 14,400), 284 (9650), 250 (18 and 223 (16,200); ν_{\max} 4140 w, 4100 w, 3960 w, 1740, 1705, 1512, 1480 m, 1445 m, 1430 m, 1395 m, 1382, 1345, 1344, 1312, 1295, 1238, 1212 m, 1195 m, 1160 m, 1122 m, 1048 m, 1030 w, 970, 892 w, 862, 808, 756, and 714 cm^{-1} .

Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_4$: C, 52.85; H, 3.68; N, 33.47. Found: C, 52.86; H, 3.76; N, 33.50.

Methyl 4-Methoxy-*v*-triazolo[3,4-*a*]quinoxaline-3-carboxylate (XII). A solution of 8.46 g of tributylphosphine in 50 ml of toluene was added slowly over 50 hr to a refluxing solution of 1.97 g of V in 50 ml of toluene. The resulting gray crystals (1.97 g) dried on a clay plate and washed with pentane. After two crystallizations from methanol the white crystalline product melted at $193.8-195.0^{\circ}$; λ_{\max} 331 μ (ϵ 11,420), 317 (13,400), 305 (13,400), 291 (7500), 280 (7530), 265 (8520), 249 (13,900), and 222 (24,900); ν_{\max} 3100 w, 2950 w, 1635, 1578, 1552, 1490 m, 1480 m, 1385, 1335, 1320 m, 1283 w, 1265, 1247, 1230 m, 1210, 1186, 1109, 1007, 970, 900 m, 793 m, 769, 764, 735 m, 720 w, 713 m, 688 w cm^{-1} ; nmr τ 1.9-2.4 (4), multiplet, 5.65 (3), and 5.83 (3).

Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_4$: C, 55.81; H, 3.90; N, 30.29. Found: C, 55.85; H, 4.02; N, 31.55.

Dinitrobenzo-1,3a,6,6a-tetraazapentalene. Compound IV (1.95 g) was added in small portions to 100 ml of 70% nitric acid at 0° and then allowed to warm to room temperature. The resulting crystals (1.95 g) of dinitro derivative were separated by filtration and after recrystallization from 400 ml of acetone melted at 280° ; λ_{\max} 420 μ (ϵ 20,900), 348 (6130), 338 (6130), 312 (11,278 sh) (8300), 270 (9380), and 250 (11,900).

Anal. Calcd for $\text{C}_6\text{H}_2\text{N}_6\text{O}_4$: C, 38.72; H, 1.62; N, 59.66. Found: C, 38.74; H, 1.83; N, 59.09.

Trinitrobenzo-1,3a,6,6a-tetraazapentalene. Compound IV (5.7 g) was added in small portions to 75 ml of 95% (yellow fuming) nitric acid at $0-5^{\circ}$ with stirring. The solution was warmed to room temperature, poured onto ice, and filtered. The olive-green product weighed 7.50 g. After successive recrystallizations from acetone and 1:1 acetone-ethanol, it melted at $305-306.5^{\circ}$; λ_{\max} 434 μ (ϵ 27,900), 335 (5300), and 294 (16,400); nmr $\text{CD}_2\text{SOCD}_2-\text{CH}_2\text{COCH}_3$ τ 0.43 (1), doublet ($J = 2.1$ cps) (1), 0.82 (1), doublet ($J = 2.1$ cps).

Anal. Calcd for $\text{C}_6\text{H}_2\text{N}_6\text{O}_6$: C, 32.77; H, 1.03; N, 66.20. Found: C, 32.62; H, 1.12; N, 66.51.

Tricyanovinylbenzo-1,3a,6,6a-tetraazapentalene (XVIII). A solution of 0.84 g of IV in 10 ml of dimethylformamide (DMF) treated with a solution of 0.70 g of tetracyanoethylene in 10 ml of DMF. The initial greenish blue color of the complex gradually changed to purple. The solution was warmed on the steam bath for 30 min and was then poured onto 200 ml of crushed ice stirred for 15 min. The precipitated purple crystals (0.85 g) were filtered and washed with water. A portion after recrystallization from benzene-hexane melted at $236-237.4^{\circ}$; λ_{\max} (acetone) 534 μ (ϵ 24,700), 333 (6470), 310 (6310), 278 (4730), and 245 (sh) (8340), and 225 (31,500); ν_{\max} 3120 w, 2210, 1565 w, 1522, 1493, 1440, 1413 m, 1360, 1313, 1270, 1207, 1170, 1152, 890 w, 863 w, 782 m, 757, 748 m, 737 m, 694 m, and 668 w cm^{-1} .

Anal. Calcd for $\text{C}_{12}\text{H}_4\text{N}_8$: C, 60.23; H, 1.94; N, 37.83. Found: C, 60.01; H, 2.23; N, 37.62.

1(6)-Methylbenzo-1,3a,6,6a-tetraazapentalenium Iodide. A solution of 0.30 g of IV and 10 ml of methyl iodide was sealed in a tube and heated for 20 hr at 100° . The yellow crystalline product (0.46 g) was separated by filtration and washed with carbon tetrachloride, mp $193.6-194^{\circ}$ dec. The product was very soluble in water, slightly soluble in acetonitrile; λ_{\max} (H_2O) 309 μ (ϵ 12,222 (38,100); λ_{\max} (ethanol) 318 μ (ϵ 14,300), 268 (12,245 sh) (8340), and 225 (31,500); nmr (D_2O) τ 1.02 (1), d ($J = 2$ cps), 1.43 (1), doublet ($J = 2$ cps), 1.70 (1), multiplet (3), multiplet, and 5.70 (3); ν_{\max} 3070, 3020 m, 1620 m, 1490 w, 1472 w, 1450, 1430, 1380, 1340 m, 1315 m, 1185, 1113, 1012 m, 935 m, 880 w, 860 w, 840, 788 m, 757 vs, and 700 cm^{-1} .

Anal. Calcd for $\text{C}_6\text{H}_5\text{N}_4\text{I}$: C, 36.02; H, 3.02; N, 30.96. Found: C, 36.04, 36.27; H, 3.02, 3.17; N, 30.90.

Dibenzo-1,3a,6,6a-tetraazapentalene (I)³ was isolated in 82% yield by treating IX² with 3.1-4.1 moles of triethyl or tri-*n*-butyl phosphite for 17 hr in refluxing xylene. When the solution cooled, nearly pure I crystallized. When IX was heated for 3 hr in refluxing xylene with 3.0 moles of tri-*n*-butyl phosphite, I was obtained in 75% yield.

Dibenzo-1,3a,6,6a-tetraazapentalene (III)³ was isolated in 61% yield when VIII was heated for 20 hr in refluxing xylene with

les of triethyl phosphite. When triphenyl phosphite (neat) substituted, only 17% of III was isolated after 96 hr at 100°.

Mercuric nitrate complex was prepared in 100% yield by mixing a solution of 11 g of III in 700 ml of warm tetrahydrofuran with a solution of 20 g of silver nitrate in 100 ml of acetonitrile; white solid, mp 282.5–283.5°.

l. Calcd for $C_{13}H_{11}N_4 \cdot AgNO_3$: C, 38.12; H, 2.13; N, 18.40. Found: C, 38.23, 38.47; H, 2.57, 2.45; N, 18.40.

Mercuric chloride complex was formed in 87% yield by treating a solution of 0.42 g of III in 150 ml of warm ethanol with 50 g of mercuric chloride dihydrate; bronze crystals, mp 281–284° dec.

l. Calcd for $C_{13}H_{11}N_4 \cdot CuCl_2$: C, 42.06; H, 2.36; N, 16.35; Cu, 34.54. Found: C, 43.10; H, 2.69; N, 16.47; Cu, 17.62.

Triethyl N-[o-(Benzo-2H-triazol-2-yl)phenyl]phosphorimidate

A solution of 16.6 g of triethyl phosphite in 50 ml of benzene was added dropwise to a solution of 20.8 g of 2-(o-azidophenyl)-1,2,4-triazole³ in 200 ml of benzene. When nitrogen evolution ceased, unreacted phosphite and solvent were removed under reduced pressure. The oily residue (32 g) was crystallized from benzene at 5°, mp 28.7–31°; λ_{max} 284 m μ (ϵ 11,420) and 237 (16,500); ν_{max} 3060 w, 2980 m, 2900 w, 1602, 1570 w, 1508 m, 1475 s, 1382, 1360 m, 1340 m, 1292 m, 1263 w, 1215 m, 1170 m, 1132 m, 1112 m, 1025, 968, 828 w, 790 m, 748, and 705 m cm^{-1} .

l. Calcd for $C_{13}H_{11}N_4O_3P$: C, 57.76; H, 6.26; N, 14.97. Found: C, 57.81, 57.90; H, 5.98, 6.31; N, 15.09.

Although this compound decomposed slowly when heated at 100°, the infrared spectrum of the product provided no evidence for presence of III.

1,3a,6,6a-tetraazapentalene. A solution of 5.0 g of III in 200 ml of methylene chloride was stirred vigorously with 25% nitric acid for 7 days. The organic layer was separated and dried with magnesium sulfate. Solvent was removed, and the residue was crystallized from 2.5 l. of boiling 95% ethanol to give 1.23 g of golden yellow platelets. After two recrystallizations from chloroform the mononitro derivative melted at 285–286°; λ_{max} 248 m μ (ϵ 24,800), 313 (11,700), 275 (8930), and 230 (30,700).

l. Calcd for $C_{13}H_7N_5O_2$: C, 56.90; H, 2.79; N, 27.66. Found: C, 57.15; H, 2.85; N, 27.91.

1,3a,6,6a-tetraazapentalene. Five grams of III was added in small portions to 100 ml of concentrated (70%) nitric acid at 0–5°. A vigorous reaction occurred, and 6.4 g of dinitro derivative separated. A portion recrystallized from acetone melted at 400–403° dec; λ_{max} 424 m μ (ϵ 36,700), 2600, 274 (14,300), and 237 (32,400).

l. Calcd for $C_{13}H_5N_5O_4$: C, 48.33; H, 2.03; N, 28.18. Found: C, 48.06; H, 2.01; N, 28.36.

1,3a,6,6a-tetraazapentalene was prepared by the addition of III or its mono- or dinitro derivatives (described above) to ice-cold yellow fuming (95%) nitric acid. The mixture was warmed briefly and poured onto ice. The resulting dinitro derivative was recrystallized from boiling acetone, mp 129–130° dec; λ_{max} 450 m μ (ϵ 54,400), 375 (3240), 308 (17,180), 260 (12,980), and 207 (39,200); ν_{max} 3070 m, 1630 m, 1595 m, 1452 m, 1410, 1375, 1325, 1258, 1190 m, 1165 m, 1116, 1073 m, 869 m, 832 m, 773, 718 m, 740, 728, and 690 cm^{-1} .

l. Calcd for $C_{13}H_4N_5O_4$: C, 37.12; H, 1.04; N, 28.86. Found: C, 36.81; H, 1.46; N, 28.66.

1,3a,6,6a-tetraazapentalenebis(sulfonyl chloride). One gram of III was dissolved cautiously in 10 ml of chlorosulfonic acid and the temperature of the solution was slowly raised to 90°. After 30 min at this temperature the solution was cooled and was poured cautiously onto ice. The solid product was separated by filtration, washed thoroughly with water, and air dried. After two recrystallizations from acetic acid–carbon tetrachloride, the pale crystals melted at 263–265° dec.

Anal. Calcd for $C_{13}H_4N_5O_4Cl_2$: C, 35.58; N, 13.83; S, 15.83. Found: C, 35.62; N, 13.53; S, 15.29.

1-Isopropylidibenzotriazole-1,3a,6,6a-tetraazapentalene Iodide. A stream of propylene was passed for 20 min through a solution of 4.3 g of III in 25 ml of concentrated sulfuric acid at 0°. The solution was allowed to warm to room temperature, and the gas stream was continued for 20 min. The cloudy solution was poured onto 400 g of ice. After standing overnight, the solution was neutralized with sodium bicarbonate and then allowed to stand for 2 weeks. It was then filtered, and a solution of 15 g of sodium iodide in 50 ml of water was added. The whitish precipitate (4.2 g) was separated by filtration. A portion recrystallized from methylene chloride–hexane melted at 174° dec; λ_{max} 276 m μ (ϵ 5480), 338 (22,900), and 348 (sh) (ϵ 21,000); nmr (CD_2SOCD_3) τ 0.9–2.4 (8), multiplet, 4.20 (1), septet (J = 6.5), and 8.17 (6), doublet.

Anal. Calcd for $C_{13}H_{11}N_4I$: C, 47.63; H, 4.00; N, 14.81. Found: C, 47.50; H, 3.99; N, 14.54.

1-(o-Aminophenyl)-4,5,6,7-tetrahydro-1H-benzotriazole (XV). A solution of 45 g of III in 650 ml of ethanol was hydrogenated at 125° and 1000 psi with 3 g of 5% palladium-on-carbon catalyst. The resulting solution was filtered, and solvent was removed under reduced pressure. The residual oil was crystallized from a mixture of 85 ml of benzene and 150 ml of hexane to yield 14.1 g (30%) of XV in two crops. A portion recrystallized from benzene–hexane melted at 115.5–116.2°; λ_{max} 299 m μ (ϵ 3470) and 231 (15,000); λ_{max} 3460, 3380, 3210 m, 2970, 2950, 2850 w, 1635, 1585 m, 1512, 1475 m, 1462 m, 1450 m, 1382 m, 1315 m, 1292 m, 1270 w, 1250 m, 1240 w, 1218, 1158 m, 1136 m, 1088, 1035 w, 1004, 963 m, 934, 848 m, 767, 721 w, and 703 w cm^{-1} .

Anal. Calcd for $C_{12}H_{11}N_4$: C, 67.26; H, 6.58; N, 26.16. Found: C, 67.49; H, 6.91; N, 26.25.

1-(o-Azidophenyl)-4,5,6,7-tetrahydro-1H-benzotriazole (XVI). A solution of 13.9 g of XV in 250 ml of 22% hydrochloric acid was poured onto 150 g of ice and was diazotized at –20 to –25° with a solution of 4.8 g of sodium nitrite in 30 ml of water. The mixture was stirred for 1 hr at –25°, and a solution of 5.0 g of sodium azide in water was added slowly at –20 to –25°. Ether was added to suppress foaming. The resulting solution was allowed to warm slowly to room temperature. It was made alkaline with potassium hydroxide, and the precipitated solid (11.7 g, 75%) was recrystallized from benzene–hexane; mp 105–106.5°; λ_{max} 248 m μ (ϵ 12,300).

Anal. Calcd for $C_{12}H_{12}N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 60.53; H, 5.27; N, 35.72.

4,5-Tetramethylene-2,3-benzo-1,3a,6,6a-tetraazapentalene (XVII). A solution of 8.0 g of XVI in 50 ml of o-dichlorobenzene was added slowly to 40 ml of o-dichlorobenzene in a flask immersed in an oil bath maintained at 180°. After 1 hr nitrogen evolution had ceased. Solvent was removed under reduced pressure (70° (0.3 mm)), and the residue was dissolved in methylene chloride and eluted continuously with methylene chloride through a column of Woelm neutral alumina.

The eluate was evaporated under reduced pressure, and the resulting nearly white crystals (3.75 g, 53%) were recrystallized from ethanol and from methanol to yield shiny colorless leaflets melting at 176.5–177.5°. A second crystalline modification could also be isolated (see Table I for ultraviolet absorptions); ν_{max} 3060, 2940, 2850 w, 1615, 1582, 1510, 1480, 1445, 1432 m, 1405 m, 1372, 1335 m, 1245 m, 1230, 1208 m, 1128, 1080 m, 1020, 995, 970, 922, 893, 872, 837, 818, m, 744, 731, 732, and 693 cm^{-1} .

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.07; H, 5.71; N, 26.17, 26.41, 26.42.

This compound, like III, formed a blue complex with tetracyanoethylene, but did not react further in DMF solution, and so did not yield a tricyanovinyl analog of XVIII.

Aromatic Azapentalenes. IV. Heats of Combustion of Monobenzo- and Dibenzo-1,3a,6,6a-tetraazapentalenes and Monobenzo- and Dibenzo-1,3a,4,6a-tetraazapentalenes. The Structure of Tetraazapentalenes

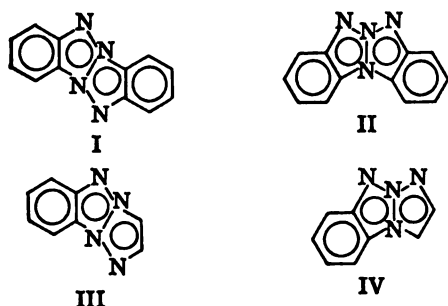
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Abstract: Precise heats of combustion and sublimation were determined for four derivatives of the recently synthesized 1,3a,6,6a- and 1,3a,4,6a-tetraazapentalene ring systems. The heats of formation referred to the gas phase in standard states were determined to be: dibenzo-1,3a,4,6a-tetraazapentalene (I), 142.8 ± 1.3 kcal/mole; dibenzo-1,3a,6,6a-tetraazapentalene (II), 132.1 ± 1.5 kcal/mole; monobenzo-1,3a,4,6a-tetraazapentalene (III), 136.4 ± 1.2 kcal/mole; and monobenzo-1,3a,6,6a-tetraazapentalene (IV), 128.2 ± 1.3 kcal/mole. From resonance energy considerations, these molecules appear aromatic in the usual thermodynamic sense. The aromaticity of the ten π -electron tetraazapentalene nuclei is discussed theoretically.

Previous papers in this series¹ have shown that dibenzo-1,3a,4,6a-tetraazapentalene (I), dibenzo-1,3a,6,6a-tetraazapentalene (II), and their monobenzo analogs III and IV have chemical properties that indicate the ten π -electron tetraazapentalene nuclei are aromatic. In the present paper the results of measurements of the heats of combustion and sublimation of I-IV are given, and the structure and spectra of these compounds are discussed in more detail.



Experimental Section

A. Purification of Compounds. The compounds studied (I-IV) were purified by recrystallization from organic solvents and sublimation, and then by temperature-gradient sublimation. Infrared, ultraviolet, and mass spectral analyses were used to assay the final products, which were judged to be of high purity.

B. Heat of Combustion Measurements. The apparatus and procedures recommended by Jessup² were generally used with the following exceptions. The Mueller bridge was connected to a microvolt-indicating amplifier (both obtained from Leeds and Northrup Co.), and the latter was then connected to a recorder. Thus, the time of each of the different resistance settings at the "fast temperature change period" and the resistance measurements (to the fifth decimal place) during the initial and final periods were obtained from the chart of the recorder.

The calorimeter used was manufactured by Precision Scientific Co. (National Bureau of Standards Calorimeter Catalog No. 63090, Serial No. 10-R-4) and was calibrated by combustion of benzoic acid (National Bureau of Standards Sample No. 39i).

(1) (a) R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Am. Chem. Soc.*, **89**, 2618 (1967); (b) R. A. Carboni and J. C. Kauer, *ibid.*, **89**, in press; (c) J. C. Kauer and R. A. Carboni, *ibid.*, **89**, 2633 (1967).

(2) R. S. Jessup, National Bureau of Standards Monograph No. 7, U. S. Department of Commerce, Washington, D. C., Feb 26, 1960.

The energy equivalent of the calorimeter was 5022.0 cal in the range 25.0–27.0° and was determined initially by an average of combustions with a standard deviation of 0.016%. The bomb was checked periodically, but no significant change was detected during the measurements.

A Parr bomb (no. 1101 double valve) was used for the combustion, however, in order to permit mass spectral analysis of the products of the combustion, a plain Hoke valve was used for the outlet valve.

The tetraazapentalenes I-IV were very difficult to burn; samples could be burned completely, but the temperature of the bomb was insufficient. By using a sample of benzoic acid as binder (wt % of benzoic acid = 35%), it was possible to achieve complete combustion (confirmed by mass analysis) of samples of adequate size. Both the benzoic acid and the tetraazapentalene were ground separately and weighed into two separate containers, then thoroughly mixed and ground again in a mortar, and desired amounts of the mixture were removed and pelletized. The percentage composition of the pellet was to be the same as the composition of the mixture before pelletization.

A total of 1 ml of conductivity-grade water was introduced into the bomb with half the water placed in a platinum combustion crucible to ensure solution of all the nitrogen produced.³ Mass spectrometry consistently showed the presence of NO₂ in the gas products.

In order to make sure that none of the nitrogen in the tetraazapentalenes was further oxidized to N₂O, NO, or other oxidation products of nitrogen, mass spectrometry was used to analyze the gas product from the combustion. No evidence of other nitrogen compounds except N₂ in the final gas product was found.

The washings of the bomb were titrated with standard sodium hydroxide solution to determine the nitric acid formed, and a correction was used in the subsequent calculation of the heat of combustion. The final solution was then analyzed for nitrate, but none was ever detected.

C. Vapor Pressure Measurements. The McLeod gauge was used to measure the vapor pressure of I-IV as a function of temperature. A 1-l. bulb was attached to the McLeod gauge through a 2-mm capillary which was about 4 in. in length. The trap was placed at the end of the capillary, and cold nitrogen was blown through the cold trap whose temperature was periodically checked by a thermocouple. Nitrogen was used as the gas in the system. A stainless steel wire soldered to a manometer hung inside the tube above the cold trap. During the vapor pressure measurements at higher temperatures, the stainless steel wire could be moved up and down by an outside magnet to prevent the wire from touching the trap.

(3) G. T. Armstrong and S. Marantz, *J. Phys. Chem.*, **64**, 17 (1960).

(4) G. W. Thomson in "Technique of Organic Chemistry, Methods," Part I, A. Weissberger, Ed., 3rd ed, Interscience Publishers, New York, N. Y., 1959, p 457.

ry tube from becoming plugged. The reference temperature i° for the dibenzo derivatives I and II and 0° for the mono-derivatives III and IV. At the reference temperature, the pressure due to the sample studied was assumed to be negligible. Vapor pressures of the dibenzo derivatives were measured from 90 to 160° (or 170°) and of monobenzo derivatives from 100° (or 110°), both at 10° intervals. The apparatus was checked by measuring the vapor pressure of purified benzene at 110 , 120 , and 130° , and the results agreed well with reported in the literature.⁶

ts and Calculations

Heat of Combustion Results. The corrected temperature rise of a combustion run was computed using a least-squares straight line through the initial (min) and final (23–30 min) periods and computing arithmetically the appropriate integral. These computations were programmed for and carried out by an IBM computer.

As noted above, nitrogen dioxide was the only oxidation product of nitrogen detected in the combustion of the four tetraazapentalene derivatives; moreover, the nitrogen dioxide formed was dissolved in the water, forming nitric acid. Thus, the combustion reactions of the compounds studied can be written as



The energy of combustion could be calculated on the basis of the above equations from the corrected temperature rise with appropriate corrections for the formation of nitric acid. Table I summarizes the results of combustion experiments. The first and second columns represent the weights in air of sample and benzoic acid, respectively, and the third column (ΔE_t) gives the total energy of combustion for the bomb process calculated from the corrected temperature rise.

The values of q_1 and q_2 are corrections for the fuse and nitric acid, respectively. The sixth column gives the bomb burn corrections,⁶ and ΔE_B in the seventh column is the energy of combustion due to benzoic acid. The last column is the energy of combustion due to the sample and has been corrected to standard state, *i.e.*

$$-\Delta E_c^\circ = (-\Delta E_t - q_1 - q_2 - q_3 + \Delta E_B)/M$$

The average value of ΔE_c° was corrected finally for density of air, and the uncertainty represents the standard deviation.

The standard state heats of combustion (ΔH_c°) were calculated from the values of $-\Delta E_c^\circ$ and the combustion reactions written above.⁷ From the values of the heat of combustion (third column, Table II) and the heat of formation of water and carbon dioxide, the heat of formation [$\Delta H_f^\circ(s)$] of the four tetraazapentalenes in solid form and standard state were derived and are reported in the last column of Table II.

⁶ S. Mortimer and R. V. Murphey, *Ind. Eng. Chem.*, **15**, 1140 (1923); but see G. W. Sears and E. R. Hopke, *J. Am. Chem. Soc.*, **71**, 3499 (1949).

⁷ F. D. Rossini, "Experimental Thermochemistry," Interscience Publishers, Inc., New York, N. Y., 1956; (b) E. J. Prosen, National Bureau of Standards Report 1119, Washington, D. C., Aug 6, 1951.

The authors are grateful to Professor J. L. Margrave and Miss L. K. Barker who communicated privately to them their preliminary results on compound I which were in substantial agreement with those reported here.

Table I. Energy of Combustion, 25°

M, g	M', g	cal					$-\Delta E_0^\circ$, cal/ g, air
		$-\Delta E_t$	q_1	q_2	q_3	$-\Delta E_B$	
Dibenzo-1,3a,4,6a-tetraazapentalene (I)							
0.83169	0.44593	8956.0	5.2	24.3	4.3	2817.5	7340.0
0.82623	0.44301	8898.9	5.2	23.2	4.3	2799.0	7343.2
0.83295	0.44661	8972.2	5.2	23.6	4.3	2821.8	7344.2
0.83355	0.44693	8974.2	5.2	25.6	4.3	2823.8	7336.5
0.83336	0.44683	8980.7	5.2	25.0	4.3	2823.1	7347.3
0.82148	0.47210	9050.2	5.2	24.3	4.3	2982.8	7344.7
							Av 7342.7
$-\Delta E_0^\circ(I) = 7337.6 \pm 4.4$ cal/g, vac							
Dibenzo-1,3a,6,6a-tetraazapentalene (II)							
0.82084	0.45884	8950.2	5.2	28.3	4.3	2899.0	7325.8
0.81883	0.45772	8923.5	5.2	22.5	4.3	2891.9	7326.9
0.83620	0.44292	8955.6	5.2	24.2	4.3	2798.5	7322.9
0.82020	0.45809	8930.6	5.2	24.8	4.3	2894.3	7317.7
							Av 7323.3
$-\Delta E_0^\circ(II) = 6805.6 \pm 3.7$ cal/g, vac							
Monobenzo-1,3a,4,6a-tetraazapentalene (III)							
0.94969	0.50462	9696.8	5.2	29.3	7.4	3188.3	6809.2
0.86309	0.48620	8995.1	5.2	28.2	7.4	3071.9	6815.5
0.86072	0.48568	8966.7	5.2	28.1	7.4	3068.6	6805.3
0.87789	0.47524	9022.3	5.2	28.0	7.4	3002.7	6810.6
							Av 6810.1
$-\Delta E_0^\circ(III) = 6805.6 \pm 3.7$ cal/g, vac							
Monobenzo-1,3a,6,6a-tetraazapentalene (IV)							
0.86113	0.49117	8978.2	5.2	24.5	7.4	3103.3	6779.2
0.86356	0.48804	8975.9	5.2	27.9	7.4	3083.5	6776.4
0.86377	0.48816	8979.8	5.2	29.3	7.4	3084.3	6776.7
0.84640	0.50534	8964.6	5.2	28.2	7.4	3192.8	6770.8
							Av 6775.8
$-\Delta E_0^\circ(IV) = 6771.3 \pm 3.1$ cal/g, vac							

lenes in solid form and standard state were derived and are reported in the last column of Table II.

The logarithm of the vapor pressures of the four compounds studied were plotted against the reciprocal of temperature. From the slopes of the straight lines obtained (Figure 1), it is possible to calculate the heats of sublimation at 298°K of these compounds. These values were also checked by the least-squares method and are listed in the fourth column of Table II; the uncertainty was also calculated by the least-squares method. No corrections were made for the variation of the heats of sublimation from the temperature range in which they were measured to 298°K . From the heats of sublimation and the heats of formation of the solid tetraazapentalene derivatives, it is possible to calculate the heats of formation referred to gaseous form in standard states. These are also listed in the last column of Table II.

As shown in Table II, the difference in heats of formation of I and II was found to be 10.7 kcal/mole, indicating that II is more stable than I. Similarly, IV was 8.2 kcal/mole more stable than III. These findings are in accord with theoretical considerations as discussed in the next sections.

Discussion

Resonance Energies. The estimation of resonance energies is always fraught with uncertainties, and it is expected to be particularly so with molecules such as the tetraazapentalenes in which many formal struc-

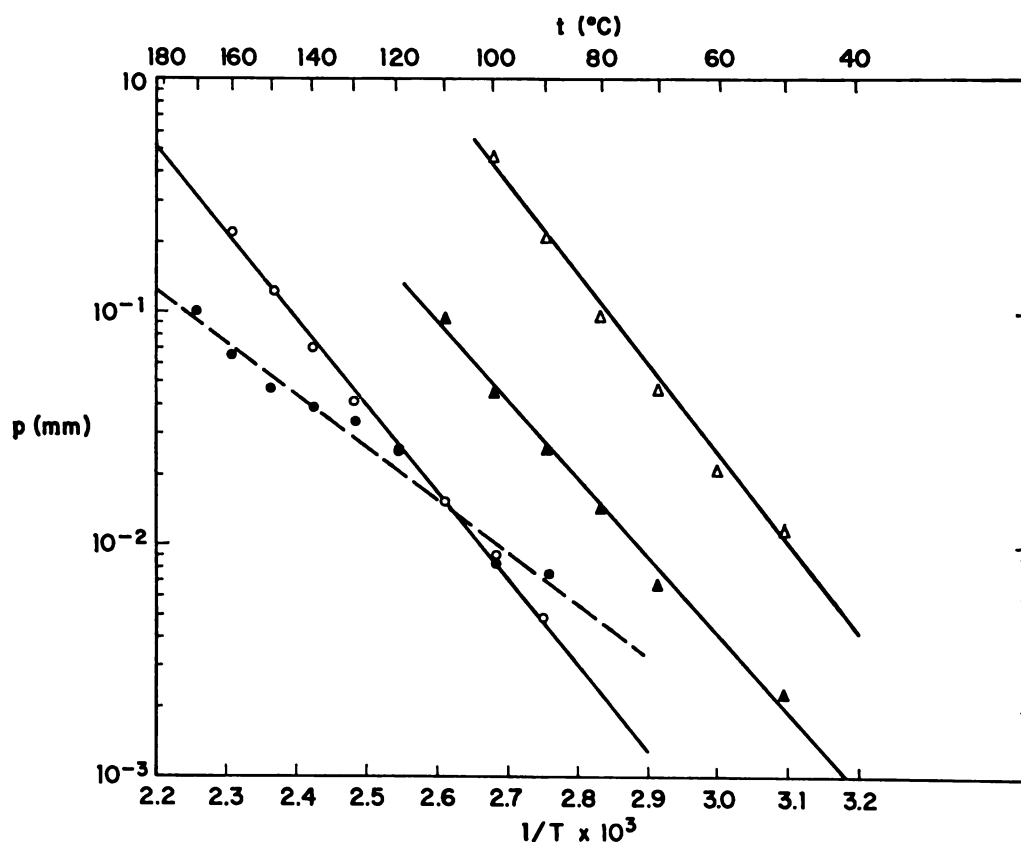


Figure 1. Temperature dependence of the vapor pressure of tetraazapentalenes: O, I; ●, II; Δ, III; ▲, IV.

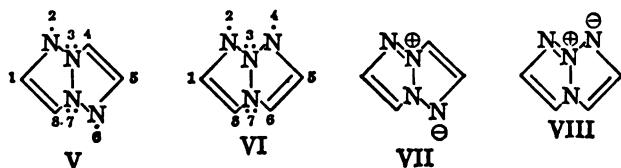
tures contribute to the ground state.^{1a} We have determined the empirical resonance energies of these compounds using two bases for the azapentalene nuclei: (1) the unique noncharge-separated structures V and

The heats of combustion were calculated according to the method of Klages as modified by Wheland.⁸ For the calculation of series 1, a uniform value for the contribution to the heat of combustion of all N-N bonds

Table II. Heats of Combustion and Formation of Tetraazapentalenes

Compd	kcal/mole			
	$-\Delta E_o^\circ$	ΔH_o°	ΔH_{sub}	ΔH_f°
I(s)	1527.9 ± 0.9	-1527.9 ± 0.9	16.8 ± 0.4	126.0 ± 0.9
I(g)				142.8 ± 1.3
II(s)	1523.9 ± 0.7	-1523.9 ± 0.7	10.1 ± 0.8	122.0 ± 0.7
II(g)				132.1 ± 1.5
III(s)	1076.4 ± 0.6	-1075.8 ± 0.6	17.9 ± 0.7	118.5 ± 0.5
III(g)				136.4 ± 1.2
IV(s)	1071.0 ± 0.5	-1070.4 ± 0.5	15.2 ± 0.7	113.0 ± 0.6
IV(g)				128.2 ± 1.3

VI, and (2) the charge-separated structures VII and VIII. The former structures emphasize that the ten π electron tetraazapentalene systems formally contain two



pyridine-like and two pyrrole-like nitrogen atoms. At first sight this seems to be a poor choice, since, e.g., VII has one more bond than V, and thus the empirical resonance energy might be overestimated when V is used as the basis. The energy of the extra bond is, however, largely offset by the large formal charge separation.

was determined from the heat of combustion of gaseous hydrazine ($\Delta H_c^\circ = -154.99$ kcal/mole)⁹ and was found to be $\lambda(\text{N-N}) = 33.0$ kcal/mole. The heats of combustion of both I and II were found to be -1666.4 kcal/mole. The resonance energies are then $E_R(\text{I}) = 121.7$ kcal/mole and $E_R(\text{II}) = 132.4$ kcal/mole. For series 2, the N=N bond contribution determined by Coates and Sutton¹⁰ was employed, $\lambda(\text{N=N}) = 34.2$ kcal/mole, giving a heat of combustion of -1667.6 kcal/mole for both I and II. The resonance energies were thus determined to be $E_R(\text{I}) = 122.9$ kcal/mole and $E_R(\text{II}) = 133.6$ kcal/mole. The agreement between the two esti-

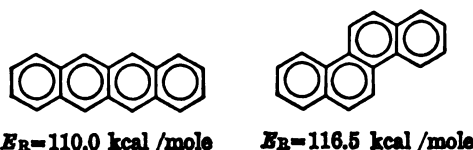
(8) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, pp 88-89.

(9) "Selected Values of Chemical Thermodynamic Properties," National Bureau of Standards Circular 500, Washington, D. C., 1952.

(10) G. E. Coates and L. E. Sutton, *J. Chem. Soc.*, 1187 (1948).

is very good. Because the models for I and II are allyl equivalent with regard to kinds of bonds, the experimental heats of formation reflect the resonance energies directly.

It is seen that the more angular-shaped molecule II is 10.7 kcal/mole stable than the linear-shaped I. This behavior is typically that of pure benzenoid hydrocarbons where the analogs of I and II, naphthalene and chrysene, respectively, have resonance energies⁸ known. Here the angular hydrocarbon is more stable

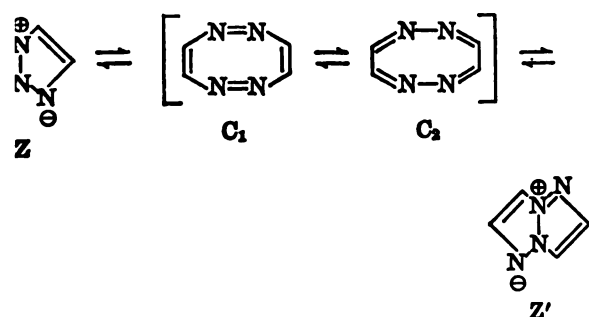


the linear by 6.5 kcal/mole. It is interesting to note that the resonance energies of I and II are larger than those of their isoelectronic hydrocarbon counterparts.

If we consider that each benzene ring in I and II contributes roughly 36.0 kcal/mole to the resonance energy, the contributions of the 1,3a,4,6a- and 1,3a,6,6a-azapentalene nuclei in I and II, respectively, are 49.7 (50.9) and 60.4 (61.6) kcal/mole for the series 1 and 2, respectively. The naphthalene-like nuclei of naphthalene and chrysene contribute 38.0 and 48.0 kcal/mole, respectively, to the resonance on this basis.

Calculations using similar models for the monobenzo derivatives III and IV give theoretical heats of combustion of -1178.4 kcal/mole for series 1 and -1179.6 kcal/mole for series 2. The empirical resonance energies $E_R(\text{III}) = 84.7$ (85.9) kcal/mole and $E_R(\text{IV}) = 94.0$ (94.0) kcal/mole. The contributions of the tetraazapentalene nuclei are then 48.7 and 56.8 kcal/mole, respectively, in rough agreement with the values derived from the dibenzo derivatives.

Electronic Structure of Tetraazapentalenes. The relationship between the structure of the tetraazapentalene and the valence isomerization (e.g., $Z \rightarrow Z'$) which destroys aromaticity was discussed in paper I.^{1a} HMO



MO theory predicts that the delocalization energy per π electron is larger in pentalene dianion than in a fictitious cyclooctatetraene, and the same situation prevails for the nitrogen analogs.

MO calculations were carried out for Z, C_1 , and C_2 assuming the reasonable parameters¹¹ $\alpha_N = \alpha_C + 1.5\beta$ (pyrrole-like), $\alpha_N = \alpha_C + \beta$ (pyridine-like), and $\alpha_N = \alpha_C$ (all $\beta = \beta_{CC}$). If we base the delocalization energy of tetraazapentalene on one covalent structure such as Z, then the results in Table III are obtained.

A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 135.

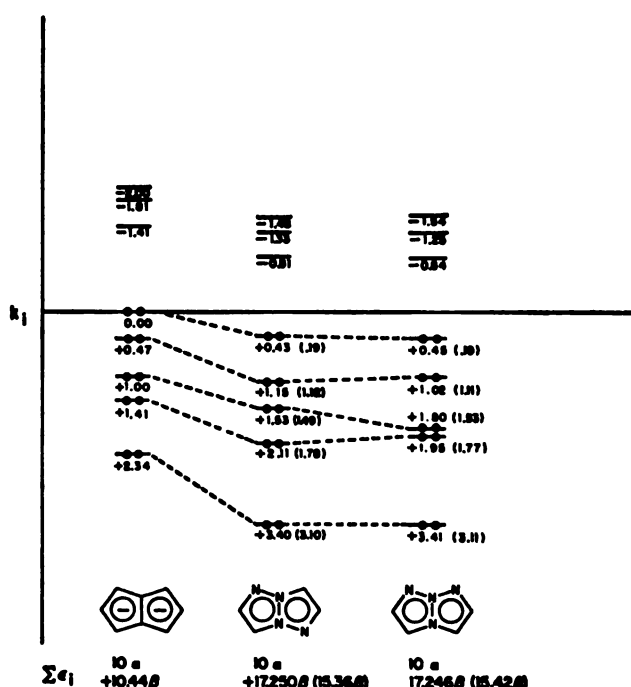


Figure 2. Energy level diagrams, $\epsilon_i = \alpha + k_i\beta$.

It is evident that the azapentalene structure is highly stabilized by electron delocalization on the basis of the delocalization energy per π electron, compared to either eight-membered ring structure. Since the latter structures would most likely exist in tub conformations, these values are also included, and it is seen that the azine form C_2 is slightly preferred over the azo form C_1 .

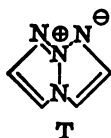
Table III. Energies of Z, C_1 , and C_2

	Total energy	Delocalization energy, β^{-1}	Delocalization energy/ π electron
Z	$10\alpha + 17.250\beta$	4.421	0.44
C_1 (planar)	$8\alpha + 14.314\beta$	2.314	0.29
C_1 (tub form)	$8\alpha + 12.000\beta$	~ 0	~ 0
C_2 (planar)	$8\alpha + 14.314\beta$	1.369	0.17
C_2 (tub form)	$8\alpha + 12.944\beta$	~ 0	~ 0

The chemical reaction C_1 (or C_2) \rightarrow Z involves the change of two nitrogen atoms from the valence state ($\text{tr}^2\text{tr}^2\pi$) to ($\text{tr}^2\text{tr}^2\pi^2$). This energy which amounts to 6.2 eV¹² must be less than the gain in π -delocalization energy plus the energy of the new N-N σ bond for this reaction to proceed. Therefore, since $E_\sigma(\text{N-N}) \sim 2.6$ eV, then $E_\pi(\text{Z}) - E_\pi(\text{C}_1) = 2\alpha + 5.25\beta$ must be greater than 3.6 eV. Any reasonable estimate of the integrals involved assures us that this is indeed so, and we conclude that the process C_1 (or C_2) \rightarrow Z will be exothermic. Similar conclusions can be drawn about the tetraazapentalene nucleus in III.

Molecular orbitals were calculated for T, the nucleus of III, using the same integral values, and the energy level diagrams in Figure 2 compare Z, T, and pentalene dianion. First, it is to be noted that all bonding levels are displaced to lower energies as expected, when nitro-

(12) J. Hinze and H. H. Jaffé, *J. Am. Chem. Soc.*, **84**, 540 (1962).



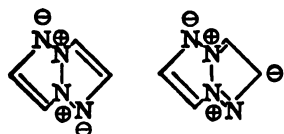
gen is introduced into the nucleus of pentalene dianion. Second, it is clear that the position of the nitrogen atoms has very little effect on the energy levels or the total energy. This kind of behavior would be expected if the tetraazapentalene nucleus is aromatic and its π electrons highly delocalized. The bond orders and charge distribution of Z and T are also very similar, in further confirmation of this conclusion (Table IV).

Table IV. Bond Orders and Charge Densities of Z and T

<div style="display: flex; justify-content: space-around; align-items: center;"> </div>			
Bond orders			
12	0.421	12	0.443
23	0.514	34	0.581
34	0.739	45	0.751
45	0.588	56	0.491
26	0.433	26	0.435
Charge densities			
1,5	1.497	1,3	1.490
2,6	1.447	2	1.436
		6	1.454
3,7	1.080	5,7	1.082
4,8	0.976	4,8	0.983

These crude calculations are sufficient for our purpose of explaining the aromaticity of the tetraazapentalenes. The results suggest that Z and T are close in energy, and similar calculations on I and II show that the mono- and dibenzo derivatives have delocalization energies that do not depend much on the location of the nitrogen atoms. More accurate calculations indicate that II is slightly more stable than I, and this conclusion is in accord with precise thermodynamic data.

A better estimate of the energy levels of the azapentalenes can be made by considering their structures more closely. In an HMO calculation some means must be found for estimating the parameters, since a given nitrogen atom occurs successively in various valence states depending on the canonical structures. In the 1,3a,6,6a system there are 12 resonance structures like VII which are nonexcited in the Pauling sense. Presumably, most of these make significant contributions to the ground state, and monoexcited structures such as



will contribute to a lesser extent.

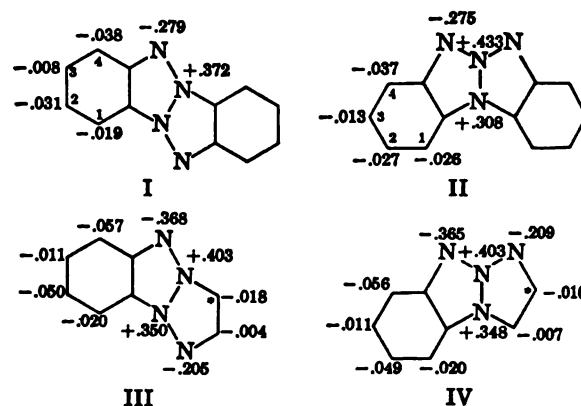
We estimate the HMO coulomb (h) and resonance (k) parameters in the following way. For each nitrogen in a fixed position a factor was determined that corresponds to the number of times it occurs as a pyridine, pyrrole, quaternary, and amide type. The usual Hückel

parameters suggested by Streitwieser¹¹ were then weighted by these factors to determine an average parameter for each nitrogen. The monoexcited structures were taken into account the same way, but weighted only one-tenth relative to the nonexcited. The β 's were determined similarly. In this manner, valence-bond structures were used to estimate the molecular orbital parameters. For our purpose, the systems are numbered as in V and VI. The resulting one-electron parameters are

V	VI
$h_2 = +0.383$	$h_2 = +0.388$
$h_3 = +1.733$	$h_3 = h_7 = +1.747$
$k_{23} = k_{27} = k_{34} = +0.80$	$k_{23} = k_{27} = k_{27} = +0.80$
$k_{12} = k_{45} = +1.00$	$k_{12} = k_{45} = +1.00$

The energy levels are given in parentheses in Table IV, and it is thought that these results are close to self-consistent values. The total energies of the dibenzo derivatives are $E(I) = 18\alpha + 26.904\beta$, $E(II) = 18\alpha + 27.002\beta$ and of the monobenzo derivatives, $E(III) = 14\alpha + 21.152\beta$, $E(IV) = 14\alpha + 21.210\beta$. The corresponding delocalization energies based on the non-charge-separated structures are $E_D(I) = 7.905\beta$, $E_D(II) = 8.004\beta$, $E_D(III) = 6.151\beta$, and $E_D(IV) = 6.213\beta$. Isomer II is predicted to be more stable than I, and similarly IV more stable than III, in accord with the experimental heats of formation. It is expected that the difference in delocalization energies, e.g., $E_D(II) - E_D(I)$, should be proportional to the difference in heats of formation. Thus, $8.004\beta - 7.905\beta = 10.7$ kcal/mole, or $\beta(\text{empirical}) = 108.1$ kcal/mole. It is calculated for the monobenzo derivatives than $E_D(IV) - E_D(III) = 0.062\beta = 6.7$ kcal/mole, while the experimental value is 8.2 kcal/mole, in satisfactory agreement.

Charge distributions were calculated for I-IV, and the results are shown below. If electrophilic substitution in these molecules parallels electron density in the



ground state, then the 2 and 4 positions in the benzene rings of I and II should be preferentially nitrated, chlorinated, etc., and this seems to be the case.^{1b,c} Electrophilic attack in the tetraazapentalene nucleus is predicted to occur preferentially at the positions marked by asterisks in III and IV, and substitution products^{1b,c} are believed to have these structures. It is interesting to note that HMO calculations employing the usual parameters¹¹ for these charge-separated structures give charge distributions that make the benzene rings assume small net positive charges and predict incorrect orientation for electrophilic substitution. Experi-

ally, I and II are nitrated, for example, more readily than benzene, an observation in accord with the nearly self-consistent calculations.

The bond orders of the N-N central bonds in the tetraazapentalene nuclei have the values $\rho_{NN} = 0.300$ (II), 0.300 (III), 0.297 (IV). The bond orders of the C-C central bonds in pentalene dianion and naphthalene are $\rho_{CC} = 0.531$ (PA), 0.518 (N), and the ρ of density in the central bond region is characteristic of normal aromatic structures. The approximate bond orders of the tetraazapentalenes in this region support the conclusion that these molecules are aromatic.

The ultraviolet spectra of I and II are complicated but not unlike those expected for fully aromatic structures.^{1a} In naphthalene, which contains ten π electrons, the three lowest observed singlet states correspond to those predicted by Pariser-Parr theory (employing singly excited configurations)^{13,14} which occur at 4.57 ($^1B_{2u}$), 4.48 ($^1B_{2u}$), and 5.92 eV ($^1B_{2u}$), and only the latter two are allowed. The B_{2u} state is derived from the configuration V_{56} , obtained by promoting an electron from MO 5 to MO 6. The two states are obtained mostly from mixing of V_{57} and V_{46} which interact strongly because their energies are close. Although $E(V_{56}) < E(V_{57}) = E(V_{46})$, the V_{56} depresses one of the resulting B_{2u} states so that it actually occurs below the B_{2u} state.

The isoelectronic pentalene dianion shows two strong absorptions in the ultraviolet region¹⁵ which agree with the spectrum calculated by Pariser-Parr configuration interaction theory.¹⁶ The three lowest singlets corre-

sponding to those observed for naphthalene are predicted to occur at 4.57 ($^1B_{2u}$), 5.12 ($^1B_{2u}$), and 7.11 eV ($^1B_{2u}$), and here all three are allowed. The states of same symmetry are formed primarily from the same configurations as in naphthalene, but the nonalternant character of the molecular orbitals precludes the strong degenerate mixing of V_{46} and V_{57} . Thus, the B_{2u} state is the lowest, in accord with the observation that $E(V_{56}) < E(V_{57})$ or $E(V_{46})$. In pentalene dianion, the high-energy B_{2u} state occurs in the vacuum ultraviolet and has not yet been identified.

Three similar absorptions are expected to occur in the tetraazapentalenes Z and T. Inspection of Figure 2 shows that on going from pentalene dianion to Z, V_{56} decreases strongly in energy, V_{57} decreases only slightly, and V_{46} increases slightly. On going to T, V_{56} decreases less strongly than in Z, V_{57} decreases more strongly, and V_{46} decreases slightly. When two benzene rings are fused on Z and T to form I and II, the characteristic properties of the states in question are anticipated to be largely preserved.

Although the assignments for the spectra of I and II are yet unknown, it is reasonable that the three regions of absorption in them correlate with the three lowest energy configurations discussed above. From Table I in paper I we see that the two longest wavelength regions of I are indeed red shifted with respect to the aromatic hydrocarbon analog chrysene, and the highest energy absorption is blue shifted, as predicted. Also, in accord with expectation, the long-wavelength absorption of II is blue shifted with respect to that of I and occurs actually at about the same place as that in chrysene. The next two bands in II, however, are also blue shifted with respect to those in I. This crude picture is satisfying and is all we might have hoped for using such poor molecular orbitals as a basis and neglecting electron repulsion effects.

R. Pariser, *J. Chem. Phys.*, **24**, 250 (1956).

H. E. Simmons, *ibid.*, **40**, 3554 (1964).

T. J. Katz and M. Rosenberger, *J. Am. Chem. Soc.*, **84**, 865

H. E. Simmons, unpublished results.

Aromatic Azapentalenes. V. 1,1'- and 1,2'-Bibenzotriazoles and Their Conversion to Dibenzotetraazapentalenes

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Abstract: The syntheses, physical properties, and structural assignments for 1,1'-bibenzotriazole (4a) and 1,2'-bibenzotriazole (8) are described. Both 4a and 8 lose nitrogen on heating to give dibenzo-1,3a,4,6a-tetraazapentalene (1) and dibenzo-1,3a,6,6a-tetraazapentalene (2), respectively.

In earlier papers in this series,^{1,2} the synthesis of dibenzo-1,3a,4,6a-tetraazapentalene (1) by thermal photochemical decomposition of *o,o'*-diazidoazobenzene was described. This interesting heteroaromatic compound has now been prepared by an alternative route,

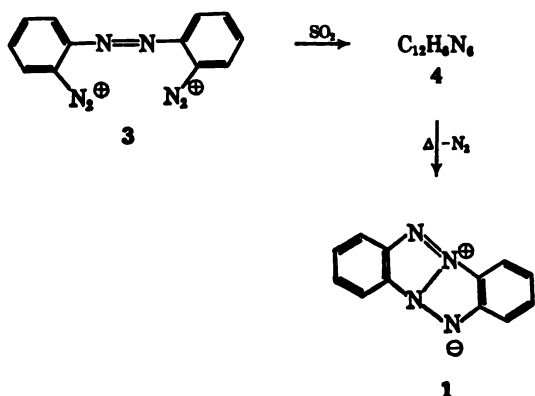
R. A. Carboni and J. E. Castle, *J. Am. Chem. Soc.*, **84**, 2453

R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *ibid.*, **89**, 2618 (1967).

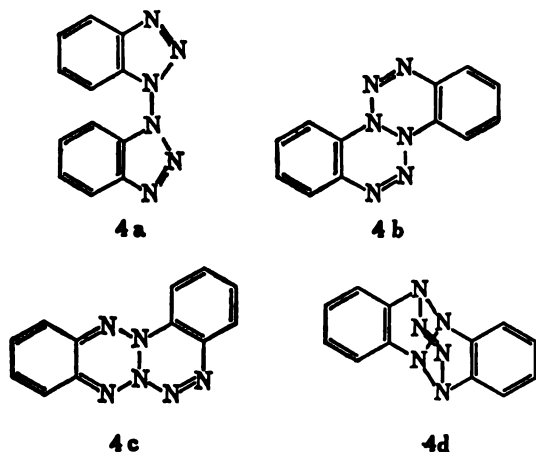
i.e., through controlled thermal decomposition of 1,1'-bibenzotriazole (4). A similar thermolysis occurs with the isomeric 1,2'-bibenzotriazole (8) to form the corresponding dibenzo-1,3a,6,6a-tetraazapentalene (2).³ This paper discusses the synthesis, proof of structure, and decomposition of the hexaaza compounds 4 and 8.

1,1'-Bibenzotriazole. The hexaaza derivative 4 was prepared in good yield from tetraazotized *o,o'*-diamino-

azobenzene. When sulfur dioxide was passed rapidly through a cold aqueous solution of the *o,o'*-azobenzene-bisdiazonium salt (3), the product 4 precipitated as a tan solid. Elemental analyses and molecular weight determinations on the purified colorless solid, mp 235° dec, are in accord with the empirical formula $C_{12}H_8N_6$.



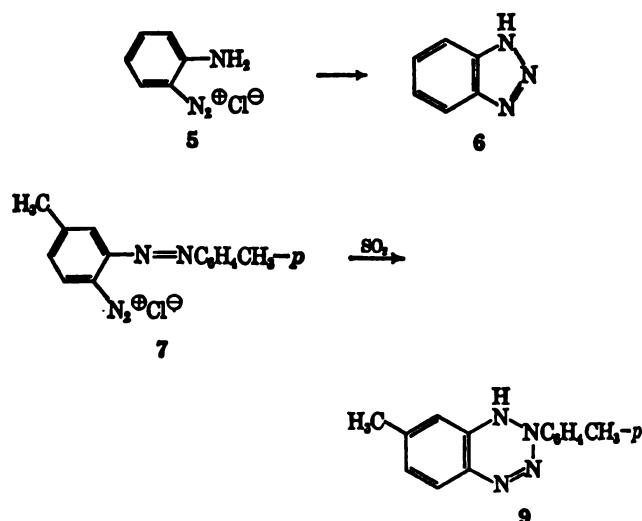
The synthetic route to 4 and the subsequent decomposition to 1 suggest four possible structures, 4a-d, for the hexaaza product. These structures may form



by the addition of an electron to each diazonium group followed by addition of the resulting radicals to the azo group, either directly or with rearrangement of electrons.

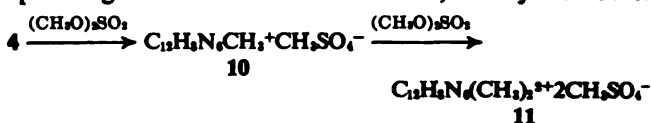
Alternatively, 4a and b may form *via* the intermediate hydrazo derivative by reaction of the diazonium groups with (a) their respective α -nitrogens (to give 4a) or (b) their respective β -nitrogens (to yield 4b). Intramolecular coupling of the first type occurs in the diazotization of *o*-phenylenediamine, where the intermediate *o*-aminobenzenediazonium ion (5) reacts with the amino substituent to yield 1H-benzotriazole (6).³ On the other hand, Zincke and Lawson⁴ observed that treatment of *o*-(*p*-tolylazo)-*p*-toluenediazonium chloride (7) with a reducing agent such as stannous chloride or sulfur dioxide produced a crystalline product which was assigned the benzotetraazine structure 9.

The ultraviolet spectrum of 4 shows two absorption maxima, at 252 $m\mu$ (ϵ 14,630) and 288 $m\mu$ (ϵ 7790). Thus a strong resemblance to the absorption spectrum of 1H-benzotriazole and 1-methylbenzotriazole is evident (Figure 1), providing a preference for the 1,1'-



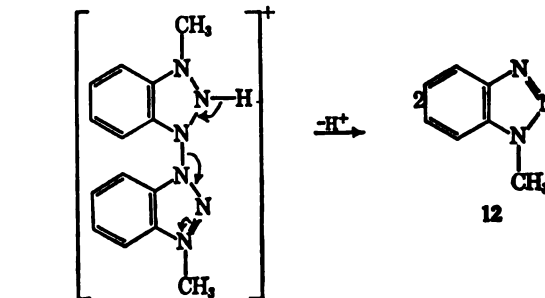
bibenzotriazole structure 4a. Compounds 4b and c which contain the aryl $-\text{N}=\text{N}-\text{N}-$ group in a six-membered ring would be expected to exhibit absorption at considerably longer wavelengths. For example, 3-phenyl-3,4-dihydro-1,2,3-benzotriazine exhibits an absorption maximum at 360 $m\mu$.⁵ Nuclear magnetic resonance (proton) spectroscopy was of little value for the structure proof, ill-defined spectra being obtained because of the low solubility of 4 in organic solvents.

Treatment of 4 with dimethyl sulfate gave successively a monoalkylation product 10 and a dialkylation product 11. Methosulfates 10 and 11 are both water soluble and can be readily converted to the corresponding isolable iodides. However, the hydroxide of



bismethosulfate 11 rapidly decomposed in water at room temperature to give 1 molar equiv of 1-methylbenzotriazole (12).⁶ This provides a clear preference for the 1,1'-bibenzotriazole structure 4a, in agreement with the ultraviolet spectral data. Thus, the formation of 12 may be represented by the sequence 4a \rightarrow 10 \rightarrow 11 shown in Figure 2.

Further evidence for the bisbenzotriazole structure was obtained by the facile reductive cleavage of the bismethosulfate 11 by lithium aluminum hydride. When an ether solution of 11 was treated with excess lithium aluminum hydride at room temperature, an excellent yield (93%) of 1-methylbenzotriazole (12) (2 molar equiv) was obtained. Presumably the same kind of scission occurs here as in the hydroxide decomposition.



(3) R. E. Damschroder and W. D. Peterson, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 106.
 (4) Th. Zincke and A. Th. Lawson, *Ber.*, 19, 1452 (1886).

(5) P. Ramart-Lucas and J. Hoch, *Bull. Soc. Chim. France*, 447 (1949).
 (6) 1-Methylbenzotriazole 2-N-oxide is assumed to be the other product of the hydroxide decomposition, but was not isolated.

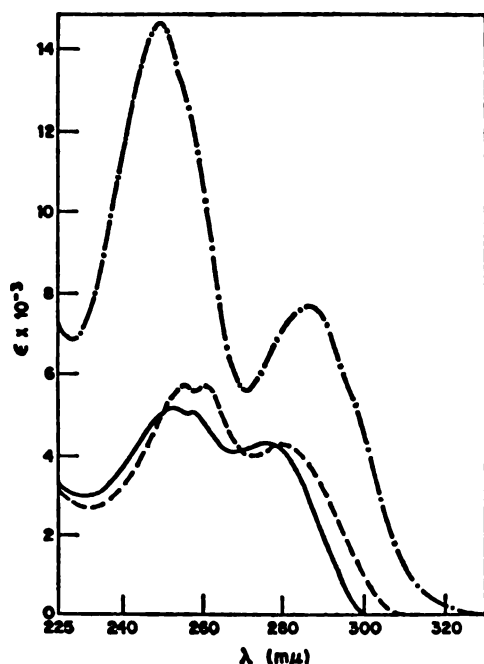


Figure 1. Ultraviolet spectra of 1H-benzotriazole, —; 1-hyl-1H-benzotriazole, ---; and 1,1'-bibenzotriazole, -.-.

The formation of more than 1 molar equiv of the izotriazole derivative 12 strongly favors structure 4a, ce 4b-d all would require extensive rearrangements. The facile reduction of the bismethosulfate with dium aluminum hydride is in sharp contrast to the bility of the unalkylated product 4 toward this gent. The reactivity of 11 is undoubtedly associ- d with its positive charges which should facilitate lride ion attack. Finally, the reduction cleavage of self was effected with aluminum amalgam in moist er⁷ to obtain somewhat greater than 1 molar equiv 1H-benzotriazole (6), thus providing additional evi- ce in favor of 1,1'-bibenzotriazole (4a).

2'-Bibenzotriazole. In view of the interesting rmal transformation exhibited by 1,1'-bibenzotri- le (4a), the synthesis of the isomeric 1,2'-bibenzo- zole (8) was undertaken. A convenient route was vided by the intermediate 2-aminobenzotriazole.⁸ e preparative route to 8 is summarized in Figure 3. ction of 2-aminobenzotriazole (13) with *o*-fluoro- *o*-chloronitrobenzene in dimethylformamide in the ence of sodium carbonate gave 2-(*o*-nitrophenyl-)-2H-benzotriazole (14) in 85% yield. Under ilar conditions, 1-aminobenzotriazole (15)⁹ gave y tars. Hydrogenation of 14 to 2-(*o*-aminophenyl-)-2H-benzotriazole (16) was readily achieved in ahydrofuran with palladium on charcoal. Treat- nt of the amine 16 with nitrous acid gave a crystal- solid, mp 124°, to which we assign the structure '-bibenzotriazole (8). The preparation of 1-sub- stituted 1H-benzotriazoles by diazotization of N-sub- stituted *o*-phenylenediamines has ample precedent in literature.^{2,10} The ultraviolet spectrum (ethanol)

1) We are indebted to Dr. C. S. Marvel for suggesting the use of this ent.

2) C. D. Campbell and C. W. Rees, *Chem. Commun.*, 192 (1965).

3) R. Trave and G. Bianchetti, *Atti Accad. Nazl. Lincei, Rend., Classe Fis., Mat. Nat.*, 28, 652 (1960).

4) F. R. Benson and W. L. Sarell, *Chem. Rev.*, 46, 1 (1950).

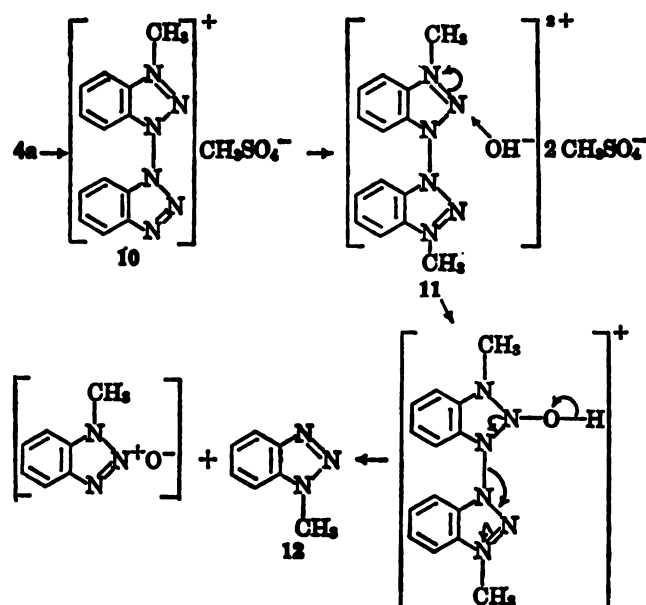


Figure 2.

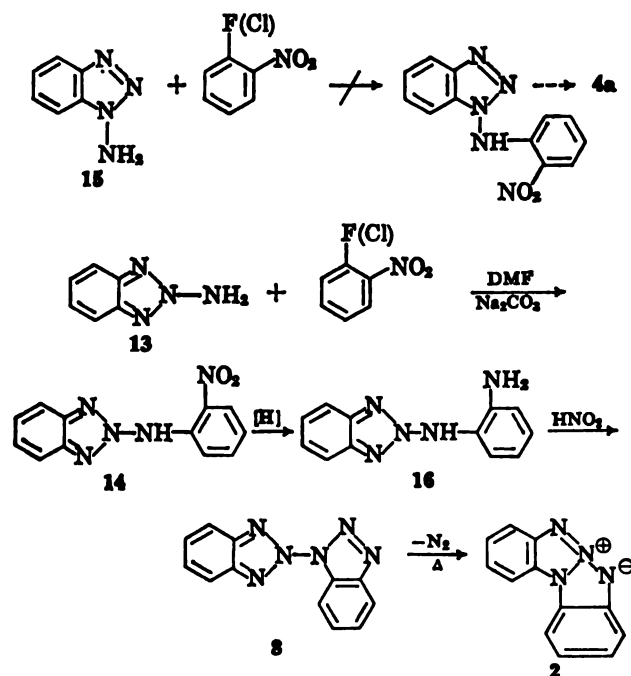
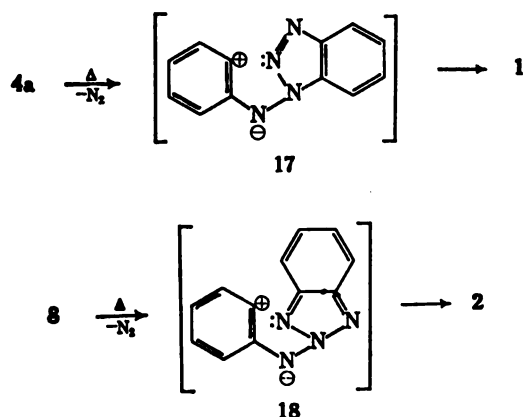


Figure 3.

of 8 showed λ_{\max} 250 mμ (ϵ 8700), 282 mμ (ϵ 17,600), and 290 mμ (ϵ 16,700), consistent with the assigned structure.

Thermal Decomposition of the Bibenzotriazoles. **Formation of Dibenzotetraazapentalenes.** When a solution of 1,1'-bibenzotriazole in di-*n*-butyl phthalate was heated at 300°, 1 mole of nitrogen was evolved with concomitant deepening in color of the solution. The well-defined, yellow, crystalline product obtained, mp 240–241°, was identified as dibenzo-1,3a,4,6a-tetraazapentalene (1) by comparison with an authentic sample. 1,2'-Bibenzotriazole (8) underwent a similar transformation at 250° with formation of the isomeric dibenzo-1,3a,6,6a-tetraazapentalene (2).

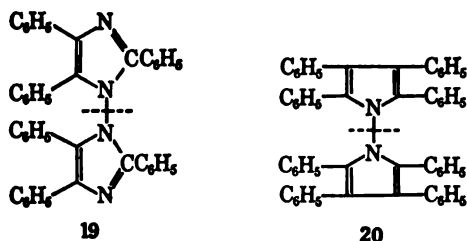
The mechanism for the tetraazapentalene formation in these thermolysis has not been studied. However, the reaction sequence may be represented as follows.



On heating, a molecule of azo nitrogen is eliminated from the 1H-benzotriazole moiety of each of the hexa-aza derivatives with incipient or intermediate formation of the 1,3-dipolar intermediates, 17 and 18, or their equivalents; subsequent bond formation between the ring carbon and the 2-N (in 17) and 1-N (in 18) yields the corresponding tetraazapentalenes 1 and 2, respectively.

The thermolysis is reminiscent of the Graebe-Ullmann synthesis of carbazoles from 1-phenylbenzotriazoles, although the latter reaction involves the formation of a carbon-carbon bond rather than a carbon-nitrogen bond and also involves migration of a hydrogen atom.¹¹

The thermal stability of the nitrogen-nitrogen bonds between each ring in the bibenzotriazoles 4a and 8 is remarkably greater than those of the closely related lophine 19 and tetraphenylpyrrole dimer 20, which are measurably dissociated into the corresponding free radicals at temperatures below 100°.¹²



Experimental Section¹³

1,1'-Bibenzotriazole (4a). To a mixture of 2.1 g (0.01 mole) of *o,o'*-diaminoazobenzene¹⁴ in 25 ml of 12% hydrochloric acid was slowly added sodium nitrite (1.5 g, 0.022 mole) in 10 ml of water. The temperature was maintained at 0–5° during the addition and throughout the subsequent treatments. The clear, homogeneous diazotization mixture was stirred for an additional 30 min, then treated with sulfur dioxide. The latter was introduced in a moderately rapid stream with stirring. A solid began to separate almost immediately. After 20 min, the light tan precipitate (1.5 g, 63%) was collected by filtration and recrystallized from ethyl acetate, to

obtain colorless needles, mp 233° dec. A second recrystallization from decahydronaphthalene gave 4a as hairlike crystals, mp 235° dec.

Anal. Calcd for $C_{13}H_8N_4$: C, 61.0; H, 3.4; N, 35.6. Found: C, 60.8; H, 3.6; N, 35.6.

The ultraviolet spectrum (ethanol) shows λ_{max} 252 m μ (ϵ 14,600) and 288 m μ (ϵ 7800). The dipole moment is 5.16 D. (0.02 M in benzene at 25°).

2-(*o*-Nitrophenylamino)-2H-benzotriazole (14). A mixture of 34 g (0.25 mole) of 2-aminobenzotriazole (13), 35 g (0.25 mole) of *o*-fluoronitrobenzene,¹⁵ 25.4 g (0.24 mole) of anhydrous sodium carbonate, and 120 ml of dimethylformamide was refluxed under nitrogen for 2 hr. The red-brown mixture was cooled and poured into 2.5 l. of water, precipitating a yellow solid. The latter was collected on a filter, washed with water, and recrystallized from 95% ethanol, giving 55 g (85%) of 2-(*o*-nitrophenylamino)-2H-benzotriazole, mp 144–145°.

Anal. Calcd for $C_{13}H_8N_4O_2$: C, 56.47; H, 3.55. Found: C, 56.53; H, 3.47.

2-(*o*-Aminophenylamino)-2H-benzotriazole (16). A mixture of 10.2 g (0.04 mole) of 2-(*o*-nitrophenylamino)-2H-benzotriazole, 0.3 g of 10% palladium on charcoal, and 75 ml of tetrahydrofuran was shaken at room temperature in a Parr apparatus under 40 psi hydrogen pressure. Hydrogen uptake was rapid, the theoretical amount being consumed in 10 min. The mixture was filtered, and the filtrate was evaporated nearly to dryness under nitrogen. The dark, partially crystalline residue was taken up in 95% ethanol, treated with charcoal, filtered, and diluted with water, giving tan leaflets (7 g, 78%), mp 100° dec. Recrystallization from ethanol-water gave colorless leaflets, mp 106° dec.

Anal. Calcd for $C_{13}H_{11}N_5$: C, 63.98; H, 4.92; N, 31.10. Found: C, 63.13; H, 5.16; N, 31.06.

The infrared spectrum of this product is consistent with the proposed structure 16.

Because of the difficulties in obtaining this amine analytically pure, the slightly crude material was employed for conversion to 1,2'-bibenzotriazole.

1,2'-Bibenzotriazole (8). A solution of 6.0 g (0.0266 mole) of 2-(*o*-aminophenylamino)-2H-benzotriazole in 250 ml of 1 N hydrochloric acid was cooled to 0°, and a solution of 1.80 g (0.026 mole) of sodium nitrite in water was added dropwise with stirring. The gray precipitate was collected on a filter and dissolved in ether, and the solution was treated with charcoal and filtered. Evaporation of the solvent and subsequent crystallization of the residue from aqueous ethanol gave 4.0 g (63%) of pale tan crystals, mp 123.5–124.5°. The melt on cooling gave crystals which melted at 98°, formed a new solid phase at 102°, and remelted at 123.5–124.5°.

Anal. Calcd for $C_{13}H_8N_4$: C, 61.01; H, 3.41; N, 35.58; mol wt, 236. Found: C, 61.02; H, 3.74; N, 35.70; mol wt, 229.

The ultraviolet spectrum (ethanol) shows λ_{max} 290 m μ (sh) (ϵ 16,700), 282 m μ (ϵ 17,500), and 245 m μ (sh) (ϵ 8350).

The product on heating to 200° in air evolved a gas with concomitant formation of a higher melting solid, presumed to be dibenzo-1,3a,6,6a-tetraazapentalene (see below).

Reaction of Bibenzotriazoles with Lithium Aluminum Hydride.

To a suspension of 1.50 g (0.04 mole) of lithium aluminum hydride in 100 ml of tetrahydrofuran was added a solution of 2.36 g (0.01 mole) of 1,2'-bibenzotriazole in 200 ml of tetrahydrofuran. The mixture was refluxed for 4 hr. After cooling, aqueous tetrahydrofuran was added to destroy unreacted hydride, and then the mixture was diluted with water and extracted with methylene chloride. The methylene chloride extracts were dried and evaporated, and the brown residue was treated with ether. The ether extract was filtered and evaporated, giving 1.3 g of brown crystals having an infrared spectrum nearly identical with that of benzotriazole. Recrystallization from water gave pure benzotriazole, identified by melting point and mixture melting point.

When 1,1'-bibenzotriazole was treated with lithium aluminum hydride as above, only starting material was recovered.

Reaction of 1,1'-Bibenzotriazole with Dimethyl Sulfate. a.

Mono-N-alkylation. A mixture of 5.0 g (0.021 mole) of 1,1'-bibenzotriazole and 50 ml of purified dimethyl sulfate was stirred at 95° for 20 min. The unreacted starting material (1.0 g) was removed by filtration, and the filtrate was diluted to 300 ml with anhydrous ether. The colorless crystals which precipitated were washed with ether and air dried, weight 4.40 g (72% based on un-

(11) C. Graebe and F. Ullmann, *Ann.*, 291, 16 (1896).

(12) H. Zimmermann, H. Baumgartel, and E. Bakke, *Angew. Chem.*, 73, 808 (1961).

(13) The ultraviolet spectra were obtained using a double-beam Model 14 Cary recording spectrophotometer. Dipole moments were determined by Mr. C. Wortz in benzene solution using a Dipol Meter Type DN-01 (Wissenschaftlich-Technische Werkstätten Weilheim, G.M.B.H., O.B., Germany).

(14) R. Willstätter and A. Pfannenstiel, *Ber.*, 38, 2349 (1905).

(15) Dr. Charles Yembrick has shown that *o*-chloronitrobenzene may be substituted for *o*-fluoronitrobenzene if a reflux time of 4 hr is employed.

ered starting material). Elemental analysis indicated that product contained 18% of the di-N-alkylation product described.

Anal. Calcd for 82% $C_{14}H_{14}N_6SO_4$ + 18% $C_{12}H_{10}N_6S_2O_3$: C, 45.13; H, 3.93; N, 22.10; S, 9.62. Found: C, 45.16; H, N, 21.55; S, 9.64.

monoalkylation product 10, mp 180° dec, is very water soluble and is stable to light and air.

Di-N-alkylation. A mixture of 5.0 g (0.021 mole) of 1,1'-bibenzotriazole and 50 ml of purified dimethyl sulfate was stirred 110° for 2 hr, followed by cooling to room temperature during the reaction. The colorless crystals were collected on a filter, washed with ether, and dried over phosphorus pentoxide at room temperature. The product 6 (8.95 g, 86%) melted at 192–194° dec.

Anal. Calcd for $C_{12}H_{10}N_6S_2O_3$: C, 39.34; H, 4.13; N, 17.21; S, 13; mol wt, 163. Found: C, 38.96; H, 4.06; N, 17.51; S, 12; mol wt, 170, 179.

dialkylation product 11 is very water soluble and is stable to light and air.

A solution of 3.0 g of the above dialkylation product was added to 17 ml of saturated aqueous sodium iodide solution. Reddish crystals precipitated immediately, and the mixture was stirred in the dark for 15 min. The crystals were then collected on a filter in the dark and washed with water. After drying, the diiodide weighed 1.70 g.

Anal. Calcd for $C_{14}H_{14}N_6I_2$: C, 32.33; H, 2.71; N, 16.16; I, 47.45. Found: C, 32.44; H, 2.72; N, 16.12; I, 47.45.

diiodide turns brown on exposure to light and forms a dark suspension standing at room temperature for several weeks, even in the

Composition of Dialkylation Product 11 with Base. To 20 ml of sodium hydroxide at room temperature was added 2.0 g (0.0041 mole) of the dialkylation product, giving a bright yellow mixture which rapidly changed to a nearly colorless mixture. The small amount of oil which formed slowly crystallized. The mixture was extracted with ether, and the ether extracts were dried and evaporated to give 0.55 g of nearly colorless crystals, mp 61.5–63.5°. Recrystallization from cyclohexane gave pure 1-methylbenzotriazole (12), mp 64.5–65.5°, identified by melting point and comparison of its infrared spectrum with that of an authentic sample.¹⁴

Reaction of 11 with Lithium Aluminum Hydride. A slurry of 0.026 mole of lithium aluminum hydride in 125 ml of ether was stirred under nitrogen at room temperature while 3.0 g (0.006 mole) of the dialkylation product 11 was added. The light purple

suspension which resulted was treated with an additional 0.65 g of lithium aluminum hydride during 6 hr, and the mixture was then allowed to stand overnight. Excess hydride was destroyed with ethyl acetate and water, then 80 ml of 10% sodium hydroxide was added, the solid was removed by filtration, and the filtrate was extracted three times with ether. The combined ether extracts were dried over sodium sulfate, and the solvent was removed, giving 1.58 g (97%) of light brown crystalline solid, mp 59–61°, the infrared spectrum of which was identical with that of 1-methylbenzotriazole. Recrystallization gave pure 1-methylbenzotriazole, mp 63–64°.

Reduction of 1,1'-Bibenzotriazole (4a). Aluminum amalgam was prepared by immersing 0.57 g (0.02 g-atom) of aluminum foil (0.001 in.) in 5% aqueous mercuric chloride at room temperature for 1.5 min. The foil was rapidly washed with water and added immediately to a suspension of 5.0 g (0.021 mole) of 1,1'-bibenzotriazole in 500 ml of moist ether. The mixture was refluxed for 3 hr, at which time all of the amalgam had been consumed. The ether layer was decanted and evaporated under a stream of nitrogen until nearly all of the unreacted starting material (1.50 g) had precipitated. The benzotriazole was removed by filtration, and the filtrate was evaporated further, giving 2.7 g of brown crystals, mp 82–89°, having an infrared spectrum nearly identical with that of benzotriazole. The yield of crude product based on unrecovered starting material was 77%. Recrystallization from benzene gave pure benzotriazole (55%), identified by melting point, mixture melting point, and comparison of its infrared spectrum with that of an authentic sample.

Thermolysis of 1,1'-Bibenzotriazole. A solution of 2.0 g (0.0085 mole) of 1,1'-bibenzotriazole in 25 ml of di-*n*-butyl phthalate was heated under nitrogen at 250° for 30 min. The dark mixture was cooled to room temperature, and the precipitate was collected on a filter, washed with pentane, and air dried. There was obtained 0.95 g (54%) of dibenzo-1,3a,4,6a-tetraazapentalene (1), mp and mmp 237–238° with an authentic sample.

Thermolysis of 1,2'-Bibenzotriazole. A solution of 0.50 g (0.0021 mole) of 1,2'-bibenzotriazole in 3.7 g of di-*n*-butyl phthalate was heated at 250° for 25 min, by which time nitrogen evolution had nearly ceased. The dark solution was cooled under nitrogen, 7 ml of petroleum ether was added, and the precipitated, feathery crystals were collected on a filter and dried. The product (0.30 g, mp 248°) was recrystallized from methylene chloride-petroleum ether, giving 0.11 g of nearly colorless crystals, mp 255°. The mixture melting point with an authentic sample of dibenzo-1,3a,6,6a-tetraazapentalene (2) was undepressed.

Acknowledgment. We are indebted to Dr. R. V. Lindsey for valuable discussions.

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Tetrahexylammonium Benzoate, a Liquid Salt at 25°, a Solvent for Kinetics or Electrochemistry¹

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Contribution from the Department of Chemistry and the Laboratory for Nuclear Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. Received November 17, 1966

Abstract: Tetrahexylammonium benzoate (THAB) is a liquid salt at 25°, miscible with most organic solvents but not with water. Its "solvent ionizing power" Y , based on rate of solvolysis of *t*-butyl chloride in THAB as solvent, is -0.39 , intermediate between ethanol and water. Its ability to dissolve organic compounds, intrinsic conductance, and electrochemical inertness over a wide voltage range make it a suitable solvent for electrochemical studies. Half-wave potentials with a dropping mercury electrode in THAB are recorded for oxygen, fumaric acid, benzophenone, anthracene, and β -naphthol.

Tetra-*n*-hexylammonium benzoate (hereafter THAB) is a viscous liquid at 25°, miscible with benzene, toluene, or carbon tetrachloride, in contrast to tetrapentylammonium or tetrabutylammonium benzoate, which are solids, only slightly soluble in benzene. As a liquid salt, it constitutes an unusual kind of solvent for kinetics or electrochemistry. Its synthesis and properties are described in the Experimental Section.

Kinetics. Reactions in fused salts are receiving increasing attention.² THAB permits such studies at 25° or below. To determine whether THAB is better regarded as a polar solvent because of its ionic bonds or as a nonpolar solvent because most of its bulk consists of saturated alkyl groups which shield and sterically hinder approach to the ionic centers, we measured its solvent polarity Y . Y values are defined operationally³ as $\log(k/k^\circ)$, where k and k° are first-order rate constants for solvolysis of *t*-butyl chloride at 25° in any solvent and in the standard solvent, ethanol-water (80:20), respectively. From the measured rate constant of $3.8 \pm 0.2 \times 10^{-6} \text{ sec}^{-1}$, in THAB as solvent, its Y value is -0.39 , of the same order as that for 80% ethanol, *i.e.*, fairly polar, more polar than ethanol (-2.03), but less polar than water ($+3.49$). Its remarkable balance of ionic and nonpolar characteristics thus permits a moderate rate of solvolysis of *t*-butyl chloride, easily measurable by conventional kinetic techniques.

Electrochemistry. Solubility and reduction potential are two important properties of tetra-*n*-alkylammonium salts when used as supporting electrolytes in electrochemical studies. Of the many available salts in the series, tetrabutylammonium perchlorate has gained wide acceptance because of its solubility in a wide variety of solvents and because it is not easily reduced, *e.g.*, in aqueous solutions not before -2.6 v vs. the saturated calomel electrode. No significant increase in

usable potential range results from further increases in alkyl chain length.

Current-voltage curves were obtained in THAB as solvent using both a dropping mercury electrode and a platinum microelectrode. Figures 1 and 2 illustrate typical results. Details are given in the Experimental Section. Relative to the silver chloride electrode, oxygen, fumaric acid, benzophenone, anthracene, and β -naphthol exhibited $E_{1/2}$ values at -0.37 , -0.50 , -1.42 , -1.7 , and -2.3 v with the dropping mercury electrode. Thus, THAB is usable as a solvent and advantageous because it is a good solvent for organic compounds, has adequate intrinsic conductance, and ions that are electrochemically inert over a wide range.

Experimental Section

Synthesis. Tetrahexylammonium iodide (Eastman White Label) was recrystallized three times from 3:1 acetone-ether solutions, mp 104–105°, or in later work used without purification without adverse effects. Freshly precipitated silver oxide (0.15 mole) was added in several portions with prolonged shaking to a solution of 25 g (0.052 mole) of the iodide in 150 ml of methanol-water (80:20). The residual iodide ion was negligible. Without isolation of the tetrahexylammonium hydroxide, the filtered solution was neutralized with reagent benzoic acid dissolved in 80% methanol to pH 7, using "pHydron" pH 7–8 paper as an indicator. The volume of benzoic acid solution required agreed with that calculated. Solvent was evaporated at or below 25° in a rotary evaporator at 10^{-3} to 10^{-4} mm . The pale yellow oil obtained was dried in a vacuum desiccator under reduced pressure over P_2O_5 or $\text{Mg}(\text{ClO}_4)_2$ for a day; yield 20 g. Last traces of water are difficult to remove. Its analysis corresponds to a hemihydrate. *Anal.* Calcd for $\text{C}_{24}\text{H}_{52}\text{NO}_2$: C, 78.25; H, 12.08; N, 2.94. Calcd for $\text{C}_{24}\text{H}_{52}\text{NO}_2 \cdot 0.5 \text{ H}_2\text{O}$: C, 76.80; H, 12.06; N, 2.93. Found: C, 76.67; H, 11.84; N, 2.90. A sample heated for 10 min at 100° (25 mm) partially decomposed to a mixture analyzing 72.62% C and 11.94% H, indicating accumulation of benzoic acid. Further drying of another sample for 2 weeks at 25° (25 mm) over $\text{Mg}(\text{ClO}_4)_2$ also gave some decomposition (75.09% C and 11.71% H).

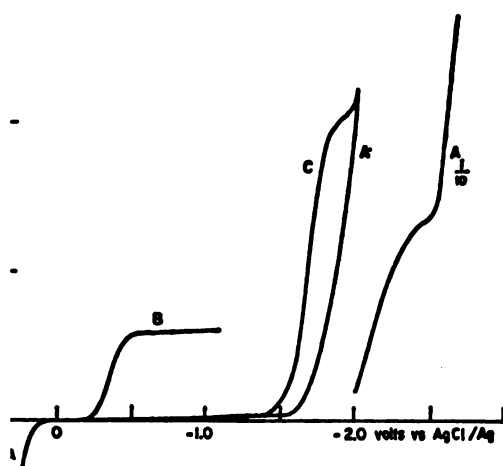
An alternate, less desirable procedure for the conversion of iodide to hydroxide involved ion exchange. The iodide (2 g) in 80% methanol was charged into 130 ml of Dowex I-X4 anion-exchange resin in hydroxide form in a 20-mm i.d. column, followed by elution with 600 ml of 80% methanol at the rate of 20 drops/min. There may be a possibility of contamination of the THAB by traces of amines derived from the resin in this procedure.

Properties. At 25° THAB has a viscosity similar to that of glycerol and a density of 0.90 g/ml. It does not have a liquid crystal state. It solidifies at Dry Ice temperature. Specific resistance was 18 kohm cm after several days in a vacuum desiccator at 25-mm pressure over $\text{Mg}(\text{ClO}_4)_2$. Some water was probably absorbed upon

(1) Supported in part by the Atomic Energy Commission under Contract No. AT(30-1)-905 and National Science Foundation Undergraduate Equipment Grant No. GE-2275.

(2) B. R. Sundheim, "Fused Salts," McGraw-Hill Book Co., Inc., New York, N. Y., 1964; M. Blander, "Molten Salt Chemistry," Interscience Publishers, Inc., New York, N. Y., 1964; J. E. Gordon, *J. Am. Chem. Soc.*, **86**, 4492 (1964); **87**, 1499, 4347 (1965); *J. Org. Chem.*, **30**, 2760, 4396 (1965).

(3) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948); A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).



Tracings of peak currents of polarograms: curve A, current, beyond -2 v at one-tenth sensitivity; curve B, of oxygen at saturation concentration; curve C, reduction of THAB.

since the specific resistance decreased to 760 ohm cm on the atmosphere, but increased to 1.6 kohm cm after a change to 90° (25 m). Relatively little water is miscible with addition of 1% by volume of water results in a two-phase

luene and carbon tetrachloride are miscible with THAB; of THAB-toluene (75:25) had a rather low specific of 3.8 kohm cm. The mixtures are much less viscous THAB, and therefore easier to use, especially in electrochemical cells where dissolved oxygen is removed by bubbling with Acetone also dissolves this salt and is useful for rinsing ware and apparatus.

the yellow-brown color is due to an unidentified impurity. In voltammetric curves it is clear that the impurity is not

nmr absorption in carbon tetrachloride with tetramethylsilane standard had τ values (and integrated areas) of 3.80 (32), and 9.18 (12) ppm. Infrared absorption was 50 (w), 715 (s), 815 (w), 850 (w), 925 (w), 1020 (w), 1050 (s), 1465 (m), 1480 (m), 1570 (s), 1605 (s), 1620 (m), 2850 (s), 2915 (vs), 2950 (vs), and 3050 cm^{-1} (w).

t-Butyl chloride was dried over Drierite (calcium sulfide, bp 52°). A 0.1 M solution (10 ml) of *t*-butyl THAB was placed in a constant temperature bath at 25° . At desired intervals, 1-ml aliquots were dissolved in benzene and shaken for 15 min with 10 ml of water to hydrolyze *t*-butyl chloride remaining. The water layer (6 ml) was extracted by 0.01 M aqueous sodium hydroxide using phenolphthalein as an indicator. One-third of the benzoic acid is in the organic phase. The acid titer decreased to zero by a first-order rate

chemistry. Current-voltage curves were obtained with dropping mercury electrode and a platinum microelectrode. Figures 1 and 2 illustrate typical results. An aqueous $\text{NaCl}|\text{Ag}$ electrode was used as a reference. Contact made by a short piece of porous glass rod (Corning 7930). Potentials of the DME at 0 v were $m = 6.10\text{ mg/sec}$, $t = 5.62$

A short piece of platinum wire was used as the counter electrode. The polarograph was a Heath EUW-401. Oxygen reduction in the THAB solvent was accomplished by a nitrogen purge. Measurements were made at room temperature, $23 \pm 3^\circ$. No compensation was made for iR voltage drop in the cell. Although the cell is essentially a potentiostat, the potential is independent of current only if zero resistance exists between the reference and indicator electrodes. As noted above, THAB solutions of high resistance and the cell used did not allow the two to be positioned close together.

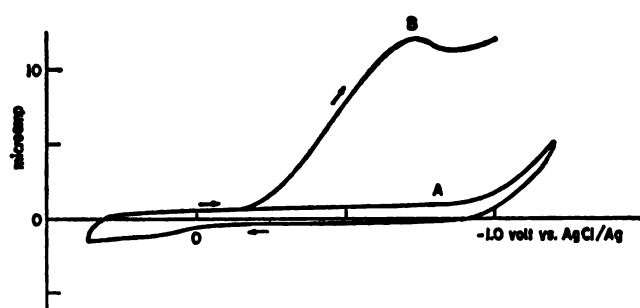


Figure 2. Scan rate 100 mv/sec: curve A, residual cyclic voltammogram of platinum microelectrode; curve B, reduction of oxygen.

From curve A in Figure 1, the anodic limit with a mercury electrode is $+0.2$ v ($\text{AgCl}|\text{Ag}$). The lack of an anodic wave at potentials negative to the reference suggests either that there is negligible iodide remaining in the salt or that mercurous(iodic) iodide is soluble in THAB.

No significant concentrations of reducible impurities, including iodine, contributed to the cathodic current at potentials positive to -1.8 v, but a reduction wave was evident beyond this point. After a perceptible diffusion plateau of $80\text{ }\mu\text{A}$ at -2.5 v, the current increased sharply. The last current rise is undoubtedly the reduction of THAB ion and the impurity wave was probably an alkali metal cation since $E_{1/2}$ was -2.09 v. Sodium or potassium ions at 0.01 M are not uncommon in reagents of the quality used in this synthesis. It is also possible that hydrogen ion reduction from traces of water may have contributed to the reduction wave, although this is not reported to be the case with neutral, aqueous solutions of tetraalkylammonium salts.

The point of zero charge of the mercury electrode was -0.25 v, based on observations of the shapes of the current-time curves of individual drops. The slope of the (peak) charging current-potential curve is very small so that the intersection on the potential axis (the point of zero charge) is difficult to determine. The change in shape of the charging current-time curves on either side of -0.25 v was very evident, however. Drop times changed rather markedly with potential beyond -1.5 v. At -1.7 v, the decrease was about 30% compared to the drop time at 0 v.

Oxygen is reduced in a single wave having $E_{1/2} = -0.37$ v. The diffusion current was $3.4\text{ }\mu\text{A}$ after prolonged contact with the atmosphere (curve B). Since the difference between the potentials at one-fourth and three-fourths of the diffusion current was 75 mv, the rising part of the wave was not related to a simple diffusion-controlled process but instead was activation controlled. Traces of water were undoubtedly present, so that reduction of oxygen to hydroxide ion was possible.

Reduction waves (and $E_{1/2}$ values) were observed for anthracene (-1.7), benzophenone (-1.42), fumaric acid (-0.50), and β -naphthol (-2.3). Curve C of Figure 1 shows a polarogram for anthracene added as a small crystal. In aqueous solution, anthracene is reduced at $E_{1/2} = -2.4$ v. Interference from the assumed alkali metal cation reduction prevented an assessment of the quarter-wave potential difference. The reduction of naphthalene was not observable over the accessible range to -2.6 v.

A platinum microelectrode in pure THAB exhibited an anodic limit at about $+0.3$ v, and at -1.2 v cathodic current became significant, as shown in Figure 2, curve A. Within this potential range, the current was essentially capacitive in that a first-power dependence on scan rate was observed. Oxygen reduction occurred as a drawn-out wave (curve B), rising from -0.2 v to a peak at -0.7 v when the scan rate was 100 mv/sec. The peak potential was very dependent upon scan rate. The addition of a small amount of water did not alter the residual curve, which suggests that traces of water were already present. A mixture of 25% by volume of toluene with THAB had essentially the same residual currents as the pure liquid.

Evaluation of the Basicity of Phosphine Oxides and Phosphine Sulfides by Measurements of Chemical Shift in Sulfuric Acid Solutions¹

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Contribution No. 2001 from the Department of Chemistry, University of California, Los Angeles, California 90024. Received October 18, 1966

Abstract: The pK_{BH^+} values of $(CH_3)_3PO_2H$, $CH_3P(O)(OCH_3)_2$, $(C_6H_5)_2P(O)CH_3$, $C_6H_5P(O)(CH_3)_2$, $(C_6H_5)_2P(S)CH_3$, $C_6H_5P(S)(CH_3)_2$, and $(CH_3)_3PS_2H$ have been determined by measurements of chemical shift of methyl groups bonded to phosphorus as a function of sulfuric acid concentration. The data indicate considerable π bonding in PS and PO bonds. Phosphine oxides are about 10^6 less basic than amine oxides, arsine oxides, and stibine oxides. Previous reports of the basicity of phosphine oxides are misleading. The method used here has been validated by study of acetophenone and N,N-dimethylacetamide; pK 's of these compounds are known from other methods.

There has been considerable interest in the nature of the P-O bond in phosphine oxides especially in regard to the role of d orbitals in π bonding.³ Bond energies,⁴ bond lengths,^{5,6} infrared spectra,⁷ C^{13} -H coupling constants,⁸ and hydrogen bonding⁹ all indicate considerable P-O π bonding in phosphine oxides. The N-O bond in trimethylamine oxide, on the other hand, appears to be a single bond.^{3,8}

There has been little work on the basicity of phosphine oxides and sulfides, and this might be expected to give indications concerning P-O and P-S bonding in both neutral and protonated forms. N Oxides are sufficiently basic to be measured by potentiometric titration; the pK_{BH^+} ¹⁰ of $(CH_3)_3NO$ is 4.7.¹¹ The pK_{BH^+} of $(CH_3)_3PO$ has been listed in a table as 0,¹¹ but this was on the basis of titration and evaluation of its effect on HBr-catalyzed hydrolysis of methyl acetate which indicated basicity immeasurably small by these techniques. This estimate for the basicity of $(CH_3)_3PO$ has been quoted in a review on the base strength of weak organic bases.¹² By measurements of proton chemical shifts as a function of sulfuric acid concentrations, we had determined the basicity of a phosphinic acid, $(CH_3)_2PO_2H$, and a phosphinate ester, $(C_6H_5)_2PO_2CH_3$,

in connection with a study of the acid-catalyzed hydrolysis of phosphinates.¹³ We have now confirmed the validity of this method and studied a more complete set of compounds which may be classed as phosphine oxides and sulfides.

Results

In the compounds studied, chemical shifts for CH_3 hydrogens were measured relative to $(CH_3)_3N^+H$; a sample plot of the data for dimethylphenylphosphine oxide is shown in Figure 1. Trimethylammonium ion was used as a standard to minimize changes in chemical shifts due only to changes in solvation. The large solvation effects should be in the media with high $[H_2SO_4]$ where most or all of the water will be involved in solvating protons. This would probably decrease solvation of the protonated phosphine oxide and lead to a change in chemical shift relative to an uncharged and/or unprotonated standard. By using $(CH_3)_3N^+H$ as a standard we should minimize this problem, since both BH^+ and $(CH_3)_3N^+H$ have one acidic hydrogen for interaction with solvent and solvation effects should, therefore, be similar.

The data are plotted against the H_0 scale¹⁴ since this is a scale conveniently available as a standard. Although there are problems with the H_0 scale based on primary anilines serving as a measure of acidity when studying other bases or substrates,¹⁵ this can be considered by use of eq 1¹⁶ where the M value is a measure

$$\log [BH^+]/[B] = M(pK_{BH^+} - H_0) \quad (1)$$

of the protonation behavior of B relative to Hammett bases (primary anilines).¹⁷ If $M = 1$, B is a Hammett

(13) P. Haake and G. Hurst, *J. Am. Chem. Soc.*, **88**, 2544 (1966).

(14) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter IX. (b) The scale used here is Hammett's with the corrections above 60% H_2SO_4 given by M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963). This scale is internally consistent since it is based on primary anilines and seems to be a reasonable one to adopt as a standard. It appears to be finding general acceptance; see, for example, K. Yates and H. Wai, *Can. J. Chem.*, **43**, 2131 (1965).

(15) We use eq 1 with M as a measure of the effect of medium relative to the effect on Hammett bases. Other forms of this equation have been used^{18,19} with a rather than M , but use of M should lead to less confusion. Equation 1 is discussed in more detail in ref 13.

(16) A. R. Katritzky, A. J. Waring, and K. Yates, *Tetrahedron*, **19**, 465 (1963).

(17) This seems preferable to development of a new scale for each substrate, as has been done: for amides, the H_a scale.²⁰

(1) Research supported by National Science Foundation Grant GP-3726 and U. S. Public Health Service Grant AM-6870.

(2) (a) Alfred P. Sloan Research Fellow, 1964-1966; (b) Trainee (1964-1965) under U. S. Public Health Service Training Grant 5T01-6M-463.

(3) For a recent summary see (a) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, Chapter 3. See also (b) R. F. Hudson, *Pure Appl. Chem.*, **9**, 371 (1964); (c) L. Larsson, *Svensk Kem. Tidskr.*, **71**, 336 (1959).

(4) S. B. Hartley, W. S. Holmes, J. K. Jacques, M. F. Mole, and J. C. McCoubrey, *Quart. Rev. (London)*, **17**, 204 (1963).

(5) A recent, accurate determination [H. K. Wang, *Acta Chem. Scand.*, **19**, 879 (1965)] of the P-O bond length in trimethylphosphine oxide, $r(P-O) = 1.48$ Å, can be compared with the sum of single bond covalent radii⁶ $P + O = 1.10 + 0.66 = 1.76$ Å.

(6) L. Pauling, "Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 224.

(7) (a) E. A. Robinson, *Can. J. Chem.*, **41**, 3021 (1963); (b) H. Gerding, J. W. Maarsen, and D. H. Zijp, *Rec. Trav. Chem.*, **77**, 361 (1958).

(8) P. Haake, W. B. Miller, and D. A. Tyssee, *J. Am. Chem. Soc.*, **86**, 3577 (1964).

(9) (a) T. Kubota, *ibid.*, **88**, 211 (1966); (b) G. Aksnes, *Acta Chem. Scand.*, **14**, 1475 (1960).

(10) We use the symbol pK_{BH^+} rather than pK_a for clarity; pK_{BH^+} specifically refers to the equilibrium $BH^+ \rightleftharpoons B + H^+$, but pK_a also could refer to $HA \rightleftharpoons H^+ + A^-$ since the protons of the methyl groups of $(CH_3)_3PO$ and $(CH_3)_3NO$ should be somewhat acidic.

(11) P. Nylen, *Z. Anorg. Allgem. Chem.*, **246**, 227 (1941).

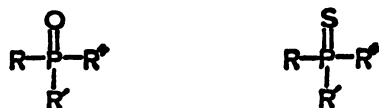
(12) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 325, 392 (1963).

Table I. Acidity Constants and H_0 Dependences for Protonated Phosphine Oxides and Phosphine Sulfides

Compd ^a	H_0 at half-protonation ^b	$\log [BH^+]/[B] = M(pK_{BH^+} - H_0)$	M	Δ_{BH^+} ^d	Δ_B ^d	No. of pts between 5 and 95% protonation ^c
Dimethylphosphinic acid (A)	-4.3	-4.07 (-1.25 \pm 0.07)	0.308 \pm 0.016	119.4	78.6	7
Dimethyl methylphosphonate (B)	-5.5	-5.22 (-2.48 \pm 0.16)	0.475 \pm 0.027	48.2	67.6	8
Diphenylmethylphosphine oxide (C)	-3.3	-3.20 (-2.23 \pm 0.25)	0.697 \pm 0.065	29.2	44.4	7
Dimethylphenylphosphine oxide (D)	-2.2	-2.09 (-0.946 \pm 0.063)	0.453 \pm 0.023	33.2	55.7	10
Diphenylmethylphosphine sulfide (E)	-4.5	-4.75 (-12.76 \pm 5.16)	2.69 \pm 0.64	15.0	30.5	3
Dimethylphenylphosphine sulfide (F)	-4.5	-4.58 (-8.31 \pm 0.15)	1.82 \pm 0.02	18.9	41.6	3
Dimethyl(dithiophosphinic acid (G)	-5.6	-5.72 (-5.57 \pm 2.18)	0.974 \pm 0.24	14.2	32.5	3
	-1.1	-1.07 (-1.54 \pm 0.07)	1.43 \pm 0.05	32.5	44.9	7

^a Chemical shifts of underlined CH_3 groups were measured. ^b This is equal to pK ; from sigmoid graph of Δ against H_0 . ^c The values in parentheses are intercepts (and their standard deviations) determined by least squares. ^d Values of chemical shifts are relative to $(CH_3)_3N^+H$; positive indicates upfield shift. ^e This is number of points used to determine M and pK_{BH^+} by least squares on eq 2. More data were obtained and used to get H_0 at half-protonation, Δ_B , and Δ_{BH^+} .

base.¹⁸ All the data we obtained could be plotted according to eq 1 and gave straight lines, from which M and pK_{BH^+} values could be obtained: $M = \text{slope}$, $pK_{BH^+} = \text{intercept}/M$.



A, R = R' = CH_3 ; R'' = OH E, R = R' = C_6H_5 ; R'' = CH_3
B, R = CH_3 ; R' = R'' = OCH₃ F, R = C_6H_5 ; R' = R'' = CH_3
C, R = R' = C_6H_5 ; R'' = CH_3 G, R = R' = CH_3 ; R'' = SH
D, R = C_6H_5 ; R' = R'' = CH_3

The pK_a 's can also be obtained by evaluation of the point where $[BH^+] = [B]$. This is the halfway point on the sigmoid curves (e.g., Figure 1), i.e., the point where $\Delta = (\Delta_B + \Delta_{BH^+})/2$. Table I gives all our data for phosphine oxides including pK 's determined by this method and pK and M values from a least-squares calculation using eq 1. The chemical shifts found for B and BH^+ relative to $(CH_3)_3N^+H$ are also given in Table I. It can be seen that $(\Delta_B - \Delta_{BH^+})$ is large enough to give reliable results. Determination of pK 's by either method depends on the values of these chemical shifts, but it turns out that application of eq 1 to determination of pK 's is not as sensitive to slope as one might expect from the fact that the pK is determined by the intercept. Since a lowering of slope lowers the absolute value of the intercept (the intercepts in these plots are negative), there is a compensating effect since $pK = \text{intercept}/\text{slope}$. Consequently, although some standard deviations are large in Table I, the pK_{BH^+} values from eq 1 and from half-protonation agree well. The larger standard deviations come from those compounds where only a few points were obtained between 5 and 95% protonation due to a steep dependence of protonation on H_0 , which results in a high M value.

Another argument for standard use of the H_0 scale in studies of basicity relates to the M values. It seems

likely that these M values may be quite useful in evaluation of solvation effects on the protonation of weak bases when there is a large enough body of these data available.

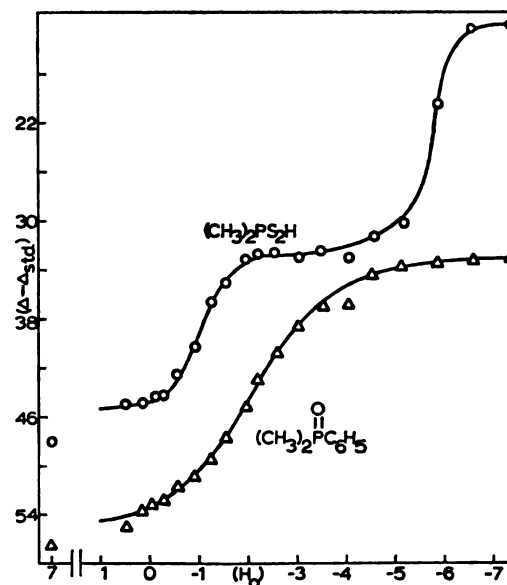


Figure 1. Dependence of chemical shift of methyl groups of dimethylphenylphosphine oxide and dimethyldithiophosphinic acid on H_0 in aqueous sulfuric acid.

Perhaps the most important question in this study has to do with the reliability of this method. Despite the use of $(CH_3)_3N^+H$ as a standard it could be argued that all the data observed here could be largely medium effects so that the apparent titration curves observed (e.g., Figure 1) could have little relation to basicity. We have several pieces of evidence which refute this line of devil's advocacy. First, we used this method to determine the pK values for N,N-dimethylacetamide (H) and acetophenone (I); the chemical shifts of the

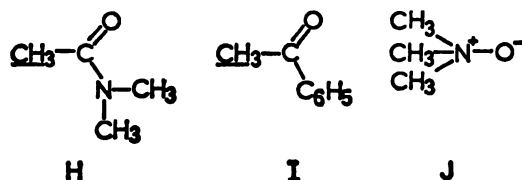
(18) K. Yates, J. Stevens, and A. R. Katritzky, *Can. J. Chem.*, **42**, 1957 (1964).

Table II. Basicity of N,N-Dimethylacetamide and Acetophenone by Nmr and Other Methods

Compound	H_0 at half-protonation	$pK_{BH^+}^a$	Nmr			Lit. pK_{BH^+}	No. of p between 5 and 95% protonation
			M^a	Δ_B^b	$\Delta_{BH^+}^b$		
$CH_3CON(CH_3)_2$	-0.34	-0.39 (-0.376 \pm 0.049)	0.97 \pm 0.04	48.1	28.0	-0.19 ^c	9
$CH_3COC_6H_5$	-6.45	-6.51 (-3.37 \pm 0.39)	0.52 \pm 0.05	21.6	-14.8	-6.45 ^d	5

^a By least squares using $\log ([BH^+]/[B]) = M(pK - H_0)$. Values in parentheses under pK_{BH^+} are the values of the intercepts and their standard deviations as determined by least squares. The \pm values under M are standard deviations of the slope by the same method.
^b Chemical shift in cps from the methyl hydrogens of $(CH_3)_3N^+H$. ^c Reference 12. ^d K. Yates and H. Wai, *Can. J. Chem.*, **43**, 2131 (1965).

underlined methyl groups were evaluated as a function of acidity. The pK_{BH^+} values obtained by the nmr method are in good agreement with those previously observed (Table II). Secondly, dimethyl sulfone is known to be very weakly basic and is only partially protonated in concentrated sulfuric acid.^{12,19} We observe no titration curve of chemical shifts for dimethyl sulfone in the region of acidity where titration curves are observed for the compounds in Table I. Finally, we have studied trimethylamine oxide (J) by this method. This amine oxide has a pK in the range



measurable by potentiometric methods: $pK_{BH^+} = 4.65$.¹¹ We find less than 3-cps change in chemical shift between $H_0 = 0$ and $H_0 = -7$ for this compound. Since protonation of J is essentially complete throughout this range, this result further supports the validity of our method.

Two pK values are listed in Table I for dimethyldithiophosphinic acid, $(CH_3)_2PS_2H$. The titration curve for this compound is shown in Figure 1; two inflections are clearly present. These are probably due to: (1) protonation of the anion, $H^+ + Me_2PS_2^- \rightleftharpoons Me_2PS_2H$, $pK_{AH} = -1.07$; (2) protonation of the acid, $H^+ + Me_2PS_2H \rightleftharpoons (CH_3)_2PS_2H_2^+$, $pK_{BH^+} = -5.72$. The pK_{AH} is inconsistent with the results of Kabachnik, *et al.*,²⁰ on other dithiophosphinic acids. The pK_{AH} values they found by potentiometric titration might be in error due to problems with false pK 's of strong acids.²¹ Alternatively, the two inflection points we observed here could be due to (1) protonation of the neutral acid and (2) another phenomenon. Since $(CH_3)_2PO_2H$ is about 1 to 2 powers of 10 less basic than phosphine oxides and phosphine sulfides have $pK_{BH^+} = -4.5$, it does seem very likely that pK_{BH^+} is -5.6 for $(CH_3)_2PS_2H$. It then is difficult to attribute $pK = -1.1$ to anything other than $(CH_3)_2PS_2H \rightleftharpoons (CH_3)_2PS_2^- + H^+$.

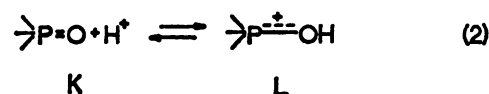
(19) R. J. Gillespie and J. A. Leisten, *Quart. Rev. (London)*, **8**, 40 (1954).

(20) M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov, and T. A. Melentyeva, *Tetrahedron*, **9**, 10 (1960).

(21) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.

Discussion

Basicity of Phosphine Oxides. The pK_{BH^+} of trimethylphosphine oxide was reported^{11,12} as 0; on the basis of our results (Table I), it seems likely that this is in error. Certainly phosphine oxides (K) are generally protonated (eq 2) to only a small extent in 1 M acid.



The basicities we have measured for phosphine oxides are compared with other oxides in Table III. Therefore, in basicity phosphine oxides resemble carbonyl

Table III. Comparison of Basicities of Some Oxides

Compound	pK_{BH^+}
$CH_3C(O)C_6H_5$	-6.5 ^{a,b}
$(CH_3)_3NO$	4.7 ^c
$(CH_3)_3P(O)C_6H_5$	-2.4 ^b
$CH_3P(O)(C_6H_5)_2$	-3.2 ^b
$(CH_3)_3AsO$	3.8 ^c
$(CH_3)_3SbO$	5.4 ^c

^a Footnote d, Table II. ^b This work. ^c Reference 11.

compounds more than the oxides of other group Va elements; the oxides of nitrogen, arsenic, and antimony are 10^6 – 10^8 times more basic than phosphine oxides. Amine oxides can have no N–O π bonding, and carbonyl groups are known to have considerable double bond character.

Although C and D do not have C_{3v} symmetry, it is probable that these phosphine oxides have two nearly equivalent π orbitals^{22,23} so that K might be better written as $\text{>P}^+=\text{O}$. The short P=O bond length⁴ and the radial density distributions of the phosphorus and oxygen orbitals probably contribute to the strength of π bonding in K.²⁵ The longer As–O and Sb–O bonds would cause weaker π bonding in arsine and stibine oxides.

(22) The interaction of the phenyl substituents with the P–O π system is probably small since there is little difference in the length of C(sp²)–P and C(sp³)–P bonds.²⁴ Therefore, in C and D there should be little perturbation of a symmetrical π (P–O) system with two π orbitals.

(23) In $(CH_3)_3PO$, $r(P-C) = 1.81$ Å;⁴ in $(C_6H_5)_3PO_2H$, $r(P-C) = 1.81$ Å.²⁴

(24) T.-T. Liang and K.-C. Chi, *Acta Chim. Sinica*, **31** (2), 155 (1965).

(25) Related discussions of d–p π bonding: D. W. J. Cruickshank, *J. Chem. Soc.*, 5846 (1961); D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel, and L. E. Sutton, *ibid.*, 332 (1954). The simple view of π bonding in K and L would involve d–p, P–O overlap. However, to mention two possible perturbations, there might be mixing of phosphorus orbitals resulting in stronger π and/or σ bonds and π bonding involving hybrid oxygen orbitals, such as sp², would be possible.

here have been no structural reports on a protonated or alkylated phosphine oxide, but the structures of aryl phosphate esters are known and indicate $r(\text{P}-\text{OR}) \sim 1.55 \text{ \AA}$ and $\angle(\text{POR}) \sim 120^\circ$.²⁶ Using these parameters, a reasonable model for the structure would involve an sp^2 oxygen atom. It is impossible to intuitively predict exactly what oxygen orbitals are involved in π bonding in L, but it is clear that the longer P-OR bond length and the use of some oxygen orbital character in σ bonding should lead to a reduction in P-O π bonding.²⁶ In addition, the presence of a lone pair on L and the consequent orbital contractions might be detrimental to strong π bonding. The large bond energies of P-O bonds in $(\text{CH}_3)_3\text{PO}$ ($\text{C}_6\text{H}_5)_3\text{PO}$ (139 and 128 kcal/mole, respectively)⁴ are consistent with strong π bonding in K. The bond length of the P-O bonds of $(\text{CH}_3\text{O})_3\text{P}$ (91 kcal/mole)⁴ indicates the kind of decrease which might be expected upon protonation.

Therefore, although many factors can affect $\text{pK}'\text{s}$, judging stability of both acid and basic forms, solvation effects, etc., the large differences in basicity shown in Table III and consideration of bonding and bond energies certainly suggest that π bonding in phosphine oxides makes an important contribution to the structure. On the other hand, it appears that π bonding is quite weak in arsine and stibine oxides.

Substitution of CH_3O or HO for C_6H_5 in phosphine oxides reduces the basicity considerably (Table I). It thus appears that the inductive effect of the CH_3O

HO groups are predominant over resonance effects. In A and B there is probably a more complex π system than in C and D, but resonance effects might be quite different from carboxylates and other systems involving only p orbitals. We assume that in A and B, protonation is on the $\text{P}=\text{O}$ oxygen, but protonation on the OR oxygen has not been excluded.

Phosphine Sulfides. The difference of basicity of $(\text{CH}_3)_3\text{S}$ ($\text{pK}_{\text{BH}^+} = -3.8$) and $(\text{CH}_3)_3\text{P}$ ($\text{pK}_{\text{BH}^+} = 4$)¹² indicates that the differences between phosphine oxides and phosphine sulfides in Table I are due largely to the substitution of sulfur for oxygen. Therefore,

π bonding must also be important. However, Pearson has concluded there is less P-S than P-O π bonding,²⁶ and our basicity data are only suggestive. More data related to P-S π bonding are needed.

M Values. The M values for phosphine oxides are less than 1 by a considerable amount, indicating that these bases are not behaving as Hammett bases. Using symbols B' for Hammett base and B for the bases in this study¹²

$$\log f_B f_{B'H} / f_{BH} f_{B'} = (1 - M)(H_0 - \text{pK}_{\text{BH}^+}) \quad (3)$$

we have previously¹² discussed the relation of a low M value to acid-inhibited hydrolysis of *p*-nitrophenyl enylphosphinate and proposed that an important factor was a decrease in f_B with increasing acidity.²⁷ The tendency of phosphine oxides to form hydrogen bonds may be an important factor in this effect, and M values (Table I) can be explained in this framework. The important interaction of a neutral base with a sulfuric acid solvent should be by hydrogen bonding. Oxygen should normally form stronger hydrogen

bonds than nitrogen and nitrogen stronger than sulfur. Since the Hammett bases are anilines, the oxygen base should be salted in more strongly and $f_B/f_{B'}$ should decrease for phosphine oxides as acid concentration increases. The sulfur bases should be salted in less strongly than anilines and $f_B/f_{B'}$ should increase with increasing acid concentration. Both of these effects would explain the M values observed. This hypothesis also explains the M values for $(\text{CH}_3)_2\text{PO}_2\text{H}$ and $(\text{CH}_3)_2\text{PS}_2\text{H}$ compared to the other phosphine oxides and phosphine sulfides. These bases have two oxygens or sulfurs which can form hydrogen bonds and therefore ought to show lower M values than $(\text{CH}_3)_2\text{P}(\text{O})\text{C}_6\text{H}_5$ and $(\text{CH}_3)_2\text{P}(\text{S})\text{C}_6\text{H}_5$, as they do.

Experimental Section

Melting points were taken with a calibrated Mel-Temp block. Analyses were performed by Miss Heather King, UCLA micro-analytical laboratory. Nuclear magnetic resonance spectra were taken on a Varian Model A-60 instrument; tetramethylsilane was used as a standard. Infrared spectra were taken on a Perkin-Elmer Model 421 spectrophotometer.

Diphenylmethylphosphine Oxide. The oxide was prepared from diphenylmethylphosphine by oxidation with oxygen. The phosphine was prepared from diphenylchlorophosphine (Columbia Chemical Co.) in ether by addition of methylolithium in ether (Alfa Inorganics Inc.), followed by distillation. The oxide was recrystallized from benzene, mp $109-110^\circ$ (lit.²⁸ mp $110-111^\circ$). The infrared spectrum in KBr included absorptions at 1430 (aromatic) and 1293 cm^{-1} ($\text{P}=\text{O}$). The nmr spectrum shows a doublet at τ 8.0 with $J_{\text{PCH}} = 13 \text{ cps}$ and two multiplets with centers at τ 2.2 and 2.5 integrating as expected.

Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{PO}$: C, 72.21; H, 6.06. Found: C, 72.30; H, 6.24.

Dimethylphenylphosphine Oxide. This oxide was prepared by oxidation of the corresponding phosphine with oxygen. The phosphine was prepared from phenyldichlorophosphine (Victor Chemical Co.) and methylolithium and purified by distillation. The oxide is very hygroscopic and when very dry melts at $115-119^\circ$ (lit.²⁹ $107-110^\circ$). The infrared spectrum shows absorption at 1430 and 1410 cm^{-1} (aromatic) and 1285 cm^{-1} ($\text{P}=\text{O}$). The nmr spectrum in CDCl_3 exhibits a doublet at τ 8.22 with $J_{\text{PCH}} = 13 \text{ cps}$ and multiplets at τ 2.47 and 2.2 integrating as expected.

Dimethyl Methylphosphonate. This ester was prepared by treating trimethyl phosphite with methyl iodide. The ester was distilled at $84-89^\circ$ ($34-35 \text{ mm}$) [lit.³⁰ 71° (13 mm)]. The infrared spectrum shows absorptions at 1245 cm^{-1} ($\text{P}=\text{O}$) and 1030 and 1055 cm^{-1} (POC) as well as 1182 cm^{-1} . The nmr shows a doublet at τ 8.55 (area = 1) with $J_{\text{PCH}} = 17 \text{ cps}$ and a doublet at τ 6.33 with $J_{\text{POCH}} = 11 \text{ cps}$; integrations were in the expected ratio.

Diphenylmethylphosphine Sulfide. This sulfide was prepared by refluxing diphenylchlorophosphine and sulfur in CS_2 overnight.³¹ The solvent was removed, ether added, and an equimolar amount of methylolithium added to the solution. The sulfide distilled at $183-185^\circ$ (2 mm) [lit.³² 181° (1.5 mm)]. The infrared spectrum shows bands at 1410 , 1434 , and 1478 cm^{-1} (aromatic) and at 619 and 608 cm^{-1} ($\text{P}=\text{S}$).³³ The nmr spectrum shows a doublet at τ 7.82 with $J_{\text{PCH}} = 12 \text{ cps}$ and multiplets centered at τ 2.25 and 2.7 with the expected integration.

Dimethylphenylphosphine Sulfide. The corresponding phosphine was treated with sulfur in ethereal solution, the solvent evaporated off, and the product, dimethylphenylphosphine sulfide, was recrystallized from hot water, mp $42-43^\circ$ (lit.³³ mp 42°). The infrared spectrum includes bands at 1431 , 1405 , and 1413 cm^{-1} (aromatic) and at 585 cm^{-1} ($\text{P}=\text{S}$).³³ The nmr spectrum shows a

(28) (a) C. Seveflos and A. F. Isbell, *J. Org. Chem.*, **27**, 2573 (1962); (b) A. Michaelis and H. v. Soden, *Ann.*, **229**, 295 (1885).

(29) G. Wittig and U. Schollkopf, *Chem. Ber.*, **87**, 1318 (1954).

(30) G. Schrader, unpublished results; K. Sasse, "Methoden der Organischen Chemie (Houben-Weyl)," XII/1, Georg Thieme Verlag, Stuttgart, 1963, p 270.

(31) Similar to procedure of A. Michaelis, *Ann.*, **181**, 335 (1876).

(32) R. A. Zingaro and R. E. McGlothlin, *J. Chem. Eng. Data*, **8**, 226 (1963).

(33) R. A. Zingaro, *Inorg. Chem.*, **2**, 192 (1963).

(1) J. D. Dunitz and J. S. Rollett, *Acta Cryst.*, **9**, 327 (1956).

(2) L. M. Sweeting and K. Yates, *Can. J. Chem.*, **44**, 2395 (1966).

doublet at τ 8.1 with $J_{\text{PClH}} = 13$ cps and multiplets at τ 2.15 and 2.52 with the expected integration.

Anal. Calcd for $\text{C}_6\text{H}_{11}\text{PS}$: C, 56.44; H, 6.52. Found: C, 56.28; H, 6.60.

Sodium Dimethyldithiophosphinate. Tetramethylbiphosphine disulfide was treated with an equimolar amount of SO_2Cl_2 to give dimethylthiophosphinyl chloride,³⁴ bp 50–55° (3 mm) [lit.³⁴ 82–83° (16 mm)]. The acid chloride was treated with sodium hydrogen sulfide³⁵ and the sodium salt of the dithio acid recrystallized from benzene–ethanol. The infrared spectrum shows bands at 3300–3400, 1619, 1400 and 1272, 937, 905, 731, and 717 cm^{-1} . The nmr spectrum in D_2O exhibits a doublet at τ 8.01 with $J_{\text{PClH}} = 13$ cps (standard = $(\text{CH}_3)_2\text{Si}(\text{CH}_3)_2\text{SO}_3\text{Na}$). The preparation of dimethylphosphinic acid has been described.¹³

(34) R. Cölln and G. Schrader, *Chem. Zentr.*, 12696 (1959).

(35) T. A. Mastryukova, A. E. Shipov, and M. E. Kabachnik, *Zh. Obshch. Khim.*, 31, 507 (1961); *Chem. Abstr.*, 55, 22101 (1961).

Measurement of pK 's. The solutions were made up as previously described¹³ at a concentration of $\sim 10^{-1} M$ for both standard and substrate.

Chemical shifts (Δ) were plotted against H_0 (Figure 1) to give approximate pK and M values according to eq 2. The approximate pK can be obtained from the H_0 value at $1/2(\Delta_B - \Delta_{BH^+})$. The approximate M value can be obtained graphically or by solution of eq 2 at some point other than $H_0 = pK_{BH^+}$. Values of Δ_B and Δ_{BH^+} were then obtained from the smoothed curve of Δ vs. H_0 : Δ_B is the Δ at H_0 (0.5% protonation) = $pK_{BH^+} - 2.3/M$, Δ_{BH^+} is the Δ at H_0 (99.5% protonation) = $pK_{BH^+} + 2.3/M$. A least-squares analysis of the data was then done using eq 2 and points between 5 and 95% protonation, i.e., between $H_0 = pK \pm (1.3/M)$.

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Comparison of Liquid-Phase and Gas-Phase Reactions of Free Radicals¹

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Abstract: The theoretical and practical effects of gas–liquid phase change on rates and products of free radical reactions are discussed, mostly in terms of ratios of rate constant for competing reactions. Effects of free volumes, concentration changes, solvent cages, and third bodies are now fairly well understood, but when enough competing reactions are involved, the effect of phase change may become complicated. Previous work provides several examples where phase change has, or has not, affected competing free radical reactions and several instances where solvent change has affected competitions. The present survey now suggests that solvation effects are widespread in free radical reactions but often obscured by the necessity of studying them in competing reactions. Solvation effects in the most inert solvents appear to be as far from gas-phase results as they are from solvation effects in the most polar solvents. Thus, comparisons of gas-phase and liquid-phase reactions of free radicals are important in any absolute measure of solvation effects.

During the development of free radical chemistry, the organic and polymer chemists have been concerned mostly with liquid-phase reactions, while physical chemists have been concerned mostly with gas-phase reactions. There has been little effort to correlate the work of the two groups. As considerable data have accumulated on each phase, with little overlap, several related questions arise. To what extent can we predict rates or products in one phase from data in the other? Is there any discernible change in rate constants with phase change? Why do some reactions proceed in both phases while others proceed only in one? Which phase should be chosen for preparative purposes? The object of this paper is to consider some reactions for which data on both phases are available, to deduce some generalizations, and to point out remaining problems. The next two portions of this section consider some theoretical aspects of phase changes, then some generalities about free radical reactions. The following section then reviews experimental data. Conclusions are summarized in the last section.

(1) This paper extends one presented to the Division of Organic Chemistry at the Symposium on Reactions of Free Radicals at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 7, 1965, and subsequently to the Colorado, California, and Santa Clara Valley Sections.

Theoretical Aspects of Phase Changes. One interesting aspect of phase change is the free-volume effect. When we assume that the activities of the reactants and the activated complex are measured by their vapor pressures and that attractive forces with other molecules are negligible, the partial pressure of each reactant is given by

$$p(v - b) = nRT$$

Here $v - b$ is the corrected volume in the van der Waals equation, corresponding roughly to the free volume of the container not occupied by molecules. When we go from (say) 0.01 M reactant in the gas phase to a 0.01 M solution in benzene at 50°, $v - b$ changes from about 999.7 ml/l. to about 250 ml/l. (assuming that there is no free volume in benzene at 0°K) and the vapor pressure of the reactant, in the absence of all interactions with the solvent, is increased fourfold. We neither find nor expect phase change to have much effect on rates of first-order reactions: although the vapor pressure of the reactant (in the liquid phase) is four times as great, the reactant is present in only one-fourth of the volume. However, for a second-order reaction, the product of the vapor pressures of the reactants is increased 16-fold while the volume is decreased only fourfold, and the

reaction per unit volume should be four times as
For a third-order reaction, the factor should be

the elegant treatments come to similar conclusions.
n^{2a} concludes that a reaction will go fastest in the
m which favors the association of reactants and
tes that a bimolecular reaction might be 20 times
in solution as in the gas phase. The collision
of reaction rates suggests that there should be
three times as many collisions between a pair
of molecules in solution as in the gas phase
at, for the same activation energy, the rate will be
proportionally higher.³ The absolute rate theory,
considerations of entropies of activation, leads
same final result.³

low pressures, the rates of some gas-phase reac-
become smaller than expected from rates at higher
res or in the liquid phase. In unimolecular
ns, first-order rate constants begin to fall off at
res which are insufficient to maintain an equi-
concentration of activated reactant molecules.
pressures range roughly from a fraction of a
eter of mercury for molecules with 6 or more
to some hundreds of millimeters for molecules
or fewer atoms.^{2c} In combinations of two atoms
all free radicals, the heat of reaction is sufficient
se immediate separation unless some of this heat
removed by collision with a third body. Thus,
ations of atoms normally require a third body
rmolecular) but bimolecular reactions of radicals
e less dependent on pressure as the complexity of
lical and the opportunities for internal dissipa-
the heat of reaction increase.^{2d}

re we examine data on rates of free radical reac-
and since the transition-state theory treats a rate
equilibrium, let us see what phase change does
easily measured and uncomplicated equilibrium
nt. Table I gives the equilibrium constants for
socation of N₂O₄ in the gas phase and in several
ts.⁴

Equilibrium Constants⁴ for N₂O₄ \rightleftharpoons 2NO₂ at 20°

Solvent	K, M	ΔH_0° , ^a kcal/mole
Gas phase	382	13.7
SiCl ₄	17.8	20.5
CS ₂	13.3	19.4
CCl ₄	8.05	18.8
CHCl ₃	5.53	21.2
EtBr	4.79	20.5
C ₆ H ₅ Br, C ₆ H ₅ Cl	3.7	19.4
C ₆ H ₆	2.23	22.2

ociations are endothermic.

n the free-volume aspect, the effect of phase
has the direction expected and is greater than
d; there is much less dissociation in solution.
er, the effect of solvent change on the equi-
constant is about one-third as large as the

W. Benson, "The Foundations of Chemical Kinetics," Mc-
ll Book Co., Inc., New York, N. Y., 1960: (a) p 504; (b) p
compiled by A. Wasserman; (c) p 234; (d) p 308.

J. Laidler, "Chemical Kinetics," 2nd ed, McGraw-Hill Book
Co., New York, N. Y., 1965, p 201.

A. Moelwyn-Hughes, "Kinetics of Reactions in Solution,"
Oxford, 1947, p 184, from data of Cundall.

effect of phase change. Further, the heats of dissocia-
tion vary erratically among the solvents and the spread
is almost as great as between gas phase and carbon
tetrachloride solution. The lack of correlation between
K's and ΔH 's shows that changes in entropies of solu-
tion largely compensate for changes in enthalpy terms.

Table II shows that the same considerations apply
in reaction rates as in the equilibria above. Rate con-
stants for the dimerization of cyclopentadiene in var-
ious media at 50° are listed in order of decreasing rate
constants.^{2b} Although the rate constants differ by
a factor of only 3 (0.5 log unit), the erratic but compen-
sating variations in frequency factors (40-fold) and in
activation energies (2.7 kcal/mole) again suggest im-
portant interactions of reactants and solvents.

Table II. Solvent Effects in the Dimerization of
Cyclopentadiene^{2b} at 50°

Solvent	-log k	log A	E, kcal/mole
Gas phase	5.2	6.1	16.7
CS ₂	5.2	6.2	16.9
Cyclopentadiene	5.2	5.8	16.2
AcOH	5.0	5.0	14.7
C ₆ H ₆	5.0	6.1	16.4
CCl ₄	4.9	6.7	17.1
EtOH	4.7	6.4	16.4
C ₆ H ₅ NO ₂	4.7	5.5	15.1
Paraffin	4.7	7.1	17.4

The examples above show that the effects of solvent
molecules on reacting solutes, whether they be com-
plexing, solvation, or restriction of motion, and even
with nonradical, nonpolar, nonhydrogen-bonding mate-
rials, are usually about as large as, and sometimes much
larger than, effects due to free volume or frequency of
collision.

Free Radical Reactions. Table III classifies reactions
of free radicals. Free radicals are commonly produced
in pairs by decompositions of peroxides or azo com-
pounds (reaction -1). They interact and destroy
each other in pairs by reactions 1 (combination) or
2 (disproportionation). Both reactions 1 and 2 cannot
be avoided, and if these were the only reactions of free
radicals, they would be of little interest. The interest
arises from the other reactions which compete with
reactions 1 and 2 and with each other. Reaction 3,
usually the abstraction of a hydrogen or halogen atom
(chain transfer in polymerization), is the most important
and most studied reaction of free radicals. Reaction
4, the addition of an atom or radical to a double or
triple bond (or to oxygen), is an essential step in the
free radical additions of many reagents to unsaturated
compounds, usually in combination with reaction 3.
Scission, reaction -4, is the reverse of 4, and is illus-
trated by the loss of ethylene units from an alkyl radical
and by the scission of *t*-butoxy to acetone and methyl.
Reaction 5, rearrangement, corresponds to internal
(unimolecular) abstraction or to other shifts of atoms
or groups within radicals.

Of the eight listed reactions of free radicals in Table
III, dissociation (-1), diffusion from cage (D), scission
(-4), and rearrangement (5) are first-order reactions;
the rest are bimolecular; occasionally 4 is termolecular.
Reaction conditions are usually chosen to limit the

Table III. Reactions of Free Radicals

No.	Type	Example (superscript indicates kinetic order)
-1 ¹	Dissociation	$ \begin{array}{c} R_2 \xrightleftharpoons[1^1]{1^1} 2R \cdot \xrightarrow{2^1} RH + (R-H) \\ \swarrow \quad \searrow \\ 1^1 \quad \quad D^1 \\ [2R \cdot] \\ \text{cage} \end{array} $
1 ²	Combination	
2 ²	Disproportionation	
D ¹	Diffusion from cage	
3 ²	Abstraction, transfer	$R \cdot + XY \xrightarrow{3^2} RX + Y \cdot$
4 ^{2(or 3)}	Addition	$ R \cdot + A=B \xrightleftharpoons[4^1]{4^2} RAB \cdot $
-4 ¹	Scission	
5 ¹	Rearrangement	$R \cdot \xrightarrow{5^1} R' \cdot$

important competing reactions to two or three. Rates, yields, or kinetic chain lengths commonly measure the competition between chain-terminating reactions 1 and 2 and chain propagations 3 and/or 4, as in halogenation, oxidation, polymerization, or telomerization. For long kinetic chains the competition between two reactions of types 3 and 4, or the competition of one of these with another of the reactions 3, 4, -4, or 5, may be measured by ratios of reaction products; reactions 1 and 2 and rate data can then be neglected. Thus both rate and product studies give us ratios of rate constants, and we need ratios of rate constants to predict rates or products. This paper will deal only with the effects of phase change on ratios of rate constants in free radical reactions, because ratios are the only bases available. Measurements of absolute rate constants require measurements of the very low concentrations of reactive radicals. Although such data are accumulating slowly, I know of no case where the absolute rate constants are available for the same reaction in both gas and liquid phases. If we had one set, we would still need another set to get ratios and to compare experimental results.

In considering the effects of phase change on these competitions, we should note that the effect of phase change on concentration can be very large. Thus the concentration of a pure organic liquid is about 10 *M*, while the concentration of a gas at standard conditions is only about 0.05 *M*. At 30-mm pressure and 200°, where many gas-phase reactions have been studied, the concentration of gas is only 0.001 *M*. Apart from any effect of phase change on equilibrium constant, normal concentration effects in phase change will favor dissociation in the gas phase (reactions -1 and -4), and association in solution (reactions 1 and 4).

Review of Experimental Data

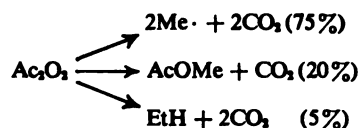
Phase change usually has little effect on ratios of rate constants. In the following discussion, emphasis is on the exceptions and on instances where concentration changes produce notable changes in results.

Unimolecular Decomposition to Product Radicals (Reaction -1). In decompositions of peroxides or azo compounds to give free radicals, we are concerned with the production of radicals, not with their reactions. Absolute rate constants are available; they show that the effect of phase change is small.

Raley, Rust, and Vaughan⁵ measured the first-order rate constants for decomposition of di-*t*-butyl peroxide in the gas phase and

in cumene, *t*-butylbenzene, and tributylamine as solvents. The vapor phase *k*₁ was about 75% as large as the *k*₁ in the three solvents. The solvent *k*₁ tended to decrease with the concentration of peroxide, an indication of induced decomposition. Apparently, the effect of phase change on *k*₁ is less than the effect of any induced decomposition. Here it would be useful to have some solution measurements at concentrations as low as those used in the gas-phase studies. Smid, Rembaum, and Szwarc⁶ carried out similar studies with dipropionyl peroxide and dibutyl peroxide. The first-order rate constants in dilute solutions in isooctane and *n*-hexane were close to those in the gas phase. They were 50-100% greater in benzene and toluene and still larger in polar solvents. Thus, the difference between the nonpolar solvents and the gas phase is less than the differences among solvents.

Cage Effects (Reactions 1 and D). When two radicals are formed very close together in solution (-1), the competition between their very fast combination (1) and their diffusion apart (D) affects the products of reaction. These competitions are normally important only in solution. Herk, Feld, and Szwarc⁷ generated methyl radicals by the decomposition of acetyl peroxide in the gas phase and in isooctane solution at 65°. In isooctane, the products were



Carrying out the reaction in the presence of styrene resulted in scavenging of free methyl radicals but did not affect the yields of methyl acetate or ethane. These are therefore nonradical or cage products, formed so rapidly that the solvent or scavenger cannot intervene. In the gas phase, the intermediate radicals separated at once and no methyl acetate was formed; it is therefore a cage product. More ethane was formed in the gas phase, but since this was largely eliminated by the addition of iodine, it is clear that ethane arises from diffusing methyl radicals in the gas phase but is mostly a cage product in solution. Recent work shows how cage recombination of radicals from acetyl peroxide leads to slightly lower rate constants for decomposition^{8a} than in the gas phase, especially in solvents of higher viscosity.^{8b}

Herk and co-workers⁷ found a much larger cage effect in the photodecomposition of azomethane in isooctane solution. Under conditions where only 6% of the methyl radicals from acetyl peroxide combined to give ethane, 65% of the methyl radicals from azomethane gave ethane. The ethane practically disappeared from the gas-phase decomposition of azomethane.

Lyon and Levy⁹ have reported an interesting comparison of the gas-phase and liquid-phase decompositions of azomethane according to the procedure of Herk, Feld, and Szwarc. They decomposed mixtures of azomethane and hexadeuterioazomethane. In the gas phase there was statistical combination of methyl and deuteriomethyl radicals to form ethane. In solution, all the ethane found was either hexadeuterated or undeuterated. Lyon¹⁰ showed also that a liquid phase

(5) J. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Am. Chem. Soc.*, **70**, 1336 (1948).

(6) J. Smid, A. Rembaum, and M. Szwarc, *ibid.*, **78**, 3315 (1956).

(7) L. Herk, M. Feld, and M. Szwarc, *ibid.*, **83**, 2998 (1961).

(8) (a) J. W. Taylor and J. C. Martin, *ibid.*, **88**, 3650 (1966); (b) W. Braun, L. Rajenbach, and F. R. Eirich, *J. Phys. Chem.*, **66**, 1591 (1962).

(9) R. K. Lyon and D. H. Levy, *J. Am. Chem. Soc.*, **83**, 4290 (1961).

(10) R. K. Lyon, *ibid.*, **86**, 1907 (1964).

necessary for a cage effect; it can be demonstrated at high pressures of gases. In the photolysis of ethane in propane at 98° at pressures up to 50 atm as the densities of the mixtures increased from 0.260 g/cc, the ethane:methane ratio increased from 0.063 to 0.10. This increase in ethane indicates that more propane does not supply more hydrogen atoms to methyl radicals as much as it favors cage combination. All of the ethane was formed in the cage.

Combination and Disproportionation of Radicals (Reactions 1 and 2). Here both competing reactions are second order and involve the same reactants. The effect of phase change are small.

Stefani, and Szwarc¹¹ measured the combination and disproportionation of ethyl radicals formed in the photolysis of ethane. The ratio of these rate constants was measured by a mixture of ethylene plus ethane to butane. In the gas phase, the ratio increased from 0.12 at +40° to 0.16 at -65°, independent of pressure (hence combination of two ethyl radicals does not require a body below 40°). In isooctane, the same ratio increased from 0.15 at 85° to 0.34 at -191°. Thus the competition between disproportionation and combination depends more on temperature than on reaction medium. These authors think that both reactions involve similar transition states, disproportionation being slightly favored by low temperatures and solvent cages.

Reactions of Alkylperoxy Radicals. The group at the Development Co.¹² was the first to suggest that termination of alkylperoxy radicals produces alkoxy radicals. It now appears that these reactions take place in the decomposition of an unstable intermediate radical.¹³ Decomposition of this intermediate produced alkoxy radicals in solution (apparently independent of the viscosity of the solvent¹⁴) but not in the gas phase.

Further, secondary and tertiary alkylperoxy and alkoxy radicals behave very differently. Since these reactions are still under investigation, discussion is deferred. However, these efficiencies of chain termination are important in determining kinetic chain lengths in the chlorination of alkanes (see below) and in induced decompositions of hydroperoxides; phase changes are important because of cage effects.

Molecular Abstractions of Hydrogen or Halogen (Reaction 3). Hass, McBee, and Weber¹⁵ made a classic study of the relative reactivities of primary, secondary, and tertiary carbon-hydrogen bonds toward chlorine in the chlorination of isopentane. Some of their experiments, carried out in both liquid and gas phases over a wide range of temperatures, are summarized in Table IV. In either phase the relative reactivities of primary, secondary, and tertiary hydrogen atoms approach unity with increasing temperature but the selectivity is lower in the liquid phase. Selectivity in the liquid phase at 100° corresponds to the low selectivity in the gas phase at 600°. The best explanation known for this phase difference is the following.

Chlorine atom in solution is so reactive and its lifetime is so short that its reactions depend on the details of a series of cage encounters ("cage effect") as well as on the relative reactivities of the surrounding

carbon-hydrogen bonds involved. It should follow that this liquid-phase-gas-phase difference will disappear as the attacking radicals become less reactive and their lifetimes become long compared with the times required for diffusion.

Table IV. Relative Rates of Reaction of C-H Bonds with Chlorine Atoms¹⁵

	Temp, °C	Tertiary	Secondary	Primary
Liquid phase	-60	13	8.5	1.00
	100	3	2	1.00
Gas phase	300	4.43	3.25	1.00
	600	3.5	2.2	1.00

This work has recently been corroborated and extended by Tedder and co-workers.¹⁶ In the gas-phase chlorination of *n*-hexane^{16a} in excess nitrogen at 40–212°, the relative reactivity of the total secondary and primary hydrogen atoms is $k_s/k_p = (2.2 \pm 0.6) \exp\{-(214 \pm 127)/RT\}$. In a solution containing carbon tetrachloride, the corresponding relation for -70 to +39° is $k_s/k_p = (0.8 \pm 0.2) \exp\{-(597 \pm 20)/RT\}$.

To the extent that these frequency factors and activation energies are reliable, the greater selectivity of the gas-phase chlorination at 39–40° ($k_s/k_p = 3.11$ vs. 2.14) is due mostly to the ratios of the *A* factors (2.74 times as great in the gas) but largely offset by the activation energy term (0.54 times as great at 40° in the gas). These authors conclude that the effect of phase change on the ratios of the *A* factors is probably associated with the cage effect, but that the differences in the activation energies are probably associated with solvation of chlorine atoms in solution, even in the least polar solvents. (For a simple cage effect, selectivities should become more similar at increasing temperatures; instead, they diverge.)

They also compared reactivities in chlorination of various C-H bonds in normal acid chlorides and fluorides of 5–7 carbon atoms.^{16b} They find that, in the gas phase, the acid halide group has no effect on reactivity of C-H bonds beyond the β -carbon atom, but in the liquid phase the effect of that group is readily detected at separations even of three additional carbon atoms. The effect of phase change is attributed to solvation in the transition state of the hydrogen chloride being formed.

When these results are compared with those of Russell and Walling¹⁷ on complexing solvents in chlorination, their "noncomplexing solvents" (alkanes and carbon tetrachloride) must instead be weakly complexing solvents in comparison with benzene derivatives and carbon disulfide.^{16a} Apparently, enough solvation to affect k_s/k_p by a factor of about 2 cannot be avoided in solution chlorinations.

No effect of phase change has appeared in competing abstraction reactions of methyl radicals, perhaps because they are less polar and less susceptible to solvation than reactions of chlorine atoms. Trotman-

(16) (a) I. Galiba, J. M. Tedder, and J. C. Mattou, *J. Chem. Soc., Sect. B*, 604 (1966); (b) H. Singh and J. M. Tedder, *ibid.*, 605 (1966).

(17) E. S. Huyser, "Advances in Free Radical Chemistry," Vol. 1, G. H. Williams, Ed., Academic Press Inc., New York, N. Y., 1963, p 77.

P. S. Dixon, A. P. Stefani, and M. Szwarc, *J. Am. Chem. Soc.*, **85**, 963.

E. R. Bell, J. H. Raley, F. F. Rust, F. H. Seubold, and W. E. Bawn, *Discussions Faraday Soc.*, **10**, 242 (1951).

P. D. Bartlett and T. G. Traylor, *J. Am. Chem. Soc.*, **85**, 2407.

R. Hiatt and T. G. Traylor, *ibid.*, **87**, 3766 (1965).

H. B. Hass, E. T. McBee, and P. Weber, *Ind. Eng. Chem.*, **28**, 333.

Dickenson¹⁸ has measured the absolute rate constants for abstraction reactions of methyl radicals with various hydrocarbons in the gas phase at 100° by comparing these rates with those for combinations of methyl radicals. Edwards and Mayo¹⁹ have measured the relative rates of abstraction reactions of methyl radicals, generated by decomposition of acetyl peroxide, with carbon tetrachloride and with hydrocarbons, all in solution at the same temperature. Table V shows that the relative reactivities of several kinds of carbon-hydrogen bonds in the two phases as measured by the two methods are nearly identical. The agreement also shows that phase change does not affect the competition between the bimolecular combination and abstractions.

Table V. Relative Rates of Reaction of C-H Bonds with Methyl Radicals at 100°

Compd	k_{RH} , gas ¹⁸ at 100° × 10 ⁶	$\frac{k_{RH}}{k_{CCl_4}}$, soln ¹⁹ at 100°	$\frac{k_{RH}(\text{gas})}{k_{RH}/k_{CCl_4}(\text{soln})}$
Benzene ^a	0.091	0.04	2.3
Acetone	1.0	0.40	2.5
Toluene	1.9	0.75	2.5
1-Octene	7.7	3.2	2.4
Cyclohexane	3.4	4.5 ^b	0.8 ^b

^a It now appears that methyl radicals do not abstract hydrogen directly from benzene but by a more complex process. ^b The discrepancy with cyclohexane is accounted for by the suggestion of DeTar and Wells²⁰ that the chain chlorination of cyclohexane by carbon tetrachloride depleted the concentration of carbon tetrachloride in the solution experiment.

Additions of Free Radicals to Multiple Bonds (Reactions 4 and -4). Additions of free radicals to oxygen or unsaturated compounds (4) are usually both exothermic and reversible; the reverse reaction is scission or cracking (-4). As in combinations of two radicals (1), when the radicals and molecules are small, a third body is needed to prevent immediate dissociation, as in reaction of methyl radicals with oxygen, a third-order reaction.

The importance of reversibility, even in the liquid phase below 100°, is demonstrated by the isomerization of *cis* to *trans* isomers by bromine atoms²¹ and thiyl radicals,²² and by ceiling temperatures in vinyl polymerization.²³ Mass action and enthalpy effects favor additions at higher concentrations and at lower temperatures; entropy effects favor scission in the gas phase at high temperatures. Benson²⁴ has recently calculated the effects of oxygen pressure and temperature on the fractional conversion of various alkyl radicals to the corresponding alkylperoxy radicals. His paper also shows the effects of changes in resonance stabilization of the initial and final radical on the balance between addition and scission.

(18) A. F. Trotman-Dickenson, *Discussions Faraday Soc.*, **14**, 230 (1953).

(19) F. G. Edwards and F. R. Mayo, *J. Am. Chem. Soc.*, **72**, 1265 (1950).

(20) D. F. DeTar and D. V. Wells, *ibid.*, **82**, 5839 (1960).

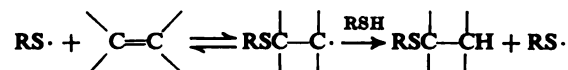
(21) M. S. Kharasch, J. V. Mansfield, and F. R. Mayo, *ibid.*, **59**, 1155 (1937).

(22) See, for example, C. Walling, and W. Helmreich, *ibid.*, **81**, 1144 (1959).

(23) F. S. Dainton and K. J. Ivin, *Quart. Rev. (London)*, **12**, 61 (1958).

(24) S. W. Benson, *J. Am. Chem. Soc.*, **87**, 972 (1965).

Sivertz and co-workers have measured rates of additions of mercaptans to alkenes in the gas phase²⁵ and in benzene solution.²⁶ They report that over-all rates in the gas phase have a negative temperature coefficient which they attribute to the reversible addition of RS· radicals ("complex formation")



In benzene solutions, the over-all activation energies are positive but small; reversibility at normal concentrations is less important. Data are inadequate to tell much more about the effect of phase change. The gas-phase addition of hydrogen bromide to propylene²⁷ also has a negative temperature coefficient.

Competition between Abstraction and Addition (Reactions 3 and 4). Abstraction and addition reactions of free radicals often compete. Since only the addition reaction is immediately reversible, both concentration and temperature may affect comparison of gas-phase and liquid-phase reactions. From a 10% solution of chlorine and toluene at 0° in the dark, Kharasch and Berkman²⁷ found that 55% of the chlorine reacted by substitution in the side chain and 45% by addition to the benzene ring. On the other hand, the gas-phase chlorination of toluene would give only benzyl chloride. In solution, the addition of a chlorine atom to the benzene ring is readily followed by reaction with another chlorine molecule and completion of addition. However, at the lower concentrations and higher temperatures used in gas-phase reactions, the concentration of the free radical formed by addition of the chlorine atom is inadequate to support much addition. The irreversible displacement of a side-chain hydrogen atom is therefore the dominant reaction, and the observed product is benzyl chloride.

The chlorination of an alkene may occur by addition to the double bond to give a dichloride or by hydrogen abstraction to give an allylic chloride. In the gas-phase free radical reaction,²⁸ addition predominates at low temperatures and is replaced by allylic substitution at high temperatures. This shift seems to be due mostly to the reversibility of the addition of chlorine atoms to alkenes at high temperatures. In the liquid phase, the results are complicated by the intrusion of an ionic reaction. Thus, Burgin and co-workers²⁹ report that pure isobutylene and chlorine do not react in the gas phase in the dark below 150°. However, as soon as a liquid film appears at lower temperatures, methallyl chloride is formed very rapidly. This reaction is not affected by the presence of oxygen, which inhibits free radical chlorinations. Poutsma³⁰ has recently and ably extended this work. In the liquid phase most alkenes chlorinate by two mechanisms, one free radical and oxygen inhibited, the other ionic and not affected

(25) C. Sivertz, W. Andrews, W. Elsdon, and K. Graham, *J. Polymer Sci.*, **19**, 587 (1956); D. M. Graham, R. L. Mieville, R. H. Pallen, and C. Sivertz, *Can. J. Chem.*, **42**, 2250 (1964).

(26) R. Back, G. Trick, C. McDonald, and C. Sivertz, *ibid.*, **32**, 1078 (1954); R. H. Pallen and C. Sivertz, *ibid.*, **35**, 723 (1957).

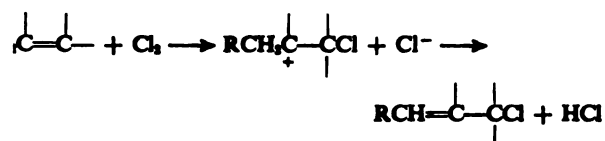
(27) M. S. Kharasch and M. G. Berkman, *J. Org. Chem.*, **6**, 810 (1941).

(28) H. P. A. Groll and G. Hearne, *Ind. Eng. Chem.*, **31**, 1530 (1939).

(29) J. Burgin, W. Engs, H. P. A. Groll, and G. Hearne, *ibid.*, **31**, 1413 (1939).

(30) M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2161, 2172, 4285, 4293 (1965).

oxygen. The ionic reaction gives mostly allyl substitution.



free radical chlorination gives both addition and substitution products, depending on the alkene. Here the change greatly affects the course of a chlorination because a competing polar reaction, requiring solution of ions, is possible only in the liquid phase.

The examples below describe abstraction and addition reactions of phenyl radicals with toluene and show that the change has little effect on other abstraction-addition competitions when the addition is not reversible.

Jacobs and Szwarc¹¹ discussed the effect of phase change on reactions of phenyl radicals with toluene. In solution, the reaction of phenyl radicals with toluene had been reported to produce only bibiphenyls, not bibenzyl. However, in the gas phase above 100°C, the principal product is bibenzyl. Only with the higher temperatures and lower temperatures usually associated with solutions is the concentration of the addition product of the phenyl radical to the benzene ring high enough for a hydrogen atom to be abstracted and for the reaction to be completed.

The recent work in solution has given better measures of the addition/abstraction ratio for reaction of phenyl radicals with toluene. For 80°C, Hey¹² gives 6.7. For 60°C, the data of Pryor,¹³ give 1.14. The apparent effect of temperature here is the opposite of that expected, but the results were obtained by different techniques. If scission of the phenyl radical-toluene adduct is fast, the addition/abstraction ratio is proportional to the concentration of phenyl radicals. Quantitative extensions of such work to other phases would be of interest. The addition/abstraction ratio is already known^{12,13} to depend on substitution in the phenyl radical.

However, where the addition reaction is irreversible, the effect of phase change on the addition-abstraction competition is small. Jacobs and co-workers have measured the relative rates of reaction of fluoromethyl radicals with 2,3-dimethylbutane (by hydrogen abstraction, k_2) and with a series of vinyl compounds (by addition, both the gas phase¹⁴ and the liquid phase.¹⁵ Differences in activation energies and frequency factors were measured in the gas phase from 65 to 180°C and in the liquid phase from 0 to 95°C. The relative reactivities of the alkenes, measured by k_4/k_2 at 65°C, increased 200-fold when the least reactive, vinyl fluoride, is compared with the most reactive, 2,3-dimethyl-1,3-butadiene. This increase is due to a decrease in $E_4 - E_2$; the A_4/A_2 factors remain essentially constant. In the liquid phase¹⁵ the values of $E_4 - E_2$ are substantially the same as in the gas phase. The k_4/k_2 and the A_4/A_2 tended to be 20–30% larger on the average than the corresponding gas-phase values. In an earlier paper,¹⁶ this phase difference was attributed to some lag in stabilization of the adduct in the liquid phase. In this case, where addition is irreversible, phase change and the low free volume of the liquid affect the addition and abstraction reactions to about the same extent.

Jacobs and Mayo¹⁷ studied the di-*t*-butyl peroxide initiated chlorination of ethylene and carbon tetrachloride at 140°C, in the liquid phase in three solvents, and in the gas phase at total pressures of 1–28 atm. The objective was to determine the effects of phase change and phase change on the variation with n of the

transfer constants of the radicals $\text{Cl}_n\text{C}(\text{C}_2\text{H}_5)_n$. The transfer constants, C_n , are defined as (rate constant for chlorine abstraction from CCl_4 by $\text{Cl}_n\text{C}(\text{C}_2\text{H}_5)_n$)/(rate constant for addition of the same radical to ethylene); they measure directly the competition between reactions 3 and 4 of ω -trichloroalkyl radicals. These transfer constants were known to change about 40-fold as n increased from 1 to 4 in the liquid phase at 70°C. Since this effect seems to be due to increasing separation of the trichloromethyl group from the free valence in the growing polyethylene radical, effects of both solvent change and phase change were expected. At 140°C, the effect of changing the solvent from *n*-octane to methanol hardly exceeded 30%. When the results in octane and at 1.2 atm in the gas phase are compared, the values of C_1 are nearly identical and the indicated value of C_1 in the gas phase is about twice the octane value. While the results for C_2 and C_3 are subject to more experimental error, phase change only exaggerates slightly the very large drift in C_n with increasing n .

Competition between Chain Propagation (3 and 4) and Termination Reactions (1 and 2). If propagation is fast enough, chain reactions can proceed nearly as well in normal low gas-phase concentrations as in the liquid phase. One example is the free radical chlorinations above. Another is the free radical addition of hydrogen bromide to double bonds.^{18,19} On the other hand, while the photochemical addition of hydrogen sulfide to 1-butene would proceed readily in the liquid phase at 0 or –78°C, reaction under ultraviolet illumination in the gas phase at room temperature at a total pressure of 300 mm was very slow.⁴⁰ At this low concentration of reactants, one of the propagation steps was unable to compete with chain termination. These relations are complicated by the reversibility of the addition reaction and by the negative temperature coefficient of the over-all addition reactions in the gas phase.²⁵

A similar situation arises in autoxidations. Although many initiated autoxidations proceed readily at or below 100°C in the liquid phase, gas-phase reactions of similar chain lengths require temperatures of 200°C or more at pressures of about 1 atm. This difference is largely an effect of reactant concentration on the competition between chain propagation and termination reactions. Although the initiated oxidation of isobutane gives chain lengths of only about one at a total pressure below 1 atm at 150°C, much longer chains can be obtained at superatmospheric pressures (see below).

Competition between Abstraction (3) or Addition (4) and Rearrangement Reactions (5). My discussion of the change in transfer constant with chain length in the telomerization of ethylene and carbon tetrachloride oversimplified the situation. In the liquid-phase reaction, kinetic chains are very long and only normal telomers are obtained. In the gas phase at 1 atm where the total concentration of reactants is only about 0.03 *M*, only 20–30% of the products obtained are normal telomers; the remaining 70–80% are isomers of normal telomers,²⁷ arising by rearrangement reactions such as



The rearrangements of the indicated radicals compete with both addition to ethylene (4) and abstraction from

(38) W. E. Vaughan, F. F. Rust, and T. W. Evans, *J. Org. Chem.*, **7**, 477 (1942).

(39) D. A. Armstrong and J. W. T. Spinks, *Can. J. Chem.*, **37**, 1002, 1210 (1959).

(40) W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **7**, 472 (1942).

M. T. Jacobs and M. Szwarc, *Nature*, **170**, 312 (1952).
D. H. Hey, "Vistas in Free Radical Chemistry," W. A. Waters, Ed., Pergamon Press, New York, N. Y., 1959, pp 217 and 218.
W. A. Pryor, J. T. Echols, Jr., and K. Smith, *J. Am. Chem. Soc.*, **88**, 59 (1966).

J. M. Pearson and M. Szwarc, *Trans. Faraday Soc.*, **60**, 553

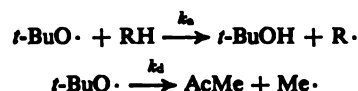
G. E. Owen, Jr., J. M. Pearson, and M. Szwarc, *ibid.*, **60**, 564

P. S. Dixon and M. Szwarc, *ibid.*, **59**, 112 (1963).

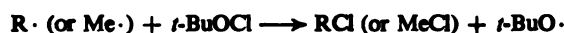
V. Jaacks and F. R. Mayo, *J. Am. Chem. Soc.*, **87**, 3371, 5811

carbon tetrachloride (3). The indicated products continue to react with ethylene and/or carbon tetrachloride to give telomer isomers. These rearrangements are due more to a concentration effect than to a phase change. As the concentrations of ethylene and carbon tetrachloride decrease, unimolecular rearrangements such as those above replace the normal bimolecular addition and displacement reactions. These rearrangements become less important at higher pressures in the gas phase. Such rearrangements become of increasing importance in solution in unreactive solvents.⁴¹

Competition between Abstraction and Scission (Reactions 3 and -4). Walling and co-workers have examined in detail the competition between the reactions



in chain decompositions of *t*-butyl hypochlorite where the fast complementary step is



Of special interest here are their measurements⁴² of k_a/k_d at 5:1 ratios of cyclohexane and *t*-BuOCl in the gas phase, in several solvents, and at several temperatures. Some of their results are summarized in Table VI. Each k_a/k_d ratio represents the slope of a (linear) plot of *t*-BuOH/AcMe found against the concentration of cyclohexane in the gas phase or in the chosen solvent. Solvents are arranged in order of decreasing values k_a/k_d .

Table VI. Solvent Effects⁴² on Reactions of *t*-Butoxy Radicals at 40°

Solvent	k_a/k_d	$E_d - E_a$	$\log A_a/A_d$
Gas phase	584	10.56	-4.61
Cl ₂ FC-CF ₂ Cl	52.8	9.65	-5.04
C ₂ Cl ₄	39	8.72	-4.49
C ₆ H ₅ Br	25.4	8.17	-4.34
C ₆ H ₆	24.7	8.66	-4.63
<i>m</i> -C ₆ H ₄ Cl ₂	24.3	8.40	-4.49
C ₆ H ₅ F	22.4	7.85	-4.15
<i>o</i> -C ₆ H ₄ Cl ₂	19.2	8.14	-4.43
C ₆ H ₅ CN	16.9	8.28	-4.58
C ₆ H ₅ Cl	16.4	7.21	-3.82
C ₂ HCl ₃	14.2	7.34	-3.99
<i>trans</i> -C ₂ H ₂ Cl ₂	14.2	7.69	-4.16
<i>cis</i> -C ₂ H ₂ Cl ₂	9.1	7.04	-3.92
MeCN	8.1	9.54	-5.73
AcOH	2.9	5.95	-3.66

In the gas phase, bimolecular hydrogen abstraction is favored over unimolecular decomposition by a factor of at least 10 in comparison with the liquid phase. Considerations of free volume or collision frequency predict a shift in the *opposite* direction. Thus, even in the most inert fluorocarbon solvent, solvation or cage effects far outweigh any effect of phase change expected from a noninteracting solvent. Among different solvents at 40°, k_a/k_d varies by a factor of up to 18. The differences in activation energies are erratic but mostly compensated by changes in ratios of *A* factors. Al-

(41) R. Kh. Friedlina, S. N. Aminov, and A. B. Terent'ev, *Dokl. Akad. Nauk SSSR*, 156, 1133 (1966); *Chem. Abstr.*, 61, 6913 (1964); 64, 1949 (1965).

(42) C. Walling and P. J. Wagner, *J. Am. Chem. Soc.*, 86, 3368 (1964).

though neither changes in $E_d - E_a$ nor in $\log (A_a/A_d)$ parallel those in k_a/k_d , changes in these factors mostly compensate each other, as in the equilibrium and non-radical reactions in the introductory section.

The effect of phase change on k_a/k_d is the largest one I know about in free radical reactions. Apparently solvation or complexing favors the unimolecular cleavage over the bimolecular hydrogen abstraction, but we cannot tell whether complexing promotes or hinders both competing reactions.

Competition between Abstraction (3), Cleavage (-4), and Termination Reactions (1 and 2). My last example deals with the oxidation of isobutane⁴³ in gas and liquid phases at 100–150°. This example shows how the competition of several reactions, each affected in a simple way by concentration changes with phase change, can affect both products and apparent rate constants. Table VII gives the liquid-phase products and the chain

Table VII. Products of Oxidation of Isobutane at 100–150°

Liquid phase \longrightarrow mostly <i>t</i> -BuO ₂ H + some <i>t</i> -BuOH + <i>t</i> -Bu ₂ O ₂	
<i>t</i> -BuO ₂ · + <i>t</i> -BuH \longrightarrow <i>t</i> -BuO ₂ H + <i>t</i> -Bu·	(6)
<i>t</i> -Bu· + O ₂ \longrightarrow <i>t</i> -BuO ₂ ·	(7)
2 <i>t</i> -BuO ₂ · \longrightarrow 2 <i>t</i> -BuO· + O ₂	(8)
<i>t</i> -BuO· + <i>t</i> -BuH \longrightarrow <i>t</i> -BuOH + <i>t</i> -Bu·	(9)
Gas Phase	
Low pressure \longrightarrow mostly AcMe + MeOH	
High pressure \longrightarrow increasing proportions of liquid-phase products	
<i>t</i> -BuO· \longrightarrow AcMe + Me·	(10)
Me· $\xrightarrow{\text{O}_2}$ MeO ₂ · \longrightarrow MeO·	(11)

steps through which they arise. In the gas phase at subatmospheric pressure at 155°, the principal products are acetone and methanol. Here, the concentration of isobutane is too low to support abstraction (6 in Table VII) in competition with reaction 8. The concentration of isobutane is also too low to support the bimolecular abstraction (9) in competition with the unimolecular cleavage (10). The resulting methyl radicals react with oxygen by an analog of reaction 7 and most of the resulting methylperoxy radicals are converted to methoxy radicals by an analog of reaction 9. As the pressure of isobutane is increased, displacement reactions 6 and 9 begin to replace chain termination and cleavage reactions 10. However, the methylperoxy and methoxy radicals are so much more reactive in chain termination than the corresponding *t*-butylperoxy or *t*-butoxy radicals, either with themselves or with the *t*-butyl derivatives, that a small proportion of surviving methyl radicals and their oxygenated derivatives retards the over-all rate of oxidation. A corresponding effect appeared when we diluted the liquid-phase oxidation with an inert solvent. Cleavage of *t*-butoxy radicals set in and decreased the effective value of $k_p/k_t^{1/2}$ for the liquid phase. Thus, both the gas-phase and the liquid-phase values of $k_p/k_t^{1/2}$ were complicated by methyl radicals from cleavage, and there were too many variables to isolate the effect of phase

(43) T. Mill, F. R. Mayo, and D. G. Hendry, paper presented to the Division of Organic Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

e. We conclude that the effect of phase change is small in comparison with other complications.

Summary

rates and products of reactions of free radicals from competition among several alternative ones. The commonly large differences in concentration between liquid-phase and gas-phase reactions are obvious differences in gross rates of reaction.

the most important competing reactions are of first (and second) order, yields and products are decided as well. Two other aspects of concentration can be experimentally important: the cage effect and the slowing of unimolecular reactions at high pressures. The former can be observed, and the latter is eliminated, at higher pressures in the gas phase. These effects are expected and largely predictable.

The most important contribution of this paper is to emphasize the importance of solvation in reactions of free radicals in solution; perhaps there are no really free radicals in solution in the gas-phase sense.⁴⁴ Chemists have been slow to recognize this situation because nearly all our information comes from ratios of rate constants for competing reactions where solvation has little effect on both.

However, in the cleavage and addition reactions of alkoxy radicals⁴⁵ there is a marked and clear effect of solvent and phase change. In two reactions as similar as the reaction of a tertiary carbon atom with a primary and a secondary hydrocarbon, an effect has now been detected.^{16a} Other examples of solvation were the association of nitrogen with olefins and (in nonradical reactions) the dimerization of isopentadiene and the chlorination of isobutylene. It now appears that solvents interact to some extent with free radicals as well as ions and that gas-phase studies are

essential to establish the effects of zero solvation in liquid-phase reactions.

Since studies of competing reactions do not tell us whether these reactions are individually accelerated or retarded by solvation, it is important to measure the absolute rate constants for the same reaction at the same temperature in the gas phase and in solution. In further studies of competing reactions, a few more of the most and least polar reactions should be compared in the two phases to see if the distinction between chlorine atoms and alkyl radicals is as sharp as it now seems. The effects of remote substituents^{16b,22} seem to be a sensitive tool. Because of the importance of reactions of aryl radicals with aromatic hydrocarbons, further work on the competition of addition and transfer reactions of alkylbenzenes^{27,31-33} also seems desirable.

In choosing experimental conditions for practical synthesis through free radicals, the following factors deserve consideration. Liquid-phase reactions require small volumes and favor bimolecular reactions and cage products. Gas-phase reactions usually employ low concentrations which can moderate fast reactions, permit use of high temperatures without high pressures, favor unimolecular reactions, and eliminate cage reactions. High-pressure gas reactions resemble those in the liquid phase. However, the choice of phase depends mostly on consideration of the competing reactions in Table III and how the competition will be affected by phase or concentration changes.

Finally, wall effects are much more important in gas-phase reactions, where diffusion is faster, than in liquid-phase reactions. However, in reactions on walls or in heterogeneous catalysis we are not concerned with free radicals but with bound or complexed radicals which are beyond the scope of this paper.

Acknowledgment. The author appreciates careful readings of this paper and/or numerous useful suggestions by Drs. S. W. Benson, David M. Golden, William A. Pryor, and Cheves Walling.

For earlier speculation on this point, see F. R. Mayo, *Discussions of the Faraday Society*, 14, 250 (1953).

Rotation of Styrene and *t*-Butylethylene in Platinum(II) Complexes with 2,4,6-Trimethylpyridine

Allan R. Brause, Fred Kaplan, and Milton Orchin

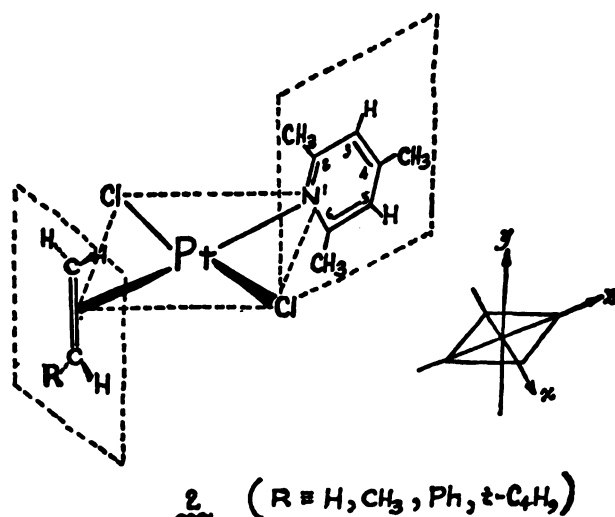
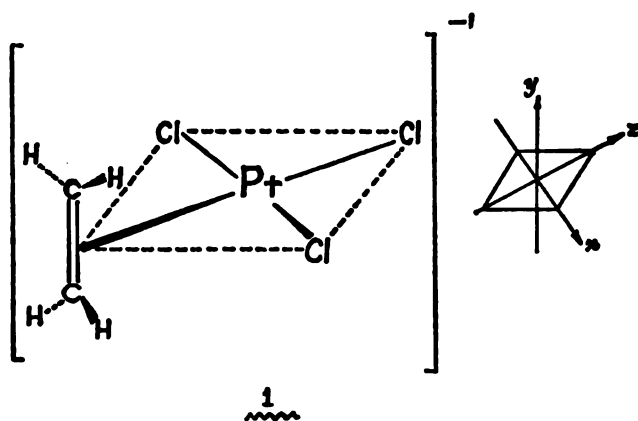
Contribution from the Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221. Received January 13, 1967

Abstract: Several 1,3-dichloro-2-olefin-4-(2,4,6-trimethylpyridine)platinum(II) complexes, **2**, have been prepared and their nmr spectra determined. Although at room temperature there is a single signal for the 2,6-methyl groups, at about -50° the signal splits. This behavior is interpreted to indicate rapid (on the nmr time scale) rotation of the olefinic species about its coordination axis and a "freezing out" at the lower temperature.

ethylene's anion, **1**, ethylene is known to be oriented at right angles to the square plane in the crystal.¹ In connection with some other work² in this

A. Wunderlich and D. P. Mellor, *Acta Cryst.*, 7, 130 (1954).
A. R. Brause and M. Orchin, submitted for publication.

laboratory, we prepared 1,3-dichloro-2-ethylene-4-(2,4,6-trimethylpyridine)platinum(II), **2**, R = H. Although the compound is almost certainly *trans*, the exact spatial arrangement of the ligands with respect to each other is of interest.



The exceptional stability of *ortho*-substituted aryl nickel complexes, e.g., *trans*-[(PPhEt)₂Ni(mesityl)]₂, has been ascribed³ to the interference of the *ortho* substituents with the bulky tertiary phosphine ligands on each side of the nickel atom which prevents rotation of the aryl group about the Ni-C bond. Although there may be some question as to the validity of the interpretation, it is quite clear that substantial steric hindrance to free rotation exists. In **2**, rotation round the Pt-N coordination bond as an axis is possible, but molecular models show that 2,6-methyl substitution would favor a geometry in which the pyridine ligand lies perpendicular to the square plane as shown. Although the ethylene group also might be perpendicular to the square plane as in **2**, the possibility of ethylenic rotation in solutions of the complex needs to be considered. If we involve the d_{xz} orbital in the dsp^2 hybrid bonding orbitals,⁴ then the availability of the d_{yz} orbital for $d-\pi^*$ bonding should facilitate such rotation. Indeed, Cramer has shown⁵ that the ethylene coordi-

(3) J. Chatt and B. L. Shaw, *J. Chem. Soc.*, 1718 (1960). These authors suggest that the perpendicular orientation of the aryl ring forces interaction between a π orbital of the aryl group and the d_{xz} orbital in the plane of the molecule. Since both of the orbitals to be combined are occupied, this should lead to a raising of the highest occupied ($d\pi$) orbital and hence a lowering of the energy difference between the highest occupied and lowest empty orbitals.

(4) We are using essentially the coordinate system employed by J. W. Moore, *Acta Chem. Scand.*, 20, 1155 (1966), in his complete treatment of the electronic absorption spectrum of Zeise's salt. The anion, **1**, and compound **2** ($R = H$) have C_{2v} symmetry and hence the necessity of using the symmetry axis in the square plane as the z axis. In $PtCl_4^{2-}$, the z axis is the fourfold symmetry axis perpendicular to the plane.

(5) R. Cramer, *J. Am. Chem. Soc.*, 86, 217 (1964).

nated to rhodium(I) in the compound $\pi\text{-C}_6\text{H}_5\text{Rh}(\text{C}_2\text{H}_4)_2$, rotates freely at room temperature.

In the complex **2** ($R = H$), the *o*-methyl groups are in magnetically equivalent environments with respect to ethylene. If, however, an unsymmetrical olefin were complexed in place of ethylene and the pyridine moiety were "fixed," the *o*-methyls would become nonequivalent and such nonequivalence should be discernible by nmr techniques. Accordingly, the complexes **2** ($R = \text{CH}_3, \text{C}(\text{CH}_3)_3, \text{Ph}$) were prepared. A single nmr resonance for the *o*-methyls would be presumptive evidence for free rotation of the olefin; splitting of the singlet at low temperature would be consistent with slowing down such rotation.

Experimental Section

1,3-Dichloro-2-ethylene-4-(2,4,6-trimethylpyridine)platinum(II), **2** ($R = H$), was prepared by addition of 2,4,6-trimethylpyridine to Zeise's salt¹ in 97% yield as a yellowish green powder, mp 155–157° dec (2-mmole scale). *Anal.* Calcd for $PtCl_2C_{10}H_{15}N$: C, 28.91; H, 3.64; Pt, 46.99. Found: C, 29.12; H, 3.85; residue (Pt), 46.60.

Compound **2**, ($R = \text{CH}_3$) was synthesized *via* the propylene platinumous chloride dimer. Simple displacement of ethylene by propylene from the ethylenic complex gave incomplete conversion. The ethylene platinumous chloride dimer (500 mg, 0.85 mmole) was placed in a small vial and immersed in a Dry Ice-acetone bath. Propylene was bubbled in until about 5–7 ml had accumulated, and then the mixture was stirred magnetically at this temperature for 15 min. The Dry Ice bath was removed, and the mixture was stirred at room temperature until all the excess propylene had evaporated. Saturated potassium chloride solution was added, and the solution was stirred until no more solid material remained and a yellowish green solution resulted. Then 0.30 ml of 2,4,6-trimethylpyridine (1.95 mmole, 15% excess) was slowly added, giving a yellow-green cloud and then a precipitate on standing. This was filtered and air dried, yielding 657 mg (90%) of a yellow powder, mp 103–105° dec. *Anal.* Calcd for $PtCl_2C_{11}H_{17}N$: C, 30.76; H, 3.99; Pt, 45.46. Found: C, 30.05; H, 3.94; residue (Pt), 46.90.

Compound **2** [$R = (\text{CH}_2)_3\text{C}$] was made by the same dimeric route, except in this case no ice bath was necessary as the boiling point of *n*-butylethylene is 76°. From 1146 mg of impure dimer, which was first dissolved in acetone and filtered to remove impurities, there was obtained 1004 mg (55%) of a yellow-green powder, mp 129–133° dec. *Anal.* Calcd for $PtCl_2C_{14}H_{21}N$: C, 35.65; H, 4.92; Pt, 41.40. Found: C, 34.80; H, 4.83; residue (Pt), 36.60.

Compound (**2** $R = \text{Ph}$) was efficiently prepared by simple displacement. The ethylenic complex (958 mg, 2.30 mmole) was dissolved in 25 ml of chloroform and 0.25 ml (2.2 mmole) of styrene was added. The mixture was stirred magnetically for 30 min, then filtered, giving a clear yellow solution. The volume of solution was reduced with a nitrogen stream and pentane was added, giving a yellow-orange oil which on scratching and refrigeration overnight gave a highly crystalline orange-yellow material, mp 133–135° dec, yield 769 mg (68%). *Anal.* Calcd for $PtCl_2C_{14}H_{11}N$: C, 39.09; H, 3.90; Pt, 39.72. Found: C, 38.45; H, 4.08; residue (Pt), 40.70.

Attempts to prepare 1,3-dichloro-2(α,α -diphenylethylene)-4-(2,4,6-trimethylpyridine)platinum(II) by either simple displacement or *via* the dimer were unsuccessful. A previous attempt to prepare the α,α -diphenylethylene dimer⁷ was also unsuccessful.

Results and Discussions

The nmr spectral data are given in Table I. Our discussion shall concern itself only with the signals for the *o*-methyl groups. When the propylene complex **2** ($R = \text{CH}_3$) was examined only a single triplet (Figure 1) was observed for the *o*-methyls and there was no significant change at -46° . Owing to instrumental limitations, the temperature could not be much further lowered. We then decided to increase the

(6) Analyses by Galbraith Laboratories, Inc.

(7) J. S. Anderson, *J. Chem. Soc.*, 1042 (1936).

Table I. Nmr Data^a for the Complexes

	R'							
	H Amb ^b	CH ₃ Amb -46°		Ph Amb -60°		t-C ₄ H ₉ Amb -46°		
δ_{H_a}	7.05	6.99	7.02	6.95	7.00	7.00	7.03	
J_{Pt-H_a}	9	9	9	10	10	10	10	
$\delta_{H_b, H_{b'}}$	4.80	Multiplet centered at 4.65		Multiplets centered at 4.65, 5.44		Multiplet centered at 4.80		
$J_{Pt-H_b, H_{b'}}$	62	... ^d		... ^d		... ^d		
δ_{o-CH_3}	3.17	2.90	3.03	2.97	2.93, 2.80	3.17	3.03, 3.00	
$J_{Pt-o-CH_3}$	12	13	13	13	~13	12	~12	
δ_{p-CH_3}	2.37	2.20	2.20	2.18	2.12	2.32	2.20	
δ_R	None	1.57 doublet	1.57 doublet	7.80, 7.48 multiplet	... ^e	1.32	1.15	

^a All chemical shifts are in parts per million (δ) and coupling constants in cycles per second. The resonance peak of $CHCl_3$ (δ 7.27) was used as an internal standard. ^b Ambient machine temperature. ^c Not examined in detail. ^d P. Kaplan and M. Orchin, *Inorg. Chem.*, in press, discuss platinum-olefin coupling in vinyl complexes.

bulk of the R group and prepared the compound 2 where R = Ph. The single triplet observed in the nmr at room temperature was split into two overlapping triplets at -60° ; the chemical shifts of the two triplets were δ 2.93 ($J_{Pt-CH_3} \sim 12$ cps) and δ 2.80 ($J_{Pt-CH_3} \sim 12$ cps), a chemical shift difference of 7.8 cps at 60 Mc. The same effect was observed with compound 2 (R = *t*-butyl) although it was not as pronounced, and a difference of only 2 cps in the chemical shift was observed

moieties free to rotate at room temperature and both frozen out at low temperatures. We do not consider either of these as likely as the "fixed" pyridine and the rotating ethylene. Rapid intermolecular exchange of free and complexed olefin would also account for the observation of a single absorption for the *o*-methyls. However, the spectrum of 2 (R = Ph) shows platinum-olefin coupling at room temperature and thus this explanation is excluded.

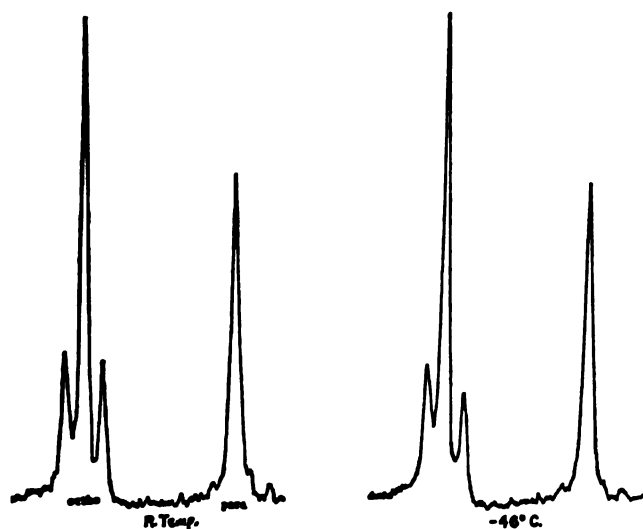


Figure 1. Nmr spectra of *o*- and *p*-methyls in the propylene complex.

(Figure 2). Since we assume that the pyridine is relatively fixed in these complexes, a single signal for the *o*-methyls in the styrene and *t*-butylethylene complexes implies a rotation of the vinyl compound around the coordination axis. Lowering the temperature "freezes" out the rotation and permits observation of the more stable conformer in the nmr spectra. Alternately, we could have considered that the olefin is fixed and the pyridine rotating at room temperature and frozen out at low temperature. Or, we may have considered both

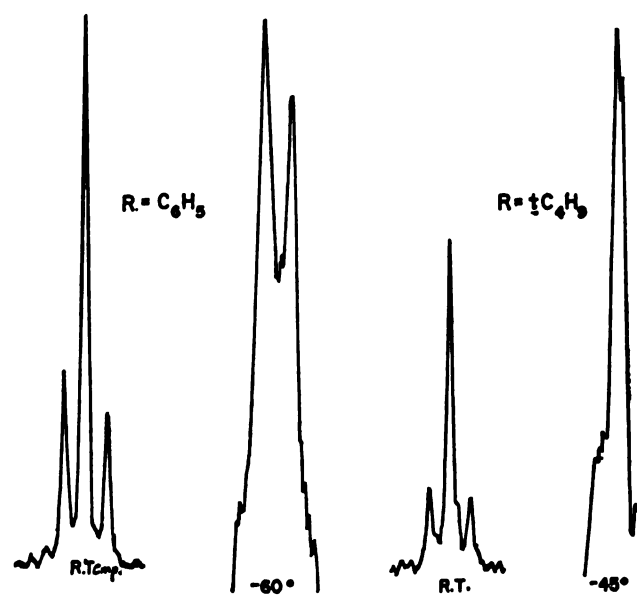


Figure 2. Nmr spectra of *o*-methyls for R-substituted complexes.

Failure to observe splitting with the propylene complex 2 (R = CH₃) may mean a smaller rotational barrier requiring temperatures lower than -60° or it may mean that the magnetic effect of the propylene on the *o*-methyl groups is too small to be observed across the square plane.

A decision as to whether the ethylenic moiety is frozen out parallel to or perpendicular to the square plane

could presumably be made by using α,α -diphenylethylene in place of ethylene in 2. If both phenyls were either above or below the square plane, two signals for the *o*-methyls should be observed. However, if the diphenylethylene were frozen out so that one phenyl was above and one phenyl below the plane, the *o*-methyls would again be magnetically equivalent and only one signal should result. Unfortunately, the compound of interest could not be prepared, but the investigation is being pursued.

Acknowledgment. The authors wish to thank Dr. P. Kaplan, Dr. W. W. Bannister, and Mr. Paul Schmidt for their valuable comments, and Mr. Frank Stary for some assistance with the Varian A-60. This research was partially supported by the Sohio Corp. through a fellowship to Mr. Brause. Further, we should like to thank Engelhard Industries for donating our platinum supplies. The nmr spectrometer used in this work was purchased with the aid of a grant from the National Science Foundation.

Catalysis of α -Hydrogen Exchange. IV. Deuterium Exchange of Methoxyacetone^{1,1a}

Jack Hine, K. Gerald Hampton,² and B. C. Menon

Contribution from the Evans Laboratory of Chemistry, The Ohio State University, Columbus, Ohio 43210. Received January 14, 1967

Abstract: The kinetics of loss of deuterium from methoxyacetone containing deuterium α to the carbonyl group have been studied in aqueous solution. Catalytic constants have been determined for hydrogen ions, hydroxide ions, water, phenoxide ions, *p*-nitrophenoxide ions, trimethylamine, triethylamine, N-methylpyrrolidine, and N-methylmorpholine. In the presence of N-methylmorpholine buffers the reaction is slightly subject to catalysis by methylammonium chloride, presumably because of the intermediate formation of an enamine. Exchange at the methyl position is faster (by up to sixfold) than at the methylene position for all the catalysts studied except hydroxide ions, which brought about slightly more rapid exchange at the methylene position.

Many physiologically important reactions, such as aldol condensations, epimerizations, etc., involve deprotonation of an organic molecule (e.g., a sugar) at a position that is α to a carbonyl group and to a hydroxy group. As a first step in studying the mechanisms of such reactions we have investigated the deuterium exchange of methoxyacetone. The methoxy substituent should have an influence on the acidity of hydrogen atoms attached to the same carbon atom that is quite similar to that of a hydroxy substituent, but the greater difficulty of oxidizing and deprotonating the methoxy substituent should decrease the probability of complicating side reactions.

Results

The proton magnetic resonance (pmr) spectrum of methoxyacetone consists of three singlets, at τ 5.97, 6.59, and 7.87, attributed to the methylene hydrogen atoms, the methoxy hydrogen atoms, and the carbon-bound methyl (referred to hereafter simply as methyl) hydrogen atoms, respectively, on the basis of their relative intensities and chemical shifts. When solutions of the compound in deuterium oxide are heated with sodium carbonate, the absorption due to the methylene and methyl hydrogen atoms decreases in intensity. We

have studied the catalytic action of hydrogen ions and various bases on the dedeuteration of the deuterated methoxyacetone prepared in this way. The reaction was followed by extracting the aqueous reaction solutions with chloroform and integrating the pmr spectra of the chloroform extracts. The methoxy group of the ketone provides an internal standard for comparison with the increasing intensities of the other two absorption peaks. First-order rate constants were determined using the equation

$$k_p t = 2.303 \log \frac{(M/R)_\infty - (M/R)_0}{(M/R)_\infty - (M/R)_t} \quad (1)$$

where R is the integrated intensity of the reference (methoxy) peak, M is the integrated intensity of the methyl or methylene peak, and the subscripts refer to the reaction time. For $(M/R)_\infty$ the theoretical values, 1 for methyl and $2/3$ for methylene, were used. For each run two rate constants may be calculated, one for loss of deuterium from the methylene group ($k_p^{\text{CH}_2}$) and one for loss of deuterium from the methyl group ($k_p^{\text{CH}_3}$).

It is assumed that the reaction is subject to catalysis by all the acids and bases present in the solution, so that in the presence of the B-BH⁺ buffer the first-order rate constant k_p may be expressed

$$k_p = k_H[H^+] + k_{OH}[OH^-] + k_w[H_2O] + k_B[B] + k_{BH}[BH^+] \quad (2)$$

where the k 's are catalytic constants for the various possible catalysts. Superscripts will be used to show

(1) This investigation was supported in part by Public Health Service Grant AM-10378 from the National Institute of Arthritis and Metabolic Diseases. For the preceding paper in this series see J. Hine, F. C. Kokesh, K. G. Hampton, and J. Mulders, *J. Am. Chem. Soc.*, **89**, 1205 (1967).

(1a) NOTE ADDED IN PROOF. Since this paper was submitted, a study of the deuterium exchange of methoxyacetone in the presence of sodium acetate and potassium bisulfate has been published by A. A. Bothner-By and C. Sun [*J. Org. Chem.*, **32**, 492 (1967)].

(2) U. S. Public Health Service Postdoctoral Fellow, 1965-1966.

Table I. Kinetics of the Deuterium Exchange of Methoxyacetone in Aqueous Solution^a

Catalyst	<i>M</i> ^c	$10^4 k_p \text{CH}_3$, sec ⁻¹	$10^4 k_p \text{CH}_2$, sec ⁻¹	$10^4 k_B \text{CH}_3$, ^b <i>M</i> ⁻¹ sec ⁻¹	$10^4 k_B \text{CH}_2$, ^b <i>M</i> ⁻¹ sec ⁻¹
NaOH ^d	0.0050	87	58	17000	12000
NaOH	0.0050	75	63	15000	13000
NaOH ^d	0.0059	84	58	14000	10000
NaOH ^d	0.0079	136	100	17000	13000
N-Methylpyrrolidine	0.0050 ^e	27	74	4400	15000
N-Methylpyrrolidine	0.0100 ^e	50	160	4400	16000
Me ₃ N	0.0152 ^e	33	116	2100	7600
Me ₃ N	0.0253 ^e	51	194	2000	7600
Et ₃ N	0.0200 ^e	41	82	1300	3700
Et ₃ N	0.0250 ^e	53	117	1500	4300
C ₆ H ₅ ONa ^d	0.0496 ^e	37	52	700	1000
C ₆ H ₅ ONa ^d	0.0992 ^e	58	91	570	900
C ₆ H ₅ ONa ^d	0.0992 ^e	69	103	680	1000
N-Methylmorpholine	0.200 ^e	7.7	50	38	250
N-Methylmorpholine	0.500 ^e	18.3	135	37	270
p-O ₂ NC ₆ H ₄ ONa ^d	0.0496 ^e	0.50	0.85	10	17
Water ^f	50.5	2.36	4.7	0.048	0.093
Water ^g	51.9	0.184	0.43	0.0035	0.0083
Water ^h	54.0	0.00024	0.00086	0.000045	0.00016
HClO ₄ ^d	0.500	0.111	0.148	0.22	0.30

^a Unless otherwise noted, all runs were made at 35°, using ~0.23 *M* methoxyacetone and enough sodium chloride to give an ionic strength of 0.500 *M*. ^b Or k_B , or k_W , or k_H , if appropriate. ^c The concentrations given are titrimetric concentrations, in which no allowance for ionization has been made. ^d ~0.33 *M* methoxyacetone used. ^e Plus an equal concentration of the conjugate acid of this base. ^f At 13°. ^g At 100°. ^h Extrapolated from data at 100 and 133°.

whether a given catalytic constant refers to attack on the methyl or methylene side of the reactant.

The catalytic constant for hydrogen ions was determined by measurements using 0.5 *M* perchloric acid, with the result shown in Table I. Catalysis by other catalysts is negligible under these conditions. From the value of k_H obtained it follows that catalysis by hydrogen ions would never contribute as much as 10⁻⁸% to the over-all reaction rate in any case except the runs with pure water, which will be discussed separately.

The catalytic constants for hydroxide ions shown in Table I give average values of 1.6×10^{-2} and 1.2×10^{-2} *M*⁻¹ sec⁻¹ for $k_B \text{CH}_3$ and $k_B \text{CH}_2$, respectively. The ratio of the catalytic constants for hydroxide ions to those for hydrogen ions (7×10^4 and 4×10^4 for attack on the methylene and methyl hydrogen atoms, respectively) is larger than in the case of isobutyraldehyde,³ where it is 1.3×10^3 . Since only the acetate ions in acetate buffers were found to catalyze the dedeuteriation of isobutyraldehyde-2-*d* significantly, it was assumed that in the present case, where the sensitivity to base catalysis relative to the sensitivity to acid catalysis is even greater and where all the buffers used contained bases much stronger than the acetate ion and acids much weaker than acetic acid, all the catalytic action of the buffers used was due to the buffer bases; i.e., the k_{BH} term in eq 2 may be neglected.

The catalytic constant for water is too small to be determined conveniently at 35°. Therefore the runs in which no catalyst (other than the solvent water) was added were carried out at 100 and 133°. From the results, shown in Table I, Arrhenius activation energies of 23.3 and 21.8 kcal/mole were calculated for reaction at the methylene and methyl positions, respectively. These activation energies were used to calculate the rate constants at 35°, which are also listed in Table I. Because of a small amount of impurity in the deuterated methoxyacetone used, the reaction solutions used for

determining k_W had a pH of about 4.6. After 240 hr at 133° the pH had dropped to about 3.5. It is, therefore, possible that some of the deuterium exchange observed is due to catalysis by acid or some other catalyst other than water. Hence the catalytic constants determined for water should be regarded as maximum values. Although the k_W 's may thus be the least reliable of the catalytic constants that we have determined, the values obtained do show that the k_W terms will not contribute more than 0.2% to the rate of reaction in any of the other runs made except the one in which perchloric acid was used, where a contribution as large as 1% is possible. Hence for the runs made using buffers, the k_W terms may also be neglected and eq 2 may be written in the form

$$k_B[B] = k_p - k_H[\text{OH}^-] \quad (3)$$

In order to use eq 3 to determine values of k_B , the basicity constants of the buffer bases (or the acidity constants of the buffer acids and the ion-product constant of water) are needed under the conditions of the kinetic experiments, so that the concentrations of hydroxide ions present in the various runs may be calculated. The thermodynamic pK_a at 35° may be interpolated from the data of Everett and Wynne-Jones⁴ for trimethylammonium ions (9.58). The value for triethylammonium ions (10.45) was reported by Fyfe;⁵ the values for phenol (9.86) and *p*-nitrophenol (7.03) were calculated from the values at 25° and the enthalpies of ionization determined by Fernandez and Hepler;⁶ the values for N-methylmorpholine (7.17) and N-methylpyrrolidinium ions (10.14) were calculated from the values at 25°^{7,8} and Perrin's method of mak-

(4) D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc. (London)*, A177, 499 (1941).

(5) W. S. Fyfe, *J. Chem. Soc.*, 1347 (1955).

(6) L. P. Fernandez and L. G. Hepler, *J. Am. Chem. Soc.*, 81, 1783 (1959).

(7) H. K. Hall, *J. Phys. Chem.*, 60, 63 (1956).

(8) S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *J. Am. Chem. Soc.*, 78, 4917 (1956).

(3) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, 87, 5050 (1965).

ing temperature corrections.⁹ According to the simplest form of the Debye-Hückel equation the acidity constant of an acid of charge type plus one should not change with changing ionic strength. Because of the difficulty in determining all the appropriate salt effects we have assumed that the acidity constants of all the substituted ammonium ions in our reaction solutions are the same as they are at infinite dilution, in spite of the fact that we have found that the acidity constant of 2,6-lutidinium ions changes when salts are added, in one direction when the salt is sodium chloride or methylammonium chloride and in the opposite direction when it is 2,6-lutidinium chloride.^{1b} We have assumed that the ion-product constant of water is 4.06×10^{-14} in all our runs at ionic strength 0.50 *M*, although this figure refers to measurements at 35° in which essentially all the 0.50 *M* ionic strength was due to sodium chloride.¹⁰ We have also assumed that the ionization constants of all electrically neutral acids change with added salt in the same way that the ion-product constant of water does. With these assumptions it was possible to calculate the hydroxide ion concentrations needed for use in eq 3. In the two runs with triethylamine the calculated value of $k_h^{\text{CH}_3}[\text{OH}^-]$ was 32–41% of $k_p^{\text{CH}_3}$ and $k_h^{\text{CH}_3}[\text{OH}^-]$ was 11–15% of $k_p^{\text{CH}_3}$. With the other weak bases the extent of hydroxide ion catalysis is less, falling below 0.1% for N-methylmorpholine and sodium *p*-nitrophenoxide. Therefore, uncertainties in the ionization constants from which the hydroxide ion concentrations were calculated may result in errors in k_B . There are some compensating effects, however. If the ionization constant of a base is increased, then $[\text{OH}^-]$ is increased and $k_p - k_h[\text{OH}^-]$ decreased, tending to decrease k_B . However, since the value of $[\text{B}]$ to be used in eq 3 is not the titrimetric value listed in Table I but the actual value present at equilibrium in solution ($[\text{B}]_{\text{titrimetric}} - [\text{OH}^-]$), an increase in $[\text{OH}^-]$ will also tend to increase k_B . In a case like that of $k_B^{\text{CH}_3}$ for N-methylpyrrolidine, which is of almost the same size as $k_h^{\text{CH}_3}$, the two effects nearly cancel and very little uncertainty in k_B results from uncertainty in the ionization constant of the base; that is, the reaction rate is very little affected by the amount of pyrrolidine that deprotonates water to give hydroxide ions since the reactivity of the hydroxide ions is about the same as that of the pyrrolidine.

The catalytic activity of methylammonium chloride was investigated for the reaction carried out in the presence of N-methylmorpholine buffers with the results shown in Table II. Inasmuch as the catalytic activity of water, hydrogen ions, and hydroxide ions are all negligible in the presence of N-methylmorpholine (Nmm) buffers, the first-order rate constant for the reaction would be expected to be equal to $k_{\text{Nmm}}[\text{Nmm}]$ if there were no catalysis by the methylammonium ions. Hence the quantity $k_p - k_{\text{Nmm}}[\text{Nmm}]$ is a measure of the extent of catalysis by methylammonium ions. The amount of catalysis observed in the runs with 0.100 *M* methylammonium chloride is too small to be clearly significant. With 0.300 *M* methylammonium chloride it seems clear that there is catalysis by methylammo-

Table II. Kinetics of the Deuterium Exchange of Methoxyacetone in the Presence of MeNH₂Cl and N-Methylmorpholine Buffers in Aqueous Solution at 35°^a

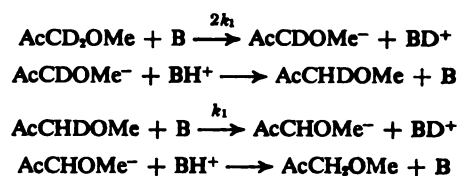
[Nmm] ^b	[MeN- H ₂ Cl]	Sec ⁻¹			
		10 ⁴ . $k_p^{\text{CH}_3}$	10 ⁴ . $k_p^{\text{CH}_3}$	10 ⁴ . ($k_p^{\text{CH}_3} - k_{\text{Nmm}}^{\text{CH}_3}$) [Nmm]	10 ⁴ . ($k_p^{\text{CH}_3} - k_{\text{Nmm}}^{\text{CH}_3}$) [Nmm]
0.400	0.100	16.2	108	1.2	4
0.200 ^c	0.100	8.9	54	1.4	2
0.200	0.300	11.4	86	3.9	34

^a In all runs methoxyacetone concentrations of about 0.22 *M* were used. ^b An equal concentration of N-methylmorpholine hydrochloride was also present. ^c 0.200 *M* sodium chloride added to bring the ionic strength to 0.500 *M*.

nium ions (or by some species derived from methylammonium ions).

Discussion

If k_1 is the rate constant per deuterium for the removal of a deuterium from the methylene group of methoxyacetone and if there is no secondary deuterium kinetic isotope effect, we may write



Let $[\text{D}]$ be the total concentration, in equivalents, of deuterium in the methylene group.

$$[\text{D}] = 2[\text{AcCD}_2\text{OMe}] + [\text{AcCHDOMe}]$$

Then the rate of loss of deuterium from the methylene group may be expressed

$$\begin{aligned}d[\text{D}]/dt &= [\text{B}](2k_1[\text{AcCD}_2\text{OMe}] + k_1[\text{AcCHDOMe}]) \\ d[\text{D}]/dt &= k_1[\text{B}][\text{D}]\end{aligned}$$

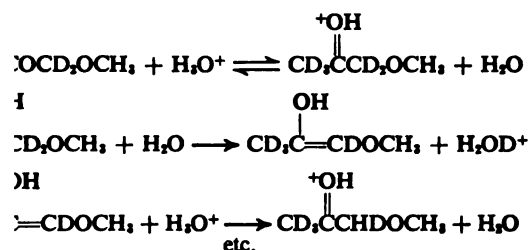
Thus, if only one base is catalytically important, the reaction is expected to follow the first-order eq 1 in which k_p is equal to $k_1[\text{B}]$ ($[\text{B}]$ does not change during a given run), where k_1 is the rate constant *per* deuterium. Analogous derivations may be made for methyl exchange and for exchange due to the simultaneous action of several catalysts to show that the catalytic constants we have listed in Table I are statistically corrected rate constants.

Although we observed no consistent tendency for our rate constants to drift either up or down, secondary kinetic isotope effects, which we have neglected, could cause such a tendency. This fact added somewhat to the uncertainty in the rate constants calculated from our data.

Our results show that the methyl hydrogens are removed more rapidly than the methylene hydrogens by every catalyst except hydroxide ions. This is certainly not the result to be expected from the inductive effect of the methoxy substituent. Discussion of the rate effect in terms of the relative stabilities of the two possible carbanions is hampered by our ignorance of which of the two is really the more stable. If the mechanism of the acid-catalyzed deuterium exchange is the following

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second step (and an analogous step for example at the methyl position) being rate controlling, a compound with a methoxy group attached to a bond is being formed in the rate-controlling step of the reaction. In view of the known ability of oxygen substituents to stabilize double bonds,¹¹⁻¹⁵ it can be assumed that the enol resulting from reaction at the methylene side would be more stable than the enol resulting from reaction at the methyl side. This is supported by the report that methoxyacetone contains 1.1% enol,¹⁶ a much larger enol content than that of acetone.^{17,18} Thus, it appears that the rapid acid-catalyzed deuterium exchange at the methylene position of methoxyacetone is an example of a transfer reaction in which the less stable product is formed more rapidly. A number of rate-equilibrium studies of this type have been observed and some can be rationalized in terms of the principle of least motion.¹⁹ According to the principle of least motion, the formation of the carbon-oxygen bond that would lead to the formation of 1-methoxy-2-hydroxypropene should tend to cause this enol to be formed more rapidly than 3-methoxy-2-hydroxypropene, the other possibility. However, the magnitude of the change in bond length to be expected is so small (compare the changes in bond lengths in the cases previously considered¹⁹) that only a very small effect would be expected.

It has been suggested that the increased electronegativity of sp^2 carbon may tend to slow reactions in which the carbon whose hybridization changes from sp^3 to sp^2 carries a highly electronegative substituent. This has been discussed in more detail in connection with the effect of α -methoxy and α -fluoro substituents on the ease of carbanion formation by esters.²⁰ In an attempt to rationalize the present data it should be noted that the relative rates of exchange at the methyl and methylene positions do not constitute a fair comparison of the methoxy substituent with a hydrogen substituent. The comparison is of a methoxy and a hydrogen substituent with a hydrogen and a methoxyacetyl substituent.

Figure 1 is a Brønsted plot for the buffer bases. The points for water and hydroxide ions were included to permit the use of a scale that would make it

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 6. Jenner and G. N. Richards, *J. Chem. Soc.*, 2240 (1953).
 7. Bell and P. W. Smith, *ibid.*, *Phys. Org.*, 241 (1966).
 8. It should be noted, however, that the determination of the enol content of acetone that are not highly enolized is subject to errors resulting from the presence of small amounts of impurities.¹⁷
 9. Bell, *J. Org. Chem.*, **31**, 1236 (1966).
 10. G. Mahone, Ph.D. Thesis, School of Chemistry, Georgia Institute of Technology, Atlanta, Ga., 1966.

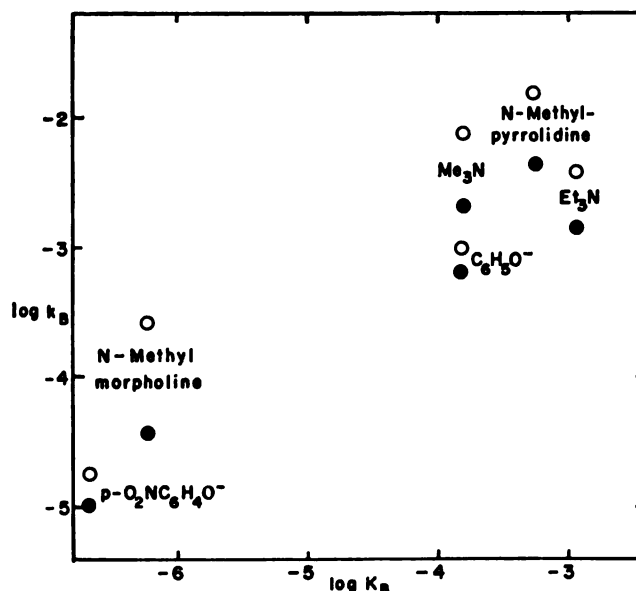


Figure 1. Brønsted plot for dedeuteriation of methoxyacetone at the methyl, O, and methylene, ●, positions.

easier to see the relationship between the points for the other bases. The points plotted certainly do not describe a good straight line for either the methyl or methylene exchange reaction, but they fall nearer straight lines than the points for the same bases in the exchange of isobutyraldehyde.³ This is probably at least partly due to a decrease in steric effects. Triethylamine, which is more than seven times as basic as trimethylamine, was only $1/20$ as reactive as trimethylamine toward isobutyraldehyde;³ it is more than one-half as reactive as trimethylamine toward either the methyl or the methylene hydrogen atoms of methoxyacetone. The points for the two phenoxides used may be considered to describe Brønsted lines with slopes of about 0.62. This is somewhat larger than the slope (0.53) obtained from data on eight phenoxide ions in the case of isobutyraldehyde. The points for trimethylamine do not lie as far above these lines as the point for trimethylamine lay above the Brønsted line for phenoxide ions in the exchange of isobutyraldehyde. Instead it is roughly collinear with the points for N-methylpyrrolidine and N-methylmorpholine. This suggests that attack of the two cyclic amines on isobutyraldehyde was slowed by steric hindrance but that their attack on methoxyacetone is not. The fact that tertiary amines often remove hydrogen more rapidly than do primary or secondary amines of equal basicity^{21,22} cannot be explained in terms of steric hindrance, however.

A Brønsted plot on a scale that permits inclusion of the points for water and hydroxide ions shows that water is somewhat less reactive than would be expected from the Brønsted line for phenoxide ions or a Brønsted line that could be drawn through the points for trimethylamine, N-methylpyrrolidine, and N-methylmorpholine. This type of behavior has been observed in several (but not all) other general-base-catalyzed reactions^{3,23,24}

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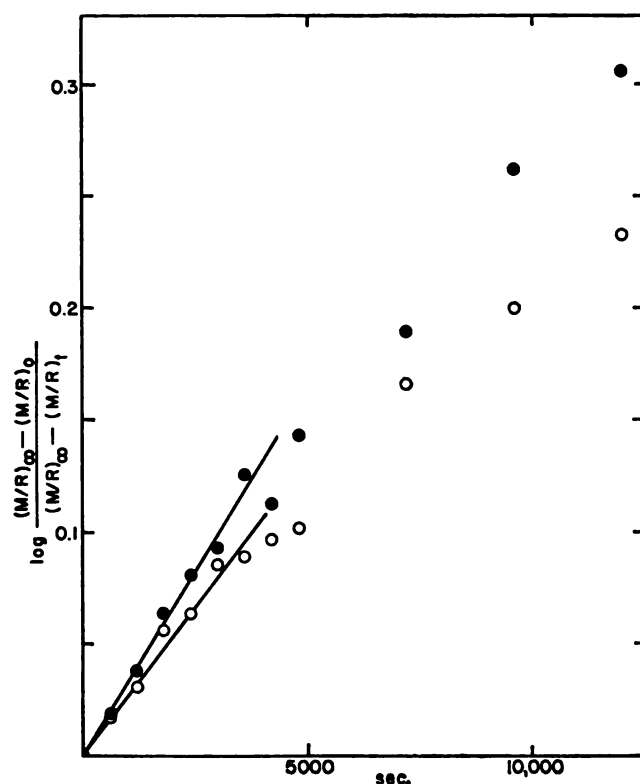


Figure 2. Kinetic plot for the dedeuterium of deuterated methoxyacetone in the presence of sodium hydroxide at the methyl, O, and methylene, ●, positions.

and is in agreement with an expected tendency for the slope of the Brønsted line (β) to decrease with increasing strength of the bases studied.²⁵

The hydroxide ion is much less reactive than would be expected from the Brønsted line for phenoxide ions or the Brønsted line for unhindered tertiary amines. Toward the methyl group of methoxyacetone it is even somewhat less reactive than N-methylpyrrolidine, although it is about 100,000 times as strong a base as the amine. Bell has pointed out that this anomalously low reactivity of hydroxide ions occurs rather commonly;²³ it was observed in the deuterium exchange of isobutyraldehyde.³

The effect of methylammonium chloride on the reaction rate shows that the deuterium exchange of methoxyacetone is catalyzed by methylammonium ions but that it is much less susceptible to such catalysis than is the deuterium exchange of isobutyraldehyde. From the data in Table II and related data in Table I it may be seen that the addition of 0.300 M methylammonium chloride to a 0.200 M N-methylmorpholine-0.200 M N-methylmorpholinium buffer increases the reaction rate by about 50–70%. In the case of isobutyraldehyde, the rate of exchange in the presence of a 0.21 M N-methylmorpholine-0.21 M N-methylmorpholinium buffer is more than doubled by addition of 0.176 M methylammonium chloride.²⁶ The catalysis by methylammonium ions is probably due to the reversible formation of a deuterated imine and then a deuterated iminium ion, which is rate controllingly transformed to an enamine.^{1b,27} The greater susceptibility of iso-

butyraldehyde to such catalysis may be due in part, at least, to a larger equilibrium constant for imine formation. In view of the larger equilibrium constants for semicarbazone formation that have been observed for aldehydes (compared to the constants for related ketones)^{28,29} the aldehyde would be expected to have a larger equilibrium constant for imine formation.

Experimental Section

Deuterated Methoxyacetone. Methoxyacetone was prepared by oxidizing 1-methoxy-2-propanol with aqueous sodium dichromate and sulfuric acid.³⁰ The material thus obtained contained up to 10% unoxidized starting alcohol. Except in one run in which only 2% alcohol was present, the methoxyacetone was purified by preparative gas-liquid partition chromatography using a stationary phase of silicone fluid XF-1150 to give material containing 1% alcohol or less. The pmr spectrum of the product in deuteriochloroform showed singlets at τ 5.97, 6.59, and 7.87 with relative areas of 2:3:3.

A solution of 33 g (0.375 mole) of methoxyacetone and 0.5 g of anhydrous sodium carbonate in 37.5 g (1.87 moles) of deuterium oxide was heated at reflux for 7 hr, then cooled and extracted with several 25-ml portions of ether. The ether solution was dried over anhydrous sodium sulfate and filtered, and the ether evaporated to give a residue that was passed through the deuterium procedure again. The residue from the second deuterium was distilled through a spinning-band column to give 12 g of deuterated methoxyacetone, bp 109–112°. The pmr spectrum of the product showed peaks at τ 5.97, 6.59, and 7.87 with relative areas of 0.24:3.0:0.36. The τ 5.97 and 7.87 peaks were significantly broader than the corresponding peaks in undeuterated methoxyacetone.

Kinetic Run. In a typical run 2.0855 g of deuterated methoxyacetone and 16.5 ml of 3.0 M aqueous sodium chloride solution were diluted to volume in a 50-ml volumetric flask at 35.0°. From this flask 3-ml samples were transferred by pipet to each of a number of 10-ml volumetric flasks that already contained 3 ml of 0.01 M aqueous sodium hydroxide. At a recorded time the reaction in each flask was stopped by the addition of a small excess of acetic acid, and then the solution was extracted with chloroform. The pmr spectrum of the chloroform extract was integrated several times. Rate constants were determined by plotting the right-hand side of eq 1 against time. In this run, as in the others in which sodium hydroxide was used as the catalyst, the plot (Figure 2) showed curvature (corresponding to a decrease in the first-order rate constant) after about 20% reaction, and therefore only the data for the first 20% of the reaction were used. No such curvature was noticed in the other runs, which were usually followed to 50–75% completion. In the cases of some catalysts, where there was a rather large difference between the rates of exchange at the methyl and methylene positions, the rate constant for exchange at the methyl position was determined from a series of points taken before very much exchange had taken place at the methylene position, and the rate constant for exchange at the methylene position was determined from a series of points taken after exchange at the methyl position was almost complete.

The methoxyacetone used contained a small amount of an unidentified acidic impurity that gave the initial reaction solution a pH of about 4 due to an acid content around 0.001 M. In the most vigorous conditions used for any of the reactions (133°) the pH dropped to 3.5 and the acid content rose to 0.004 M after a time four times as long as that used for the last kinetic point taken. Because of the presence of these small amounts of acidic impurities, the catalytic constants we have reported for basic catalysts will tend to be too low. This will be significant only in cases where the concentrations of basic catalysts are relatively small. The errors resulting from these impurities must not be very large, because if they were we would not get about the same catalytic constant using significantly different concentrations of catalysts.

Acknowledgments. We wish to acknowledge our indebtedness to the National Science Foundation for a grant that permitted the purchase of the nmr spectrometer used in this investigation, and to Dr. John P. Idoux for experimental assistance.

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Equilibrium in Formation and Conformational Isomerization of Imines Derived from Isobutyraldehyde and Saturated Aliphatic Primary Amines¹

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Abstract: The following dimensionless equilibrium constants were determined for the formation of imines and water from isobutyraldehyde and saturated aliphatic primary amines in aqueous solution at 35°: *i*-PrCH=NMe, 4950; *i*-PrCH=NEt, 3490; *i*-PrCH=NPr-*n*, 4180; *i*-PrCH=NBu-*n*, 4040; *i*-PrCH=NPr-*i*, 1840; *i*-PrCH=NBu-*t*, 200. Two of the experimental methods used were based on ultraviolet measurements at the aldehyde and imine absorption maxima (at 2850 and about 2300 Å, respectively). These measurements gave satisfactory agreement with a pH method based on the fact that addition of isobutyraldehyde to primary amine buffers decreases the pH by transforming the amine to the much less basic corresponding imine. Largely on the basis of nuclear magnetic resonance data it is concluded that all the imines are very largely *trans* compounds and that in the principal conformations one of the carbon-methyl bonds of the isobutylidene group eclipses the carbon-nitrogen double bond. Both the nmr data and the equilibrium constants for imine formation may be rationalized semiquantitatively by the assumption that rotation around the carbon-nitrogen single bond so as to eclipse the carbon-nitrogen double bond with a carbon-hydrogen bond yields a conformation that is about 2.0 kcal/mole more stable than a conformation in which the carbon-nitrogen double bond has been eclipsed by a carbon-carbon bond.

ates, equilibria, and reaction mechanisms have been studied carefully in many reactions of the type



where RNH₂ is a hydroxylamine or hydrazine derivative.² Several studies have also been made of the reactions of aromatic aldehydes with aromatic³ and aliphatic amines⁴⁻⁸ (and of the reverse reactions). Quantitative studies of the reaction in cases where R, R', and R'' are all hydrogen atoms or saturated alkyl groups are less common. In his review on imines, which covers their chemistry from the time of their discovery by Schiff in 1864 through Sept 1962, Layer cites no such studies.⁹ Zuman reported the polarographic determination of the equilibrium constant for imine formation in the reaction of ammonia and several amino acids with pyruvic acid and several aldehydes and ketones,¹⁰ and Březina and Zuman described a similar investigation of the reaction of cyclopentanone and cyclohexanone with ammonia, methylamine, glycine, and other aliphatic amines.¹¹ More recently Le Sueur, Lefebvre, and Coussemant have studied the reaction of acetone with isopropylamine,¹² and Williams and Bender have studied the reaction of acetone with

methylamine.¹³ We have not been able to find any measurements of the equilibrium constant for imine formation from a saturated aliphatic aldehyde and an aliphatic amine.

For this reason, as part of a study of reactions involving the formation of imines as intermediates,¹⁴ we have investigated the formation of imines from several saturated aliphatic amines and isobutyraldehyde, an aldehyde whose equilibrium constant for aldolization is rather unfavorable¹⁵ and whose aldol cannot undergo simple dehydration to an α,β-unsaturated aldehyde.

Determination of *K*

Ultraviolet Measurements at the Aldehyde Maximum. The addition of primary amines to aqueous solutions of isobutyraldehyde causes a decrease in the intensity of absorption at the aldehyde maximum (2850 Å). By measurements of the absorption at 2850 Å in the presence of known initial concentrations of isobutyraldehyde and amine, the equilibrium constant for the reaction



may be calculated.

If *I* is the concentration of imine, *W* the concentration of water, *B* the concentration of amine, and *A'* the concentration of isobutyraldehyde in the free (unhydrated) form

$$K' = IW/A'B \quad (1)$$

Isobutyraldehyde is about 30% hydrated at equilibrium in aqueous solution at 35°.¹⁶ Inasmuch as equilibrium is quite rapidly established between the free aldehyde

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(d) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

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and its hydrate,^{16,17} it is convenient for many purposes to treat the equilibrium mixture of aldehyde and hydrate as a single substance. The total concentration of free aldehyde and hydrate may be referred to as the apparent aldehyde concentration and denoted A . The apparent equilibrium constant is then

$$K = IW/AB \quad (2)$$

where K is equal to $K'A/A'$.

The absorbance D of a solution containing aldehyde, amine, and imine may be expressed

$$D = A\epsilon_A + B\epsilon_B + I\epsilon_I \quad (3)$$

where the ϵ 's are the respective extinction coefficients. Substitutions and rearrangement lead to the expression

$$A_0/(A_0\epsilon_A + B_0\epsilon_B - D) = 1/(\epsilon_A + \epsilon_B - \epsilon_I) + W/[KB(\epsilon_A + \epsilon_B - \epsilon_I)] \quad (4)$$

where $A_0 = A + I$ and $B_0 = B + I$. The value of A_0 is simply equal to the concentration of aldehyde added initially. The value of B_0 , however, is equal to the initially added, titrimetrically determined concentration of amine minus the concentration of substituted ammonium ion (conjugate acid of the amine).

To use eq 4 for the determination of K , ϵ_A and ϵ_B were determined by measurements on solutions containing only isobutyraldehyde or only amine. Then, for solutions containing various amounts of aldehyde and amine, absorbances (D) were determined and values of A_0 were calculated from the volumes and concentrations of the standard solutions that had been used. From this point the method of successive approximations was used. Values of B_0 and B were estimated from data on the solutions used to prepare the equilibrium solution, from the approximate equation $D = A\epsilon_A$ (the last two terms in eq 3 are relatively small), and from estimates of the concentration of ammonium ions based on the ionization constant of the amine and the concentration of isobutyric acid determined titrimetrically to be present in the isobutyraldehyde solutions used. A knowledge of the concentration of the ammonium ions is of even greater importance in the determination of K by ultraviolet measurements at the imine maximum and by pH measurements. Therefore the basis for the calculations will be treated in some detail here, using the formation of the N-methylimine as a specific example.

Everett and Wynne-Jones determined the acidity constant of the methylammonium ion in water at ionic strengths (due to potassium chloride) 0.05, 0.10, 0.15, 0.20, and 0.25 M at 10° intervals from 10 to 50° .¹⁸ Plots were made of the $\log K_a$ values at each ionic strength (and also the values extrapolated to zero ionic strength) vs. temperature. From these plots, values of $\log K_a$ at 35° at the various ionic strengths were determined and a plot of $\log K_a$ vs. ionic strength at 35° made. At any desired ionic strength a value of $\log K_a$ may be read off this plot and combined with the value of the ion-product constant of water at the same ionic strength¹⁹ to give the ionization constant of methylamine.

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The value of W , the water concentration, was calculated from the partial molar volumes of the amines used, which were determined by measuring the densities of amine solutions of known concentrations, and from the partial molar volume of isobutyraldehyde, which was assumed to be equal to the molar volume of the pure material. Except in the case of the measurements made using *t*-butylamine, where W was as low as 50.5 M , W was in the range 53.2–55.1 M in all our reaction solutions.

In this manner we obtained the values (or first approximations of the values) required for a plot of $A_0/(A_0\epsilon_A + B_0\epsilon_B - D)$ against W/B , using the D values obtained experimentally;²¹ in some cases, where W was essentially the same for all points, the abscissa in the plot was $1/B$ rather than W/B . According to eq 4, the intercept of the best possible²² straight line through the points is equal to $1/(\epsilon_A + \epsilon_B - \epsilon_I)$, and K (or K/W in plots against $1/B$) is equal to the intercept divided by the slope. From the preliminary value for K thus obtained, values of B_0 and B were calculated with increased accuracy and the entire process for the calculation of K repeated until no further changes were found in the values obtained. In the later plots the best line was determined by the method of least squares.

This method for determining K was used for a careful study of the reaction of methylamine with isobutyraldehyde and for preliminary studies using other amines. From the final plot obtained in one run on methylamine the value 4900 ± 160 was obtained.

Ultraviolet Measurements at the Imine Maxima. The decrease in absorbance at 2850 Å brought about by the addition of saturated aliphatic primary amines to aqueous solutions of isobutyraldehyde is accompanied by an increase in absorbance around 2300 Å. In hexane solution unsubstituted aliphatic aldimines have been reported to have absorption maxima around 2460 Å with extinction coefficients of about $80 M^{-1} cm^{-1}$.^{23,24} On going to the more polar solvent, ethanol, these extinction coefficients increase somewhat and the maxima shift to around 2380 Å. The extinction coefficients of the imines at their absorption maxima in water are about ten times as large as the apparent extinction coefficient of the aldehyde at its maximum. For this reason the equilibrium constants for the formation of some of the higher imines of isobutyraldehyde, which separate from aqueous solution at the concentrations most suitable for measurements at the absorp-

(19) These values were obtained from the data listed by Harned and Owen.²⁰ Values for the ion-product constant of water (K_w) in the presence of potassium chloride, sodium chloride, and sodium bromide are listed in terms of molalities. These values were converted to molarities and plotted against the square root of ionic strength. Inasmuch as the values obtained for the three different salts are identical, within the experimental uncertainty, up to an ionic strength of 0.06 M , a single line was drawn through the three set of points. The use of this line is equivalent to the assumption that the substituted ammonium salts that are responsible for the ionic strength in our reaction solutions have the same effect on K_w that the three alkali-metal salts do at a given ionic strength. The highest ionic strengths used were about 0.015 M .

(20) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, pp 638, 725, 752–754.

(21) In all cases equilibrium was shown to be established in a much shorter time than had elapsed when our equilibrium D values were measured.

(22) The intercept cannot be smaller than $1/(\epsilon_A + \epsilon_B)$, a known quantity.

(23) R. Bonnett, N. J. David, J. Hamlin, and P. Smith, *Chem. Ind. (London)*, 1836 (1963).

(24) R. Bonnett, *J. Chem. Soc.*, 2313 (1965).

maximum for isobutyraldehyde, may be determined conveniently by measurements at the absorption maxima of the imines.

Although the extinction coefficients of the amines at 2300 Å are considerably smaller than those of the imines, the concentration of amine is often considerably larger than that of imine. For this reason it was convenient to use in the reference cell an amine solution of about the same strength as that in the sample cell instead of using pure water as was done in the experiments at 2850 Å. When this is done the term in eq 4 must be replaced by $B_0 - B'$, where B' is the concentration of amine in the reference cell. In order to avoid working with negative numbers, the equation is also multiplied by -1 to give

$$-A_0\epsilon_A - (B_0 - B')\epsilon_B = 1/(\epsilon_I - \epsilon_A - \epsilon_B) + W/[KB(\epsilon_I - \epsilon_A - \epsilon_B)] \quad (5)$$

Equation 5 was used to determine K graphically by the method of successive approximations, as described in the preceding section. The necessary ionization constants and various ionic strengths were obtained from literature for methylamine,¹⁸ ethylamine,²⁵ *n*-butylamine,²⁶ and *t*-butylamine²⁶ (in the first four cases by interpolation between data at higher and lower ionic strengths) and determined in the present investigation for isopropylamine. The values of K determined from eq 5 are listed in Table I.

Table I. Equilibrium Constants for the Formation of Imines of Isobutyraldehyde and Primary Amines in Water at 35°

Primary amine	K^a	
	Ultraviolet measurements at imine maximum	pH measurements
EtNH_2^b	5050 ± 190	4910 ± 110
tNH_2	3560 ± 170	3420 ± 120
PrNH_2	4210 ± 50	4140 ± 70
PrNH_2	1830 ± 20	1850 ± 70
BuNH_2	4060 ± 80	4010 ± 40
BuNH_2	199 ± 4	

^a These are the dimensionless equilibrium constants defined by eq 5, in which W is the actual molar concentration of water. ^b Ultraviolet measurements at the aldehyde maximum gave a K value of 160.

Measurements. When isobutyraldehyde is added to a primary amine-amine hydrochloride buffer the pH increases. It is plausible that this is due to the formation of some of the primary amine to aldimine which is considerably less basic. Although we found no report of the determination of the ionization constant of an aliphatic aldimine, there are theoretical reasons why the sp^2 nitrogen atom of an imine should be less basic than the saturated nitrogen atom of the corresponding amine. Furthermore, the available data on aromatic aldimines and on cyclic ketimines support the argument that aliphatic imines are significantly less basic than the corresponding amines. Cordes and Jencks, for example,

L. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, **47**, 34

L. B. Hetzer and R. G. Bates, *J. Phys. Chem.*, **66**, 308 (1962).

found that the ionization constants of substituted *N*-benzylidene-*t*-butylamines vary from 5×10^{-7} for the *p*-methoxy compound to 2.5×10^{-9} for the *p*-nitro compound.⁷ Březina and Zuman reported that the imines derived from methylamine and cyclohexanone and cyclopentanone have ionization constants of 2.7×10^{-5} and less than 10^{-6} , respectively.¹¹ On the basis of data on related compounds it has been estimated¹⁴ that the ionization constant of *N*-isobutylidenemethylamine is around 10^{-7} or less. In comparison, typical unsubstituted saturated primary and secondary amines have ionization constants in the range 4×10^{-4} to 1.5×10^{-3} .

If it is assumed that the imine formed is protonated to a negligible extent, the effect of adding isobutyraldehyde to a primary amine buffer is to remove some of the amine and thus increase the ratio $[\text{RNH}_3^+]/[\text{RNH}_2]$. The concentration of amine present after the addition of isobutyraldehyde to an amine buffer may be expressed

$$[\text{RNH}_2] = \frac{[\text{RNH}_2]_0 [\text{RNH}_3^+]_0 [\text{OH}^-]_0 K_b^0}{[\text{RNH}_3^+]_0 [\text{OH}^-]_0 K_b} \quad (6)$$

where the subscript and superscript zeros refer to concentrations before the addition of aldehyde and the ionization constant at the initial ionic strength, and the concentrations and ionization constant after the addition of aldehyde are written without zeros. The concentrations of hydroxide ion are calculated from the observed pH's and the ion-product constant of water at the proper ionic strength.¹⁹ The concentration of ammonium ions is equal to the sum of the buffer anion concentration and the hydroxide ion concentration. The concentration of imine may be expressed

$$I = (V_0/V)([\text{RNH}_3^+]_0 + [\text{RNH}_2]_0) - [\text{RNH}_3^+] - [\text{RNH}_2] \quad (7)$$

where V_0 is the volume of buffer solution before the aldehyde solution is added and V is the volume afterwards. From eq 6 and 7 and the concentration of aldehyde known to have been added, the equilibrium concentration for imine formation may be calculated.

From 14 to 31 different measurements were made for each of the amines studied, with the ratio of amine to aldehyde added being varied by at least fourfold and the hydrogen ion concentration being varied by an even larger factor. The results obtained are listed in Table I. Preliminary measurements were made using *t*-butylamine, but the equilibrium constant for imine formation is so small that the pH changes observed were not large enough to permit reliable results to be obtained.

Properties of *N*-Isobutylidenealkylamines

The various *N*-isobutylidenealkylamines were isolated from the reaction of isobutyraldehyde with the primary amine. The nmr spectra of the imines isolated are summarized in Table II.

The ultraviolet absorption spectrum of each of the imines isolated was measured in 2,2,4-trimethylpentane solution, and the spectra of three imines were measured in acetonitrile. The wavelength of the absorption maxima and extinction coefficients at the maxima thus obtained are listed in Table III. Also listed

Table II. Nmr Spectra of N-Isobutylidenealkylamines

Chemical shifts, τ , and types of proton							Coupling constants, cps				
A	B ^a	C	D	E	F	G	J_{AB}	J_{BC}	J_{CD}	J_{DE}	J_{EF}
(CH ₃) ₂ CH—CH=N—CH ₂ —CH ₂ —CH ₂ —CH ₃	8.96	2.51	6.70	~8.5	b	b	7.0	4.0	1.3	6.0	
(CH ₃) ₂ CH—CH=N—CH ₂ —CH ₂ —CH ₃	8.94	2.52	6.75	8.48	9.18		6.8	4.3	1.4	6.4	6.9
(CH ₃) ₂ CH—CH=N—CH ₂ —CH ₃	8.94	2.51	6.72	8.91			7.2	3.9	1.3	7.5	
(CH ₃) ₂ CH—CH=N—CH(CH ₃) ₂	8.98	2.49	6.80	8.92			6.2	4.1	<0.5	6.3	
(CH ₃) ₂ CH—CH=N—CH ₃	8.95	2.50	6.84				7.0	4.2	1.6		
(CH ₃) ₂ CH—CH=NC(CH ₃) ₃	8.91	2.54	8.85				6.9	4.1			

^a The absorption by type B protons was too broad and weak to permit a reliable assignment of the chemical shift, but in all cases τ was about 7.7. ^b The peaks due to these protons were obscured by other absorption.

Table III. Ultraviolet Spectral Data on N-Isobutylidenealkylamines

Imine	Me ₂ CCH ₂ —CHMe ₂		CH ₃ CN		Water	
	λ_{\max} , m μ	ϵ	λ_{\max} , m μ	ϵ	λ_{\max} , m μ	ϵ
<i>i</i> -PrCH=NMe	2425	67			2265	146
<i>i</i> -PrCH=NEt	2420	83	2450	108	2300	127
<i>i</i> -PrCH=NPr- <i>n</i>	2450	91			2300	155
<i>i</i> -PrCH=NPr- <i>i</i>	2410	85	2400	110	2250	187
<i>i</i> -PrCH=NBu- <i>n</i>	2440	88	2410	108	2200	144
<i>i</i> -PrCH=NBu- <i>i</i>	2500	84			2260	163

are the extinction coefficients and absorption maxima determined in water by the measurements in which the equilibrium constants for imine formation were also determined. The increase in extinction coefficients and shift of the absorption maxima to shorter wavelengths noted on going from saturated hydrocarbons to the more polar solvent ethanol²² also occur on going to acetonitrile and to the even more polar solvent, water.

Each of the imines studied had a strong absorption band in the infrared at $1670 \pm 5 \text{ cm}^{-1}$ due to the carbon-nitrogen double bond. This is in agreement with several Raman observations²⁷⁻²⁹ and with previous infrared studies.^{30,31} Densities, boiling points, and refractive indices are listed in Table IV.

Table IV. Physical Properties of (CH₃)₂CHCH=NR Compounds

R	d_4	n_D	Temp, °C	Bp, °C (mm)	
				Obsd	Lit.
Methyl	0.7388 ^a	1.4041 ^a	12.5	69.5	69.5 ^a
Ethyl	0.7325 ^b	1.3979 ^b	35	87	90 ^a
<i>n</i> -Propyl	0.7518 ^a	1.4158 ^a	13.5	115	115 ^a
Isopropyl	0.7269 ^c	1.3934 ^c	35	97	100 ^a
<i>n</i> -Butyl	0.7580	1.4090 ^d	35	139–140	142.7 ^f
<i>i</i> -Butyl	0.7453	1.4055 ^e	25	115–116	51–53 (83) ^g

^a R. T. Tiollais, *Bull. Soc. Chim. France*, 708, 716 (1947). ^b Lit. ^c d_{15}^{20} , 0.7395, n_D^{20} 1.4072. ^d Lit. ^e d_{15}^{20} , 0.7341, n_D^{20} 1.4064. ^f Lit. ^g n_D^{20} 1.4151. ^h W. D. Emmons, *J. Am. Chem. Soc.*, 79, 5739 (1957). ⁱ G. E. Coates and L. E. Sutton, *J. Chem. Soc.*, 1187 (1948). ^j Lit. ^k n_D^{20} 1.4078.

(27) A. Kirmann and P. Laurent, *Bull. Soc. Chim. France*, 1657 (1939).

(28) L. Kahovec, *Acta Phys. Austriaca*, 1, 307 (1948); *Chem. Abstr.*, 42, 6665 (1948).

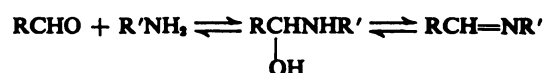
(29) R. Cantarel, *Compt. Rend.*, 210, 480 (1940).

(30) L. J. Bellamy, "Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co., London, 1958, Chapter 15.

(31) F. H. Suydam, *Anal. Chem.*, 35, 193 (1963).

Discussion of Results

The formation of an imine from an aldehyde and a primary amine almost undoubtedly involves the intermediate formation of an α -hydroxyamine.⁸



It seems extremely unlikely that either of the two products shown would be formed to the complete exclusion of the other. Therefore, it seems probable that the equilibrium constants we have measured are for the formation of a mixture of imine and α -hydroxyamine. Some of the methods we have used give little information as to the composition of this mixture. All the methods, as employed, give evidence that one molecule of aldehyde reacts with one molecule of primary amine to give one molecule of product, but this does not distinguish between imine and α -hydroxyamine formation. In principle, a distinction could be based on the fact that a molecule of water is a by-product in the formation of imine but not in the formation of α -hydroxyamine. In practice, however, the concentration of water in our reaction mixtures was never varied by so much as 10%, so this distinction cannot be made.

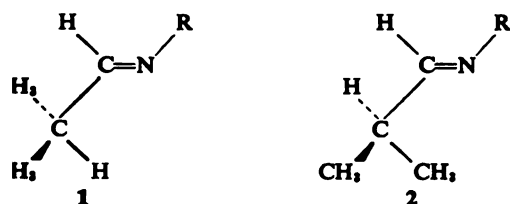
The determination of K by pH measurements is based on the assumption that a product is being formed whose basicity is negligible in comparison to that of the primary amine being studied. If this assumption is in error the values of K determined should show a tendency to decrease as increasing amounts of aldehyde are added to a given buffer. No such tendency may be seen in the experimental results. Evidence that imines should be relatively weakly basic has already been described.^{7,11,14} However, it is not unlikely that α -hydroxyamines are also significantly weaker bases than the primary amines from which they are formed. From Hall's correlation of the basicities of aliphatic amines³² it may be estimated that an α -hydroxy substituent will decrease the ionization constant of an amine by 50–100-fold. Such a decrease will be partially offset by the greater basicity (by about twofold) usually observed for secondary amines, compared to primary amines. Thus an α -hydroxyamine would probably be a weaker base than the primary amine from which it was formed, and it might be so weak as to be protonated to a negligible extent in the presence of the primary amine buffer.

(32) H. K. Hall, Jr., *J. Am. Chem. Soc.*, 79, 5441 (1957).

ultraviolet measurements at 2850 Å showed that the product is formed that absorbs almost negligibly at this wavelength, a property that is at least as plausible for α -hydroxyamine as for the imine. The measurements around 2300 Å, however, show that a product is formed with an absorption maximum and an extinction coefficient greater than $120 \text{ M}^{-1} \text{ cm}^{-1}$ at this wavelength. Such properties are quite plausible for a saturated α -hydroxyamine but are unreasonable for an aldimine. Therefore, it seems that the product whose formation we are studying is an imine. Nevertheless, the spectral properties expected of our imines cannot be predicted with enough quantitative reliability to rule out the possibility that some α -hydroxyamine may also be present in our product mixtures in aqueous solution.

These results may be summarized by stating that the equilibrium constant for the isobutylidenation of formaldehyde is rather larger than those for ethylamine, propylamine, and *n*-butylamine, and the constants for the latter amines are more than twice as large as for isopropylamine, which is almost nine times as large as the constant for *t*-butylamine. This variation in equilibrium constants seems most plausibly explained by steric hindrance. Before discussing such hindrance, however, we should discuss the detailed structure of the imines we have studied.^{32a}

In analogy with the extensive studies that have been made on olefins and carbonyl compounds³³ it would be expected that our imines would exist in a conformation in which the carbon-nitrogen double bond is eclipsed by the hydrogen atom, 1, or one of the methyl substituents of the isobutylidene group, 2. We would expect the



coupling constant between the α -hydrogen of the isobutyl group and the hydrogen attached to sp^2 carbon (Table II) in 1 to be intermediate between the

1.5 cps reported as characteristic for such *trans* coupling constants in analogous olefins³⁴ and the value estimated for such *trans* coupling constants in α -hydroxy aldehydes.³⁵ Although we have not found any other relevant published data on imines, Leonard and Paukstelis found a coupling constant of 10.0 cps for the two corresponding hydrogen atoms of the isobutylidene group in N-2-ethylbutylidenepyrrolidone perchlorate,³⁶ where steric effects would be expected to cause the compound to exist principally in a conformation like 1. For conformation 2, where these hydrogens are *gauche* to each other, a value inter-

mediate between the olefin value 3.7 cps³⁴ and the aldehyde value -0.3 cps ³⁵ would be expected. The assumption of coupling constants for the imines exactly halfway between those for the analogous olefins and aldehydes (9.2 and 1.7 cps for *trans* and *gauche* coupling, respectively) plus the observed values of J_{BC} ($4.1 \pm 0.2 \text{ cps}$) leads to calculation of a 29–35% content of conformation 1 and a 65–71% content of conformation 2 in the imines studied. In view of the uncertainty in *trans* and *gauche* coupling constants used, this estimate of the relative fractions of the two conformations present is not highly reliable. We feel that the presence of significant amounts of conformation 2 is rather well established, and the simultaneous presence of significant amounts of conformation 1 is probable. Although conformation 2 appears to be the more abundant conformation, this abundance is not necessarily any greater than would be explained by the fact that there are two methyl groups that can eclipse the carbon-nitrogen double bond (as in 2) but only one hydrogen atom that can.

There is good evidence that aldimines in which the carbon-nitrogen double bond is conjugated with one or more aromatic rings exist preferentially in the *trans* form³⁷ (by the *trans* form we refer to the isomer in which the isopropyl group from the aldehyde is *trans* to the R group of the amine). In the *cis* forms of such compounds there would be steric interference with the coplanarity required for the maximum resonance stabilization. For imines derived from saturated aliphatic aldehydes and amines, however, little convincing evidence as to the relative stabilities of the two forms seems to have been published. The high rate of formation and hydrolysis of the imines studied under the conditions of their preparation makes it seem likely that the more stable forms were obtained. Conformations 1 and 2 have been written as *trans* isomers because of several lines of evidence that our compounds are *trans* isomers and that they are more stable than the corresponding *cis* isomers. Even in the case of N-isobutylidenemethylamine, the imine for which the *cis* isomer should be least strained, it may be pointed out that with the analogous hydrocarbons, the 4-methyl-2-pentenes, equilibration studies show that the *trans* isomer is about 1.2 kcal/mole more stable than the *cis* isomer at 55°.⁴⁰ The differences in stability between the *cis* and *trans* isomers are probably larger in the case of the imines than in the case of the olefins. If we assume carbon-nitrogen single- and double-bond distances of 1.44 and 1.30 Å and a C=N—C bond angle of 116.9° as reported for N-methylenemethylamine,⁴¹ a C—C—N angle equal to the C—C—C angle in propylene (124.3°),⁴² and an sp^2 -carbon- sp^2 -carbon bond distance of 1.501 Å, like that in propylene, an internuclear distance of 2.80 Å may be calculated for the two carbon atoms attached to sp^2 carbon and sp^2 nitrogen in the *cis* isomer of an aldimine. The same assumptions

(37) In derivatives of N-benzylidenaniline, for example, dipole measurements provide evidence that the compounds ordinarily obtained are *trans* isomers,³⁸ and flash photochemical studies show that these ordinarily obtained materials may be photoisomerized to less stable isomers that rapidly isomerize back to the starting materials.³⁹

(38) V. de Gaouck and R. J. W. Le Fèvre, *J. Chem. Soc.*, 741 (1938).

(39) D. G. Anderson and G. Wettermark, *J. Am. Chem. Soc.*, **87**, 1433 (1965).

(40) A. Schriesheim and C. A. Rowe, Jr., *ibid.*, **84**, 3160 (1962).

(41) K. V. L. N. Sastry and R. F. Curl, *J. Chem. Phys.*, **41**, 77 (1964).

(42) D. R. Lide and D. Christensen, *ibid.*, **35**, 1374 (1961).

NOTE ADDED IN PROOF. Dr. N. J. Leonard has kindly brought to our attention the similar conclusions concerning conformational and isomerization in imines reached by W. J. Musliner, Ph.D. thesis, University of Illinois, Urbana, Ill., 1965.

L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Interscience Publishers, Inc., New York, 1966, Sections 1–3b.

A. Bothner-By, C. Naar-Colin, and H. Günther, *J. Am. Chem. Soc.*, **84**, 748 (1962).

J. Karabatsos and N. Hsi, *ibid.*, **87**, 2864 (1965).

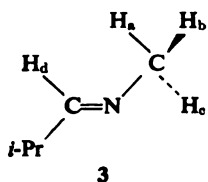
J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021

plus a 1.336-A carbon-carbon double-bond distance, as in propylene, lead to an internuclear distance of 3.03 A for the two carbon atoms attached to sp^2 carbon and *cis* to each other in a *cis* olefin. The difference of 0.23 A should be sufficient to make the *cis* imine considerably more destabilized (with respect to the *trans* isomer) than the corresponding *cis* olefin. It should also be noted that the difference in stabilities of the two geometric isomers of the 4-methyl-2-pentenes is related to the difference between an isopropyl-methyl *cis* interaction and an isopropyl-hydrogen *cis* interaction, whereas the difference in stabilities of the geometric isomers of our imines is related to the difference between an isopropyl-R *cis* interaction and an isopropyl-unshared pair *cis* interaction.

Furthermore, if our argument that there are significant amounts of both conformations 1 and 2 is correct, the relative amounts of these conformations and hence the magnitude of the J_{BC} values in Table II would be expected to vary markedly as the R group attached to nitrogen is changed from methyl through ethyl and isopropyl to *t*-butyl if any or all the imines studied existed to a significant extent as *cis* isomers. The essentially constant character of J_{BC} therefore provides evidence that the imines are practically all *trans*.

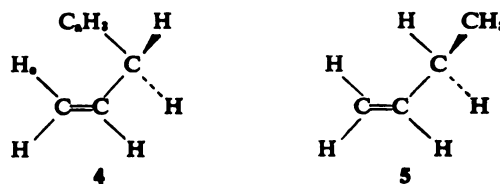
In none of our nmr spectra were extra bands that might have been expected from small amounts of *cis* isomer noted. This might be explained by the hypothesis that all the corresponding hydrogen atoms have the same chemical shifts in the two isomers, but nmr data on geometrically isomeric ketimines make this hypothesis implausible.^{43,44} It might also be hypothesized that the *cis-trans* equilibrium is established so rapidly that the nmr spectra of the two isomers have become fused. However, this hypothesis, too, is implausible. A survey of data on rate of *cis-trans* isomerization of imines shows that all the N-alkyl compounds studied isomerize much too slowly for fusion of nmr spectra.⁴⁴ These data also show no detectable tendency for aldimines to isomerize more rapidly than analogous ketimines. Therefore it appears that our imines consist very largely of one isomer.

Yardley, Hinze, and Curl have shown that the carbon-nitrogen double bond in N-methylenemethylamine is eclipsed by one of the hydrogen atoms of the methyl group.⁴⁵ By analogy with this observation as well as with the studies on olefins^{33,34} and carbonyl compounds,^{33,35} we expect N-isobutylidenemethylamine to exist in a conformation like 3. We suggest



that with the imines derived from ethylamine, *n*-propylamine, and *n*-butylamine the conformation with an alkyl group in place of H_a is considerably less stable than the conformations in which the alkyl group

is in the place of H_b or H_c . It is true that such a conformation may be considered to be analogous to conformation 4 for 1-butene, which has been reported to be about as heavily populated as either of the other two conformations, of the type of 5.³⁴ However, the same



assumptions concerning molecular geometry made earlier in this section plus a 1.091-A sp^2 -carbon-hydrogen bond distance, 120.5° H-C= bond angles (as in propylene),⁴² 1.54-A sp^2 -carbon- sp^3 -carbon bond distances, and 109.5° bond angles around sp^3 carbon lead to an internuclear distance of 2.06 A between H_d and an sp^3 carbon atom in the place of H_a in conformation 3, in contrast to a 2.39-A distance between H_a and C_a in conformation 4. This difference of 0.33 A seems large enough to explain the suggested difference in relative conformational stabilities. The imine derived from isopropylamine would have one relatively stable conformation (with methyl groups in the place of H_b and H_c of 3) and two unstable conformations (with one methyl group in the place of H_a and another in the place of H_b or H_c). All three conformations of the imine derived from *t*-butylamine would be destabilized by interaction between H_d and a methyl group in the place of H_a .

The nmr spectra of the imines support these suggestions. There is good evidence that coupling constants between pairs of protons analogous to H_a and H_d (in olefins, for example) are much smaller than between pairs like H_b (or H_c) and H_d .⁴⁶ It is therefore to be expected that J_{CD} is largest for the methylimine, smaller for the ethyl-, *n*-propyl-, and *n*-butylimines, and smallest for the isopropylimine.

The equilibrium constants for imine formation may be rationalized fairly satisfactorily in terms of steric effects alone if we assume that replacement of H_b or H_c in 3 by an alkyl group leads to a conformation with a free energy content 2.0 kcal/mole (at 35°) lower than when H_a is replaced by an alkyl group. Then relative to an equilibrium constant of about 70 (one-third of the equilibrium constant for the formation of the *t*-butylimine) for the formation of an imine in a conformation with an alkyl group in place of H_a in 3, the equilibrium constant for the formation of an imine in a conformation that lacks this destabilizing feature should be about 1800. These two figures may be used to calculate the equilibrium constants for the formation of the various imines. For the methylimine, with three stable conformations, the equilibrium constant should be 3×1800 or 5400; for the ethyl-, *n*-propyl-, and *n*-butylimines, with two stable and one unstable conformation, about $(2 \times 1800) + 70$ or 3670; for the isopropylimine, with one stable and two unstable conformations, about $1800 + (2 \times 70)$ or 1940; and for the *t*-butylimine, with three unstable conformations, about 3×70 or 210. This assumed difference in conformational stabilities may also be used to calculate relative populations of conformations, which may be combined with

(46) Cf. S. Sternhell, *Rev. Pure Appl. Chem.*, 14, 15 (1964).

(43) H. A. Staab, F. Vögtle, and A. Mannschreck, *Tetrahedron Letters*, 697 (1965).

(44) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Am. Chem. Soc.*, 88, 2775 (1966).

(45) J. T. Yardley, J. Hinze, and R. F. Curl, Jr., *J. Chem. Phys.*, 41, 2563 (1964).

$-H_d$ type coupling constant of 0.2 cps and an H_c (or H_c-H_d) coupling constant of 2.3 cps, calculate values of J_{CD} (Table II) of 1.6, 1.3, 1.3, 1.3, 4 cps for the methyl-, ethyl-, *n*-propyl-, *n*-butyl-, isopropyl-, respectively. Support for this variation of the J_{CD} values is found in the reported coupling constant of 1.6 cps between the methyl protons and the carbimino hydrogen of *N*-benzylamine⁴⁷ (which we assume to be *trans*), in the range of coupling constants in the range 1.8–2.1 cps between the carbimino hydrogens and the hydrogens bonded to nitrogen-bound carbon in the ring of *N*-enepyrrolidinium salts⁴⁸ (where the relationship between the hydrogens is nearer to that between H_d and H_c) than to that between H_d and H_a in 3), in the range of a coupling constant of about 1.5 cps between the α -methylene hydrogen atoms in *t*-BuCH=NCH₃ (1.3 cps would be expected from our correlation) and in the reports of no coupling between the α -methylene hydrogens of *t*-BuCH=NCHMeEt²⁴ and compounds of the type RCH=NCHRAr⁴⁹ (where steric effects should favor a conformation like 3). By analogy with observations on olefins⁴⁶ it is presumed that these coupling constants (J_{CD}) are negative.

Enough destabilization resulting when a primary group is put in place of H_a rather than H_b or H_c to form 3 provides a plausible rationalization of the observations, there is some uncertainty in the amount of 2 kcal/mole, postulated for the amount of this destabilization. The observed coupling constants could be related with any amount of destabilization that largely prevents alkyl groups from taking the place in 3; therefore they could be correlated satisfactorily with any amount of destabilization larger than about 1 kcal/mole. The existence of significant steric effects would indicate uncertainty in the amount of 2.0 kcal/mole, which is derived from an extension of the equilibrium constants solely in terms of steric effects. Part of the decrease in equilibrium constants observed in the series Me, Et, *i*-Pr, *t*-Bu could be attributed to decreased stabilization of the carbon-nitrogen double bond by hyperconjugation.⁴⁸ It is clear that polar effects can be important in imine formation, inasmuch as preliminary observations on the series in which the steric factor has been held essentially constant show that the Taft reaction constant is somewhat negative.^{1b} However, in view of the generally negative substituent constants for the isopropyl, and *t*-butyl groups, it may be seen that steric effects would act so as to offset hyperconjugation.

Evidence against the major importance of conjugation in the present case is provided by the observation that the largest change in log *K* occurs in the isopropyl and *t*-butyl cases. Hyperconjugation seems a poor explanation for most of this in view of our nmr evidence that the isopropyl exists very largely in a conformation in which the carbon-hydrogen bond is in a plane orthogonal to the orbitals of the carbon-nitrogen double bond. In addition to the various effects on the stability of the imine being formed, the relative magnitudes of the equilibrium constants for imine formation may also be

influenced by effects on the relative stabilities of the amine reactants (that are not balanced by analogous effects on the relative stabilities of the imines). However, we have no evidence for the importance of such effects nor arguments that any such effects should be important. We therefore conclude that steric effects of the type postulated are the predominant factors in bringing about the observed variation in equilibrium constants for imine formation but that other factors are probably significant. A plot of log *K* vs. Taft's E_s values (acyl component)⁴⁹ gives a good straight line for the methyl, ethyl, isopropyl, and *t*-butyl compounds, but the equilibrium constants for the *n*-propyl- and *n*-butylimines are almost twice as large as they should be to fall on this line. Our rationalization of the data gives no explanation of why these two equilibrium constants are larger than the equilibrium constant for the formation of the ethylimine.

Experimental Section

Reagents. The isobutyraldehyde and amines used were distilled and stored under nitrogen. The *N*-isobutylidenealkylamines were prepared from isobutyraldehyde and primary amines by a method based on that of Campbell, Sommers, and Campbell.⁵⁰ They were purified by distillation and stored under nitrogen. Their properties are listed in Tables II–IV.

Instrumentation. The ultraviolet spectra were determined using Cary recording spectrophotometers (Model 14). A Beckman Research pH meter (Catalog No. 101900) and glass and calomel electrodes were used for the pH measurements. The infrared spectra were determined with Perkin-Elmer spectrophotometers, Models 21 and 337. The nmr spectra were determined on the neat liquids using Varian A-60 spectrometers. Tetramethylsilane was used as an internal standard.

Ionization Constant of Isopropylamine. The acidity constant of isopropylammonium ions was determined by titration of aqueous solutions of isopropylamine potentiometrically with perchloric acid using a Beckman Research pH meter. The pK_a was calculated from the pH at half-neutralization with due allowance for the concentration of hydroxide ions, which was not negligible in comparison to the concentrations of amine and its conjugate acid. The titration container was thermostated at $35 \pm 0.5^\circ$. The acidity constant of the isopropylammonium ion was found to be 10.334, 10.309, 10.294, 10.265, and 10.231 at ionic strengths 0.0625, 0.0377, 0.0236, 0.0106, and 0.0030 *M*, respectively, and the value extrapolated to infinite dilution is 10.21. The most nearly comparable value listed in Perrin's compilation is a pK_a of 3.40 for isopropylamine at room temperature.⁵¹ If "room temperature" was 25° , this corresponds to a pK_a of 10.60 for the isopropylammonium ion, from which a value of 10.28 at 35° may be calculated by use of Perrin's methods of correcting for temperature changes.⁵² The agreement of this value with ours is as good as could be expected in view of the uncertainty in temperature. The agreement with de Ligny's pK_a of 10.15 for the isopropylammonium ion at 25° ⁵³ is rather poor.

Determination of Equilibrium Constants for Imine Formation. The operations were carried out under nitrogen and solutions were made up using water from which the dissolved air had been replaced by nitrogen. In a typical experiment using the ultraviolet procedure, a volumetric flask was 95% filled with water, a weighed amount of isobutyraldehyde added, and the flask was filled to the mark with water. After the flask had been shaken a sample was titrated with standard base to determine the concentration of isobutyric acid present in the solution. Amine solutions were prepared similarly by weighing except in the case of the more volatile amines, the strength of whose solutions were determined by titration. When ultraviolet measurements were made on such solutions and their mixtures, water at 35° was circulated through the cell

(49) R. W. Taft, *ibid.*, 74, 3120 (1952).

(50) K. N. Campbell, A. H. Sommers, and B. K. Campbell, *ibid.*, 66, 82 (1944).

(51) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co. (Publishers), Ltd., London, 1965, p 33.

(52) D. D. Perrin, *Australian J. Chem.*, 17, 484 (1964).

(53) C. L. de Ligny, *Rec. Trav. Chim.*, 79, 731 (1960).

Tori, M. Ohtsuru, and T. Kubota, *Bull. Chem. Soc. Japan*, (1966).

R. W. Taft and M. M. Kreevoy, *J. Am. Chem. Soc.*, 79, 4011

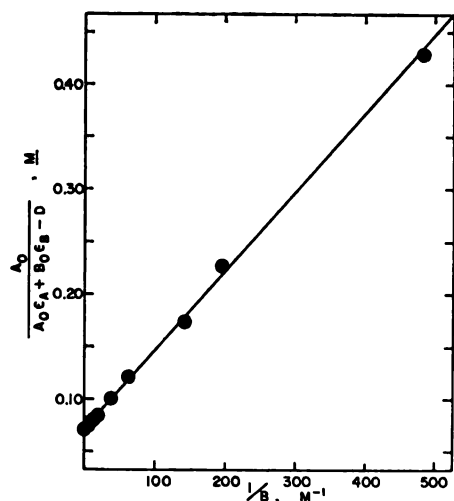


Figure 1. Determination of equilibrium constant for the formation of N-isobutylidenemethylamine by a plot according to eq 4.

compartment and through the thermostatable cell holder. The wavelength of the absorption maximum for the imine was determined by measurements in which the amine was present in large excess.

The data for a run in which measurements were made at the absorption maximum of the aldehyde are shown in Table V and plotted in Figure 1. Those for a run in which measurements were made at the absorption maximum of the imine are shown in Table VI and plotted in Figure 2.

Table V. Measurements on Aqueous Solutions of Isobutyraldehyde and Methylamine at 2850 Å

Components of sample soln, ^a ml			Absorbance
<i>i</i> -PrCHO ^b	MeNH ₂ ^c	H ₂ O	
10.00	0	2.00	1.968
10.00	0	2.00	1.970
10.00	0.100	1.90	1.655
10.00	0.200	1.80	1.375
10.00	0.250	1.75	1.190
10.00	0.40	1.60	0.835
10.00	0.50	1.50	0.637
10.00	0.70	1.30	0.372
10.00	0.85	1.15	0.280
10.00	1.00	1.00	0.243
10.00	1.50	0.50	0.160
10.00	2.00	0	0.120

^a Reference solution pure water in all cases. ^b 0.1610 M (and 0.00173 M in isobutyric acid). ^c 3.0100 M.

Table VI. Measurements on Aqueous Solutions of Isobutyraldehyde and *n*-Propylamine at 2300 Å

Sample soln, ml			Ref soln, ml		Absorbance
<i>i</i> -Pr-CHO ^a	<i>n</i> -Pr-NH ₂ ^b	H ₂ O	<i>n</i> -Pr-NH ₂ ^b	H ₂ O	
10.00	0	25.00	0	35.00	0.002
10.00	0	25.00	0	35.00	0.000
10.00	2.00	23.00	2.00	33.00	0.230
10.00	4.00	21.00	4.00	31.00	0.460
10.00	5.00	20.00	5.00	30.00	0.540
10.00	8.00	17.00	8.00	27.00	0.778
10.00	10.00	15.00	10.00	25.00	0.880
10.00	15.00	10.00	15.00	20.00	1.102
10.00	20.00	5.00	20.00	15.00	1.230
10.00	25.00	0	25.00	10.00	1.302

^a 0.04292 M (and 0.00027 M in isobutyric acid). ^b 0.07680 M.

When the equilibrium constant was determined by pH measurements, bromothymol blue was added to the aldehyde solution, to which enough base was then added to turn the indicator green

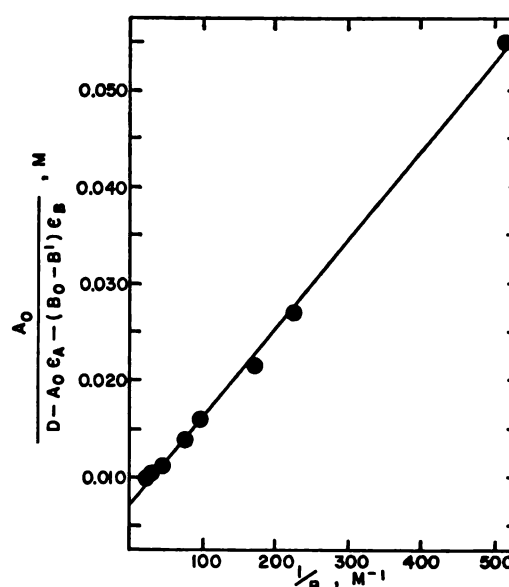


Figure 2. Determination of equilibrium constant for the formation of N-isobutylidene-*n*-propylamine by a plot according to eq 5.

(characteristic of a pH of about 7) in order to neutralize the isobutyric acid present. This aldehyde solution was added from a stoppered buret through a cover (to exclude air) to a beaker of the amine buffer in which the electrodes of the pH meter were immersed. The results obtained with *n*-butylamine are summarized in Table VII.

Table VII. Determination of the Equilibrium Constant for the Formation of N-Isobutylidene-*n*-butylamine by pH Measurements

Sample soln, ml		pH	[H ₂ O]	K
<i>i</i> -PrCHO soln	<i>n</i> -BuNH ₂ buffer			
0	70.0 ^b	10.432		
15.0 ^a	70.0 ^b	10.010	54.89	4087
20.0 ^a	70.0 ^b	9.930	54.84	4036
25.0 ^a	70.0 ^b	9.868	54.80	3988
30.0 ^a	70.0 ^b	9.814	54.77	4017
35.0 ^a	70.0 ^b	9.771	54.73	4009
40.0 ^a	70.0 ^b	9.733	54.70	4033
45.0 ^a	70.0 ^b	9.704	54.68	4008
0	70.0 ^d	10.446		
15.0 ^a	70.0 ^d	10.022	54.89	3967
20.0 ^a	70.0 ^d	9.934	54.84	4024
25.0 ^a	70.0 ^d	9.880	54.80	3871
30.0 ^a	70.0 ^d	9.823	54.76	3924
35.0 ^a	70.0 ^d	9.773	54.73	4003
40.0 ^a	70.0 ^d	9.734	54.70	4030
45.0 ^a	70.0 ^d	9.697	54.67	4088

Av 4006 ± 39

^a 0.2157 M. ^b 0.01387 M *n*-BuNH₂, 0.00607 M *n*-BuNH₃⁺. ^c 0.2185 M. ^d 0.01388 M *n*-BuNH₂, 0.00607 M *n*-BuNH₃⁺.

Acknowledgments. We wish to acknowledge our indebtedness to the National Science Foundation for grants that made possible the purchase of the nmr spectrometers used and contributed toward the purchase of the ultraviolet spectrophotometers, to the Charles F. Kettering Foundation for a grant that contributed toward the purchase of an ultraviolet spectrophotometer, and to the Eastman Chemical Products Co. for a gift of the isobutyraldehyde used. We also wish to thank Dr. Julien Mulders and Miss Shirley Lee for having made preliminary measurements in this investigation.

The *meso*-*dl* Isomerization of 2,3-Dimethyl-2,3-diphenylsuccinonitrile¹

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Abstract: The *meso* and *dl* diastereomers of 2,3-dimethyl-2,3-diphenylsuccinonitrile have been interconverted both thermally and photochemically. The equilibrium constant (*dl*/*meso*) is 1.22 and is relatively insensitive to temperature. From the rate of isomerization, studied in the 125–175° range, one calculates $\Delta H^\ddagger = 42.4$ kcal/mole, $\Delta^\ddagger = 17$ cal/deg mole. The isomerization probably proceeds via the 1-phenyl-1-cyanoethyl radical, $C_6H_5(CH_2)\dot{C}(CN)$, as suggested by trapping experiments with thiophenol and with oxygen. The greater stability of the *dl* isomer, compared to *meso*, implies an attractive interaction between *gauche* cyano groups.

Meso and *dl* diastereomers of appropriately substituted ethane derivatives represent classical examples of stereoisomerism. It has been recognized for some time that such configurational isomers are not only in their physical and chemical properties but also in their thermodynamic energy contents.² In spite of the generally accepted energy differences in *meso*-*dl* systems, very few experimental data are available to support these conclusions. It is not yet possible to predict with any confidence which isomer is more stable in even relatively uncomplicated or hexasubstituted ethanes. Usually it is assumed that where strong intramolecular forces are present, the *dl* form is thermodynamically more stable than the *meso* and in the absence of such forces that the *meso* isomer is the more stable. Although these statements are probably correct, the necessary limitations are not always observed. Unfortunately much of the experimental data which would support these statements is of a nature some of the existing and especially older data on relative isomer stabilities in these systems is owing to difficulties and attendant errors in making structural assignments, determining isomer ratios, and establishing equilibrium constants.

The interconversion of *meso* and *dl* isomers has been observed in only a few isolated instances, and no conditions have been made on a related series of compounds. Of the conventional means for effecting isomerization, namely, thermal, photochemical, Lewis acid metal, and basic catalysis, only the latter methods have been employed to interconvert *dl* diastereomers in acyclic systems.³ G. M. Stille and P. E. Spoerri have shown that *dl*-2,3-dimethyl-2,3-diphenylsuccinonitrile is partially converted to the *meso* isomer in the presence of aluminum chloride.^{6a} A similar

study by Nenitzescu and Glatz^{4b} suggests that the *meso* form may be the more stable. However, in both cases there remains some question as to whether equilibrium conditions prevailed. Buckles, *et al.*,⁷ found that the presence of halogens effects the isomerization of *dl*- α,α' -dibromobibenzyl and *dl*- α,α' -dichlorobibenzyl to their *meso* forms. Solid *dl*- α,α' -dibromobibenzyl upon standing in bromine vapor for an extended period reportedly was converted 90% to the *meso* isomer. It should be pointed out, however, that this may not truly reflect the relative free energy differences between the two isomers since crystal lattice forces may be the dominating influence.

dl-2,3-Dimethylsuccinic acid was found to be partially isomerized to the *meso* diacid upon prolonged treatment with acid, leading Linstead and Whalley to conclude erroneously that the *meso* isomer was the more stable.⁸ Eberson⁹ subsequently has shown that when the *dl*- and *meso*-2,3-dimethyl-, -2,3-diethyl-, and -2,3-diisopropylsuccinic acids are equilibrated with strong hydrochloric acid, the racemic forms predominate. The somewhat unexpected stability of the *dl* isomers was attributed to intramolecular hydrogen bonding between adjacent carboxyl groups. Recently, similar intramolecular interactions have been invoked to explain the predominance of *dl*-2,3-butanediol which arose from the treatment of *meso*-2,3-butanediol with sodium in toluene followed by hydrolysis.¹⁰ *d*-Tartaric acid upon prolonged refluxing with aqueous potassium hydroxide gave a mixture of *dl* and *meso*-tartaric acid which yielded twice as much *dl* as *meso* upon isolation, however, only about half of the initial tartaric acid was recovered.²

Since polyphenylated ethanes are well known to dissociate thermally into polyphenylmethyl radicals, substitution of the phenyls by groups which also will weaken the central carbon-carbon bond either through steric or electronic forces and concurrently satisfy the necessary requirements for *meso* and *dl* isomerism should provide convenient systems for studying the phenomenon of *meso*-*dl* isomerization. Such compounds

¹ Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 11–16, 1966.
² P. E. Verkade, *Rec. Trav. Chim.*, **44**, 987 (1925).
³ R. M. Sack, "Conformation Theory," Academic Press Inc., New York, 1965, p 335.
⁴ G. M. Stille, "Stereochemistry of Carbon Compounds," McGraw-Hill, Inc., New York, N. Y., 1962, pp 138–139.
⁵ G. M. Stille, P. D. Bartlett and J. M. McBride (International Symposium on Free Radicals in Solution, Ann Arbor, Mich., Aug 23, 1966), reported a thermal isomerization wherein *meso*- and *dl*-2,3-dimethyl-2,3-diphenylsuccinonitrile dissociate at 80° into radicals which undergo both recombination and disproportionation. At the *meso*/*dl* ratio is approximately 1.5.
⁶ T. Somerville and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**,

3803 (1952); (b) C. D. Nenitzescu and A. Glatz, *Acad. Rep. Populare Romine, Studii Cercetari Chim.*, **7**, 505 (1959); *Chem. Abstr.*, **54**, 19546c (1960).

(7) R. E. Buckles, W. E. Steinmetz, and N. G. Wheeler, *J. Am. Chem. Soc.*, **72**, 2496 (1950).

(8) R. P. Linstead and M. Whalley, *J. Chem. Soc.*, 3722 (1954).

(9) L. Eberson, *Acta Chem. Scand.*, **13**, 203 (1959).

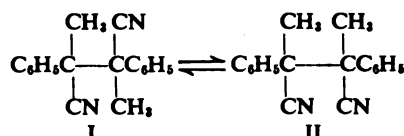
(10) F. Bottari and B. Macchia, *Chim. Ind. (Milan)*, **47**, 308 (1965).

are the isomeric *meso*- and *dl*-2,3-dimethyl-2,3-diphenylsuccinonitriles.^{11,12} In these compounds, the steric interactions between the various groups are not of the magnitude present in hexaphenylethane, but each substituent is capable of stabilizing the resulting radical through inductive effects or by delocalization of the electron into a π -electronic system.

The present work concerns the study of the *meso*-*dl* isomerization of the diastereomeric 2,3-dimethyl-2,3-diphenylsuccinonitriles. The results which we now report give some new information with regard to *meso* and *dl* isomer stabilities, and an attempt has been made to clarify some of the factors which influence isomer stabilities in these systems.

Results

When an *o*-dichlorobenzene solution of either the *dl* (I) or *meso* (II) isomer of 2,3-dimethyl-2,3-diphenylsuccinonitrile is heated at 150°, a mixture of the two forms is soon obtained. The isomerization is uncomplicated by potentially undesirable competing reac-



tions such as reaction with solvent molecules, disproportionation,¹³ or ketenimine formation.¹⁴ At equilibrium the *dl* isomer predominates with the *dl*/*meso* ratio being about 1.23 (55% *dl* and 45% *meso*). This isomer ratio corresponds to a free energy difference between the two isomers of 0.12 kcal/mole. As can be seen from Table I temperature has a negligible effect on the equilibrium constant.

Table I

Temp, °C	% <i>dl</i>	k_{eq}	$\text{sec}^{-1} \times 10^4$		$t_{1/2(\text{meso})}$, hr
			$k_{\text{meso} \rightarrow \text{dl}}$	$k_{\text{dl} \rightarrow \text{meso}}$	
125.0	55.3 ± 1.0	1.24 ± 0.05	0.186	0.153	103
150.0	54.9 ± 1.0	1.22 ± 0.05	4.11	3.53	4.7
175.0	55.0 ± 1.0	1.22 ± 0.05	64.5	55.4	0.30

No solvent effect was noted upon the *dl*/*meso* ratio when the isomerization was conducted in tetrachloroethylene, benzonitrile, and nitrobenzene. In all cases the *dl*/*meso* ratio was 1.22 ± 0.05 .

The *meso*-*dl* isomerization of I and II can also be effected photochemically at 25° by irradiating a benzene solution of either isomer at 2537 Å. Although the photostationary state has not yet been rigidly established, initial results suggest that the *dl*/*meso* ratio is about 1.0.¹⁵

(11) M. S. Kharasch and G. Sosnovsky, *Tetrahedron*, **3**, 97 (1958).

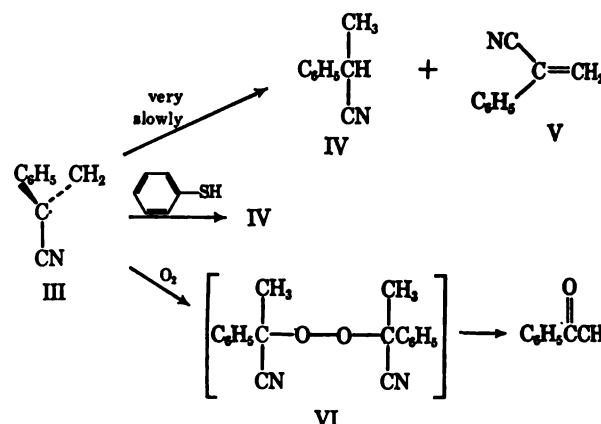
(12) R. L. Huang and L. Kum-Tah, *J. Chem. Soc.*, 2570 (1954).

(13) 2,2,3,3-Tetraphenylbutane dissociates in solution to give 1,1-diphenylethyl radicals which subsequently disproportionate into 1,1-diphenylethane and 1,1-diphenylethylene. See K. Ziegler, *Ann.*, **551**, 127 (1942). Bartlett and McBride observed a similar disproportionation of 2,3,4,5-tetramethyl-3,4-diphenylhexane. At 100° they observed a disproportionation/combination ratio of 0.7.⁸

(14) Recombination of 2-cyanopropyl radicals produced in the thermal decomposition of azobisisobutyronitrile affords dimethylketenecyanoisopropylimine (33%) in addition to tetramethylsuccinonitrile (66%). See M. Tañlt-Erben and S. Bywater, *J. Am. Chem. Soc.*, **77**, 3710 (1955).

(15) The isomer ratio obtained at equilibrium should not necessarily correspond to that observed at the photostationary state since the

The isomerization of I to II appears to proceed by homolytic scission of the central carbon-carbon bond to give methylphenylacetone radicals (III) which then recombine. The ratio of combination to disproportionation must be greater than 100 at 150° since no disproportionation products could be observed over ten half-lives. At 175°, however, after 100 half-lives (>30 hr) a disproportionation product was detected by nmr spectroscopy and gas chromatography, namely, methylphenylacetone (IV). The other product of disproportionation, 1-cyanostyrene (V), was not observed but this is not unexpected since 1,1-disubstituted olefins such as V polymerize readily. When the isomerization was studied in nitrobenzene at 150–160° a much larger amount of disproportionation was observed than in *o*-chlorobenzene (40% vs. 0% after 23 hr).



Evidence supporting the radical intermediate III was gained by conducting the isomerization in the presence of a good hydrogen donor. If *meso*-2,3-dimethyl-2,3-diphenylsuccinonitrile is dissolved in thiophenol and the solution heated to 170–180°, quantitative reduction to methylphenylacetone occurs within 2 hr. After only 1 hr in thiophenol, the *dl*/*meso* ratio of the remaining succinonitrile was 0.8 (vs. 1.22 at equilibrium), indicating that reduction proceeds at a rate comparable to that of isomerization. The fact that isomerization to the *dl* isomer is observed at all suggests part of the reaction may proceed within a solvent cage or that thiophenol is somewhat inefficient as a radical scavenger.¹⁶

Oxygen was also found to be a scavenger of methylphenylacetone radicals. When an *o*-dichlorobenzene solution of *meso*-2,3-dimethyl-2,3-diphenylsuccinonitrile was placed under 6 atm of oxygen at 175°, the slow formation of acetophenone was observed. The rate of acetophenone formation appeared to be much slower than the rate of isomerization since less than 10% of the succinonitrile was converted to acetophenone after 24 hr. Again, either a significant portion of the isomerization takes place within a solvent cage¹⁶ or oxygen is a poor scavenger of methylphenylsuccinonitrile radicals. The latter explanation is consistent

former is thermodynamically controlled whereas the latter should not be. See G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowain, R. C. Counsell, V. Vogt, and C. Dalton, *ibid.*, **86**, 3197 (1964).

(16) Experiments are in progress to determine the portion of the isomerization which occurs within the solvent cage. Preliminary results from crossover experiments suggest that the cage effects may be quite small.

the results of Hartzler who found that the dimer of dicyanobenzyl radicals was not apparently inhibited by the presence of oxygen.¹⁷ Although not proved, the peroxide VI seems to be a likely intermediate which would be produced by the reaction of I with III. Thermal decomposition of VI presumably would produce acetophenone.¹⁸

Attempts to observe the methylphenylacetone nitrile by electron spin resonance spectroscopy were fruitless. Even at temperatures up to 300° under conditions where radicals have been observed in similar systems,¹⁸ no esr signal was detected. A calculation of the equilibrium constant at 300° for dissociation of dicyanobenzyl radicals indicates the radical concentration would be about 10^{-6} M, a value approaching the lower limits of detection.

The isomerization of the 2,3-dimethyl-2,3-diphenylsuccinonitriles is conveniently followed by nmr spectroscopy. The methyl protons of the two isomers show two distinct resonance peaks which are separated by 8 ppm. The methyl absorption of the *meso* isomer occurs at δ 1.80 while that for the *dl* form is slightly downfield, at δ 2.08.

Attempts to study the rates of the *meso*-*dl* interconversion were hampered by the low solubility of the compounds in *o*-dichlorobenzene. Attempts to obtain the activation parameters for the reaction were unsuccessful.

The *meso* and *dl* ratios were determined periodically until equilibrium was found to be established. The equilibrium constants were approached from both sides in each case. The data are tabulated in Table II and treating the isomerization as a first-order reversible reaction, rate constants were obtained at each temperature for the isomerization of one isomer into the other (see Table I).

Plots of the logarithms of the rate constants against the reciprocal of the absolute temperature gave good straight lines (Figure 1). Since the equilibrium constants do not vary significantly with changes in temperature, the activation parameters must therefore be the same for carbon-carbon bond scission in both isomers. The enthalpy of activation, ΔH^\ddagger , was calculated to be 42.4 ± 1.0 kcal/mole and the entropy of activation was found to be about 17 eu.

As much as the original structural assignments made for the isomeric 2,3-dimethyl-2,3-diphenylsuccinonitriles were based solely on the melting points of the two isomers, that of the *meso* being higher than that of the *dl*,¹² further characterization was necessary if any conclusions could be drawn regarding relative stabilities. Both isomers were hydrolyzed, separately, to their respective diacids; the *meso* diacid melted at 224°, while the *dl* diacid melted at 195–196° (lit.¹⁹ 196–197°). Thus the structural assignments were confirmed since the *dl* diacid had previously been prepared in an optically active state.

Additionally, both diacids upon heating to their melting points yield anhydrides, the *meso* giving the anhydride VII (mp 106–107°) and the *dl* affording the anhydride VIII (mp 159–160°). The nmr spectra of the anhydrides further support the structural assignments since the methyl proton resonance in the

anhydride VII (mp 106–107°) and the *dl* affording the anhydride VIII (mp 159–160°). The nmr spectra of the anhydrides further support the structural assignments since the methyl proton resonance in the

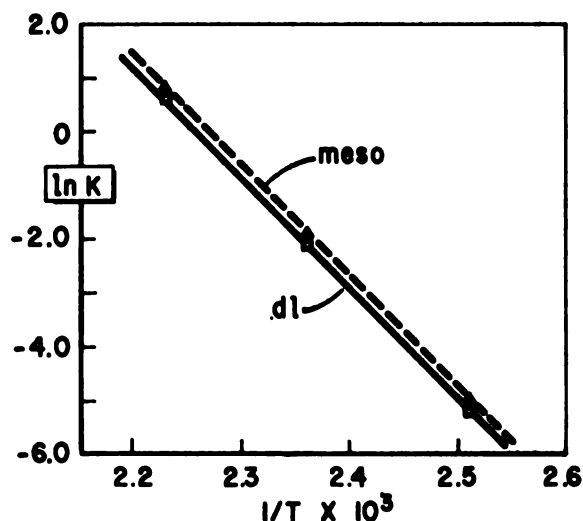
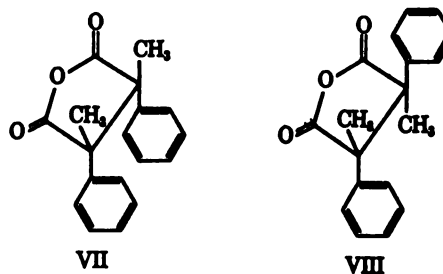


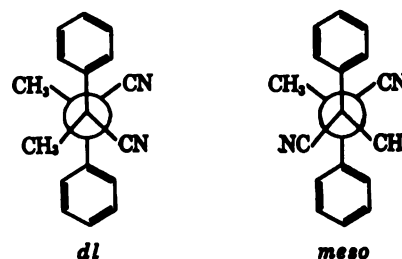
Figure 1. Plot of $\ln k_{\text{meso}}$ and $\ln k_{\text{dl}}$ vs. the reciprocal of the absolute temperature.

trans (δ 1.35) was found to be 0.47 ppm upfield from that for the *cis* isomer (δ 1.82, CDCl_3). This difference in chemical shift is in accordance with that predicted by the shielding effect of the adjacent phenyl groups.²⁰



Discussion

In assessing the relative stability of *meso* and *dl* diastereomers as well as that of the related *erythro* and *threo* isomers, qualitative arguments based primarily on steric factors (nonbonded repulsive interactions) have been invoked to explain or predict the free energy differences. In nonpolar compounds where there are no strong attractive interactions (such as the hydrogen bonding present in vicinal diols) and therefore where all of the nonbonding interactions between neighboring substituents are essentially of a repulsive nature, the *meso* isomers have been claimed to be more stable than their *dl* counterparts.^{3,4} Inspection of Newman projections will show how similar reasoning can be applied to the *meso*- and *dl*-2,3-dimethyl-2,3-diphenylsuccinonitriles.



I. D. Hartzler, *J. Org. Chem.*, **31**, 2654 (1966).

A similar peroxide has been proposed to intervene in the reaction of I with 1,2-dimethoxy-1,1,2,2-tetraphenylethane to afford benzo- and methyl benzoate. See G. E. Hartzell, C. J. Bredeweg, and J. D. Hartzler, *J. Org. Chem.*, **30**, 3119 (1965).

J. McKinzie and A. Ritchie, *Ber.*, **71B**, 643 (1938).

(20) D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind. (London)*, 1205 (1958).

In the 2,3-dimethyl-2,3-diphenylsuccinonitriles, A values²¹ can be used as a measure of the relative steric bulk of each substituent and indicate the order as being phenyl > methyl > cyano.^{21,22} If the two isomers are considered in their most preferred conformations, where the phenyl groups are *anti* to one another, then the *gauche* nonbonded interactions can be expressed as follows

gauche interactions_{*dl*} =



gauche interactions_{*meso*} =



The difference in nonbonded interactions between the two forms is then

Δ *gauche* interactions_{*dl-meso*} =

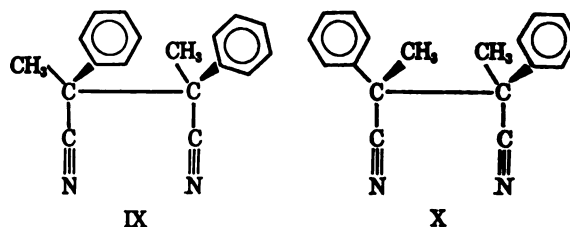


Since the crossed steric interactions between two substituents of unequal size are less than the sum of the interactions between substituents of like size (provided the interactions are purely repulsive in nature), the *meso* isomer would possess less pronounced steric factors and should be adjudged the more stable.⁴ A more quantitative treatment of these interactions can be performed by assigning values to the *gauche* interactions which are expressed in eq 3. The *gauche* CH_3/CH_3 (0.85 kcal/mole) and CH_3/CN (0.10 kcal/mole) interactions can be ascertained from the conformational energy difference between the axial and equatorial substituent on a cyclohexane ring.²³ The value of a *gauche* CN/CN interaction is probably less than the comparable CH_3/CN interaction, *i.e.*, less than 0.1 kcal/mole. Insertion of these values in eq 3 indicates that the maximum difference in steric interactions between the *dl* and *meso* forms is then about 0.65 kcal/mole. This undoubtedly is a maximum value since we assumed the two isomers to be in their most preferred conformation. Inasmuch as the other possible conformations are also populated, but probably to a lesser extent,²⁵ the actual difference in steric interactions is probably less than the calculated value. In considering the other extreme case where there is completely free rotation, and all the conformations are populated to the same extent, one predicts that the steric interactions are the same in both isomers. In view of these extremes, the actual energy difference due to steric repul-

sions must be between 0.65 and 0 kcal/mole. Additionally, since the values for the *gauche* interactions were obtained from relatively rigid cyclohexane systems, the extension of these quantities to mobile, acyclic systems might introduce considerable error. Consequently, only the direction and not the magnitude of these effects have significance.

Recently it has been pointed out that in considering entropy differences between *meso* and *dl* forms, the *meso* isomer must be compared with the *dl* pair and not simply with one of the active isomers.²⁶ Since the *d* and *l* isomers are distinctly different species, the entropy change which results from mixing the two forms is $R \ln 2$ and the free energy of the *dl* form is lowered with respect to the *meso* isomer by $RT \ln 2$ due to the entropy of mixing. However, since the *dl* isomer (symmetry number of two) possesses a higher degree of symmetry than the *meso* isomer (symmetry number of unity), reduction of the rotational degrees of freedom in the *dl* form increases its free energy by $RT \ln 2$, thereby offsetting the entropy of mixing. Consequently, the *meso* and *dl* isomers are essentially equivalent entropically, and the relative isomer stabilities are enthalpy controlled.²⁷

The foregoing discussion of *gauche* steric interactions (enthalpy differences) in the two isomers predicts the *meso* form should be the more stable and is contradictory to the experimental data. A possible explanation of this discrepancy can be found if one assumes that some of the nonbonded interactions are attractive rather than repulsive. For example, if *gauche* CN/CN interactions give rise predominantly to attractive forces, then substitution of a sufficiently negative value for the *gauche* CN/CN term in eq 3 could more than offset the steric interactions which favor the *meso* isomer.²⁸ If this were the case, the sum of the nonbonded interactions would be represented by a negative value and the *dl* isomer would be adjudged the more stable form. Qualitatively, this result can also be ascertained from an inspection of the conformation of each isomer where attractive interactions between neighboring cyano groups might be most favorable (IX and X). The steric requirements imposed by the methyl and phenyl groups will obviously be more severe in conformation IX for the *meso* isomer than the comparable conformation for the *dl* form (X) due to the eclipsed or partially eclipsed phenyl groups.



Similar explanations involving nonbonded attractive forces, ascribed by some authors to London dispersion forces,²⁹ have been advanced to rationalize the predominance of the *cis* isomers resulting from the equil-

(21) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(22) B. Rickborn and F. R. Jensen, *J. Org. Chem.*, **27**, 4606 (1962).

(23) One-half of the conformational energy difference between axial and equatorial forms of a methyl and a cyano substituent on a cyclohexane ring provides a good estimate of a *gauche* methyl/methyl and methyl/cyano interaction.¹⁴ Since the conformational free energy difference between an axial and equatorial methyl group is 1.7 kcal/mole and that for cyano is 0.2 kcal/mole, then a *gauche* methyl/methyl interaction is about 0.85 kcal/mole and a *gauche* methyl/cyano is about 0.1 kcal/mole.²³

(24) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 42-44.

(25) Nmr studies have shown that the *meso*- and *dl*-2,3-diphenylbutanes, -2,3-diacetoxybutanes, and -2,3-dibromobutanes reside in their most preferred conformation less than 70% of the time at room temperature, thus at higher temperatures the most preferred conformations would be occupied to even a lesser extent. See A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, **84**, 743 (1962); F. A. L. Anet, *ibid.*, **84**, 747 (1962).

(26) Reference 24, p 25.

(27) The entropy contribution from the differences in symmetry has been pointed out by a referee, and this offsetting term invalidates an earlier explanation¹ of the greater stability of the *dl* isomer.

(28) The literature indicates that *gauche* CH_3/CH_3 and CH_3/CN interactions are both repulsive terms.^{21,22}

(29) H. A. Stuart, *Physik. Z.*, **32**, 793 (1931).

of a variety of halogenated olefins including 1-propene,³⁰ 1,2-dichloroethylene,³¹ and 1-butadiene.³² London forces have also been to explain the anomalous conformational of some halogenated ethanes.³³

istence of attractive nonbonded interactions the participation of the nitrile group is not mented. The predominance of the *cis* is- equilibration of crotononitrile and 3-chloro- ile, however, may be indicative of this type of n.³⁰ Similarly, the greater stability of the ver the *trans* conformation in 1,2-dicyano- the preponderance of *cis*-1,2,3-tricyanocyc- le in the base-catalyzed decarboxylation r-1,2,3-tricarboethoxy-1,2,3-tricyanocyclo-pro- und the predominance of *cis*-1,2-dicyano- ne in the thermal dimerization of acrylonitrile could be explained by London dispersion tween the vicinal cyano groups. Further ill be necessary to establish the substance appositions.

discussed earlier, the free energy differences *meso* and *dl* isomers is a function of the non- interactions between the various substituents. me, it is not yet possible to assess the effect irection or magnitude of a given substituent lative stability of such diastereomers. Only i continuing investigation of a related series nd *dl* isomers will this information be forth- Such a study is in progress.

ntal Section²⁷

rmal Isomerization of *meso*- and *dl*-2,3-Dimethyl-2,3- cionitrile. The *meso* and *dl* isomers of 2,3-dimethyl- succinonitrile were prepared according to the procedure h and Sosnovsky by the Cu(II)-catalyzed oxidative methylphenylsuccinonitrile.¹¹ The pure isomers were y fractional crystallization from methanol. The *meso* ed at 224° and the *dl* at 146–147°. The nmr spectra of r revealed no extraneous peaks (*i.e.*, none of the *meso* bserved in the spectrum of the *dl* isomer, etc.). The r exhibits a methyl resonance peak at δ 1.80 and that mer came at δ 2.08 (CDCl₃).

of each isomer (0.5 M) were prepared in *o*-dichloro- 80°. The *o*-dichlorobenzene solutions were placed in hich were sealed under nitrogen and immersed in a mperature bath at the indicated temperatures. The es were removed periodically and their nmr spectra 80°. The relative areas of the methyl resonance peaks ner were determined by integration. Good reproduci- obtained in all cases ($\pm 2\%$). The data in Table II ed for the thermal isomerizations at 125.0, 150.0, and .

um was approached from both directions at each tem- d the same equilibrium constants were obtained within The rate constants shown in Table I were obtained from ng data by simulating the simple first-order reaction an analog computer and then finding the best fit of the al points.

erization was also studied as 0.5 N solutions in three

. Crump, *J. Org. Chem.*, **28**, 953 (1963).

. Ditzer and J. L. Hollenberg, *J. Am. Chem. Soc.*, **76**, 1493

i. Viehe, *Angew. Chem.*, **75**, 793 (1963).

rence 24, pp 15–17, and references therein.

. W. LeFevre, G. L. D. Ritchie, and P. J. Stiles, *Chem.* **46** (1966).

i. Griffin and L. I. Peterson, *J. Org. Chem.*, **28**, 3219 (1963). sche Anilin- and Soda-Fabrik AG., Netherlands Appl. une 20, 1966); *Chem. Abstr.*, **65**, 18507 (1966).

ear magnetic resonance spectra were obtained on a Varian 1-60 instrument. Melting points were taken on a Thomas lary melting point apparatus and are uncorrected.

Table II

125.0°		15.0°		175.0°	
Time, hr	% <i>meso</i>	Time, hr	% <i>meso</i>	Time, min	% <i>meso</i>
0.0	100.0	0.0	100.0	0.0	100.0
8.0	93.5	1.0	83.7	10.0	73.0
16.0	90.0	2.0	78.0	20.0	60.2
32.0	81.5	3.0	69.9	30.0	52.6
56.0	71.8	4.0	63.9	40.0	48.6
104.0	62.0	5.0	61.5	60.0	46.5
154.0	53.5	7.0	54.0	100.0	45.0
208.0	49.5	9.2	50.0		
300.0	44.7	11.0	48.8		
		15.5	46.0		

other solvents at $150 \pm 2^\circ$ for 3 hr. The following results were obtained (solvent, *dl/meso* ratio): tetrachloroethylene, 1.23; benzo- nitrile, 1.27; and nitrobenzene, 1.22.

Photoisomerization of *meso*-2,3-Dimethyl-2,3-diphenylsuccinonitrile. A benzene solution (100 ml) containing 0.20 g of *meso*-2,3-dimethyl-2,3-diphenylsuccinonitrile was irradiated in a quartz vessel for 17 hr at 40° with 2537-Å light from low-pressure mercury lamps (Rayonet photochemical reactor, Southern New England Ultraviolet Co.). The solvent was removed under vacuum at 30°. The nmr spectrum of the resulting solid revealed that isomerization had occurred and the *dl/meso* ratio was 0.60. Under the reaction conditions in the absence of light no isomerization takes place. The photoisomerization of the *dl*-2,3-methyl-2,3-diphenylsuccinonitrile to *meso*-*dl* isomer mixture has been effect in a similar manner.

Reduction of *meso*-2,3-Dimethyl-2,3-diphenylsuccinonitrile in Thiophenol. A thiophenol solution 0.5 M in *meso*-2,3-dimethyl-2,3-diphenylsuccinonitrile was prepared in an nmr tube. The tube was sealed and placed in a bath at 170–180°. The progress of the reaction was followed by nmr spectroscopy. After 1 hr 90% of the succinonitrile had been converted to methylphenylacetoneitrile and the *dl/meso* ratio of the remaining 2,3-dimethyl-2,3-diphenylsuccinonitrile was 0.8, indicating that equilibrium had not been reached. After 2 hr, all of the succinonitrile had been reduced to methylphenylacetoneitrile. The presence of the acetoneitrile was established by peak enhancement of its characteristic nmr spectrum and comparison of the glpc retention time with authentic methylphenylacetoneitrile.

Isomerization of *meso*-2,3-Dimethyl-2,3-diphenylsuccinonitrile in the Presence of Oxygen. *o*-Dichlorobenzene (1 ml) containing 25 mg of *meso*-2,3-dimethyl-2,3-diphenylsuccinonitrile was heated at 170° under 100 psi of oxygen for 24 hr. After this period of time, the *dl/meso* ratio of the remaining 2,3-dimethyl-2,3-diphenylsuccinonitrile was about 1.2 and a small amount of acetophenone (~5%) was detected by its glpc retention time and its methyl resonance peak in the nmr spectrum of the crude product.

Hydrolysis of the *meso*- and *dl*-2,3-Dimethyl-2,3-diphenylsuccinonitriles. Each dinitrile (0.50 g) was suspended in a solution of 4.0 ml of concentrated sulfuric acid and 4.0 ml of acetic acid in 4.0 ml of water. The resulting suspensions were heated at reflux for 24 hr. The reaction mixtures then were poured into 25 ml of ice water, and the precipitates were collected on filter pads. These solids were dissolved in 20 ml of a 2.5% aqueous solution of potassium hydroxide by heating on a steam bath. The diacids were precipitated upon acidification with dilute hydrochloric acid and recrystallized from benzene. The *meso* dinitrile gave a dicarboxylic acid which melted at 224–225° and the *dl* isomer afforded a diacid melting at 197–198°. The melting point of the *dl* isomer corresponds well with that reported previously (mp 196–197°) for the racemic pair.¹⁹

Dehydration of the 2,3-Dimethyl-2,3-diphenylsuccinic Acids. Both the *meso*- and *dl*-2,3-dimethyl-2,3-diphenylsuccinic acids lose water upon melting and form an anhydride.¹⁹ The *meso* isomer affords *cis*-2,3-dimethyl-2,3-diphenylsuccinic anhydride, mp 106–107°, and the *dl* isomer yields the related *trans* anhydride, mp 159–160°. The nmr spectrum of the *cis*-anhydride revealed the methyl resonance peak at δ 1.82 and the *trans* form exhibits its methyl peak at δ 1.35 (CDCl₃). The infrared spectra of both compounds exhibited strong absorption bands at 1870 and 1798 cm⁻¹ characteristic of anhydrides.

Acknowledgment. The author wishes to thank Professor M. Stiles, Dr. J. C. Little, and Dr. A. E. Young for helpful and stimulating discussions of this work.

The Effect of Pressure on Rate and Equilibrium in Nucleophilic Addition to Mesityl Oxide

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Contribution from the Department of Chemistry, New Mexico Institute of Mining and Technology, Socorro, New Mexico. Received February 6, 1967

Abstract: The rates of addition of water, methanol, ammonia, and thiophenol to mesityl oxide have been determined at various pressures up to 1360 atm, and the activation volumes derived therefrom. It is inferred that the transition state for acid-catalyzed hydration involves two water molecules. The addition-elimination equilibrium involving methanol has been approached from both sides, and the difference between forward and reverse activation volumes agrees with the measured volume of reaction. The acid-catalyzed addition of methanol appears to be mechanistically similar to that of water. The activation volume for addition of ammonia decreased by 8 ml/mole on change of solvent from water to methanol, and a zwitterionic transition state is postulated. The activation volume for thiophenoxide ion is surprisingly large and nearly independent of solvent composition. It is inferred that the carbon-sulfur bond is nearly complete in the transition state.

Although the mechanistic details of reactions involving addition to carbon-carbon double bonds have been intensively studied for several decades, there still are important questions unanswered, and recently some conclusions which once seemed firmly based have been thrown into doubt. It was long thought that the rate-determining step of acid-catalyzed hydration of simple olefins did not involve participation by water because the rate is approximately proportional to Hammett's acidity function, h_0 ; but Baliga and Whalley¹ have shown that the activation volume is substantially negative, and the opposite conclusion now seems inescapable. The Zucker-Hammett hypothesis has been challenged on more general grounds by Bunnett² who proposes another method for demonstrating the kinetic participation of water in aqueous reactions.

In contrast to the behavior of simple olefins it has been reported that α,β -unsaturated carbonyl compounds³ have rates proportional to (H_3O^+) rather than h_0 . It appeared to us that this case too might profitably be studied by determination of activation volumes, and to this end we have selected mesityl oxide as substrate. This well-behaved substance gives clean acid-catalyzed addition of water and alcohols as well as uncatalyzed addition of neutral or negatively charged nucleophiles. Furthermore, the position of equilibrium in the alcohol reaction permits rate measurement from either side. The possibility of using a single substrate for such a variety of reactions ought to justify a rather stringent interpretation of variations in activation volume.

The use of activation volumes in the study of reaction mechanisms has been amply reviewed,⁴ and we will only briefly state the empirically validated principles. Reactions which on other grounds are thought to have a bimolecular rate-determining step involving no net change in the number of ionic charges are char-

acterized by activation volumes in the range -5 to $ml/mole$.⁵ Contrariwise, the simple bond-breaking processes have positive activation volumes of comparable magnitude.⁶ If the rate-determining step is any preceding step back to the "starting material" (as defined by the rate law) involves ionization or neutralization of charges, the change in the electrostatic energy of solvent contributes a component of $25-45$ $ml/mole$ per pair. The smaller value is for water, and the larger for organic solvents of low polarity. There is some evidence that ionization or deionization in the transition state can be detected by testing the dependence of activation volume on solvent polarity.⁷

Results and Discussion

Acid-Catalyzed Addition of Water. The kinetic data for this reaction are listed in Table I. By dilatometry it was found that the over-all change in volume of the reaction system is -9 $ml/mole$, and the difference in molar volume of product and reactants in pure water form is also -9 ml . Both mesityl oxide and diacetyl alcohol have considerable volumes of mixing with water (-7.5 $ml/mole$ each) due to their influence on the structure of water,⁸ but this effect could not be expected to vary during the activation process. We have taken the precaution of proving that it shows no over-all change. The volume of activation was determined to be -9 $ml/mole$. Since this figure considerably exceeds the final volume of hydration, we believe that the transition state has partial bonds to a water molecule and a hydronium ion, and that proton transfer is concerted with the formation of the new carbon-oxygen bond. The results are strikingly similar to those obtained with the hydrolysis of two square-planar metal complexes⁹ which had already been thought to coordinate with two water molecules in or prior to the rate-determining step.

Bell, Preston, and Whitney³ investigated the kinetics of mesityl oxide hydration with various acid catalysts up to concentrations of 3 M and their data have

- (1) B. T. Baliga and E. Whalley, *Can. J. Chem.*, **42**, 1019 (1964).
- (2) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961).
- (3) R. P. Bell, J. Preston, and R. B. Whitney, *J. Chem. Soc.*, 1166 (1962).
- (4) (a) S. D. Hamann, "High Pressure Physics and Chemistry," Vol. II, Academic Press Inc., New York, N. Y., 1963, pp 163-205; (b) S. D. Hamann, "Physico-Chemical Effects of Pressure," Butterworth and Co. (Publishers), Ltd., London, 1957; (c) S. D. Hamann, *Ann. Rev. Phys. Chem.*, **15**, 349 (1964); (d) E. Whalley, *Advan. Phys. Org. Chem.*, **2**, 93 (1964).

- (5) J. Koskikallio and E. Whalley, *Can. J. Chem.*, **37**, 783 (1959).
- (6) K. R. Brower, Bruce Gay, and T. L. Konkol, *J. Am. Chem. Soc.*, **88**, 1681 (1966).
- (7) K. R. Brower, *ibid.*, **85**, 1401 (1963).
- (8) G. Némethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3401 (1962).
- (9) H. E. Brower, L. Hathaway, and K. R. Brower, *Inorg. Chem.*, **5**, 1899 (1966).

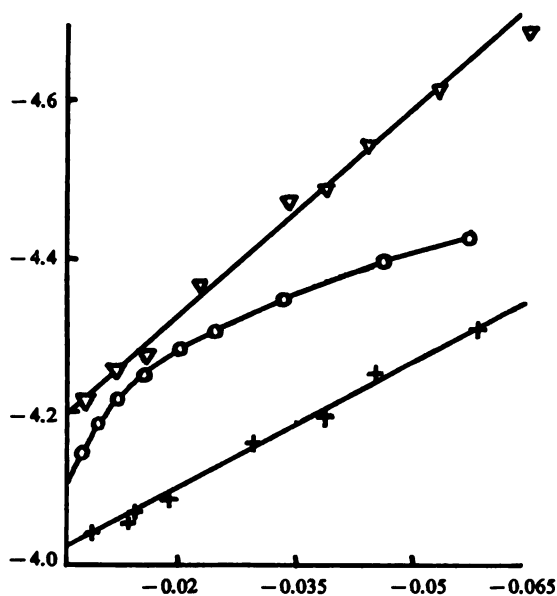


Figure 1. Determination of Bunnett's ω parameter for the hydration of mesityl oxide. Plot of $(\log k - H_0)$ vs. $\log a_{H_2O}$: ∇ , $HClO_4$; \circ , HCl ; $+$, H_2SO_4 .

used to calculate Bunnett's parameters,² ω and ω^* . The former is illustrated in Figure 1. Straight lines were obtained for H_2SO_4 ($\omega = 5.3$) and $HClO_4$ (ω

Table I. Summary of Kinetic Data

P , atm	$k \times 10^4$	$\ln k_p/k_1$
Mesityl oxide (0.140 M) and HCl (0.490 M) in H_2O at 30°		
1	51 sec ⁻¹	0
272	59	0.146
680	79	0.438
1088	95	0.622
1360	114	0.804
Mesityl oxide (0.105 M) and NH_3 (0.365 M) in H_2O at 30°		
1	1321./mole sec	0
272	155	0.161
612	184	0.332
1088	247	0.627
1360	276	0.737
Mesityl oxide (0.070 M) and NH_3 (0.575 M) in $MeOH$ at 30°		
1	251./mole sec	0
272	32	0.247
612	44	0.566
1088	64	0.940
1360	85	1.224
Mesityl oxide (0.100 M), $PhSH$ (0.125 M), and $NaOMe$ (0.025 M) in $MeOH$ at 30°		
1	58 sec ⁻¹	0
272	72	0.216
612	96	0.504
1088	140	0.881
1360	165	1.045
Mesityl oxide (0.100 M), $PhSH$ (0.125 M), and $NaOH$ (0.025 M) in $EtOH-H_2O$ (55:45 by vol.) at 30°		
1	60 sec ⁻¹	0
1088	137	0.826

= 8.3), but for HCl the curvature is pronounced. In such cases it is recommended to evaluate ω^* for which HCl gives a value of -3.0 as shown in Figure 2.

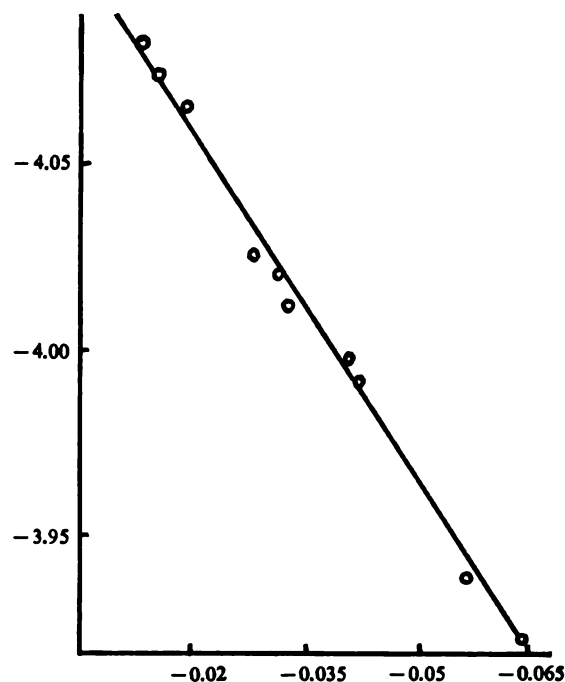


Figure 2. Determination of Bunnett's ω^* parameter for the hydration of mesityl oxide. Plot of $[\log k - \log (HCl)]$ against $\log a_{H_2O}$.

Bunnett's table correlating ω and ω^* values with reaction mechanism is shown in Table II. It appears that the hydration of mesityl oxide proceeds by a con-

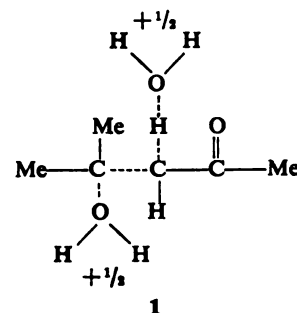
Table II. Mechanistic Interpretation of ω and ω^* Values

ω	ω^*	Function of water in the rate-determining step
-2.5-0.0		Is not involved
1.2-3.3	< -2	Acts as a nucleophile
> 3.3	< -2	Acts as a proton-transfer agent

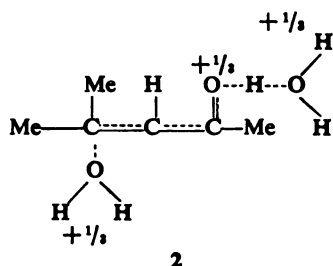
certed proton transfer and nucleophilic addition. This is in complete agreement with a transition state consisting of the aggregate (mesityl oxide, H^+ , $2HOH$) as deduced from the activation volume and the over-all volume of reaction.

Three conceivable transition states are illustrated below.

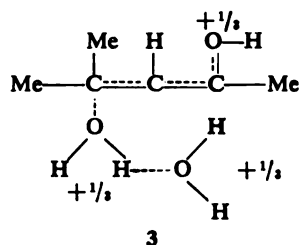
(i) Rate-determining proton transfer to the α -carbon



(ii) Rate-determining proton transfer to the carbonyl oxygen



(iii) Rate-determining proton transfer at the oxygen of the attacking nucleophile, the substrate having been previously protonated



It is not possible to discriminate among these mechanisms by using either activation volumes or Bunnett's parameters. Bell, Preston, and Whitney³ proposed transition state 1 for this reaction with a rate-determining step the same as for enol-keto transformation. However, a termolecular mechanism with a transition state similar to 2 has been widely accepted for the hydration of acetaldehyde.¹⁰

Bunnett has suggested that the number of water molecules involved, that is, molecules of water able to affect reaction rates, can be correlated with ω values, one ω unit corresponding to one molecule of water. For this reaction ω values of 5 and 8 imply that 5–8 water molecules are involved, but the activation volume can be accounted for by only two molecules provided the interaction is strong. It is difficult to think of an operational test for the diffuseness of solvent participation in view of the fact that the water molecule oscillators are coupled by H bonding.

Acid-Catalyzed Addition of Methanol. The reversibility of the addition of methanol to mesityl oxide allows measurement of the effect of pressure on the equilibrium constant as well as the forward and reverse rates. The data are given in Table III. By plotting the logarithm of the equilibrium constant against pressure in accordance with the relation

$$RT(\partial \ln K / \partial P)_T = -\Delta V \quad (1)$$

we obtain a value of -11 ml/mole for the volume of reaction. The same value was obtained by subtracting the sum of the molar volumes of methanol and mesityl oxide from that of 4-methoxy-4-methyl-2-pentanone. By direct measurement the activation volume is -23 ml/mole for the forward reaction and -13 ml/mole for the reverse. The difference should be equal to the volume of reaction according to the principle of microscopic reversibility, and the agreement is satisfactory.

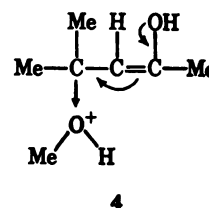
It is worthy of note that the reverse (elimination) reaction cannot be a simple unimolecular decomposition of the conjugate acid of the ether in enolic form as shown below, else the activation volume would almost certainly be positive. The values of both the forward

(10) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960).

Table III. Kinetic and Equilibrium Data for Methanol-Mesityl Oxide System

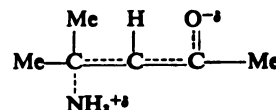
<i>P</i> , atm	<i>k</i> × 10 ³ , sec ⁻¹	<i>K</i> , <i>c</i> _{product} / <i>c</i> _{reactant}
Mesityl oxide (0.035 <i>M</i>) and H ₂ SO ₄ (0.050 <i>M</i>) at 30°		
1	26	1.49
272	34	1.69
612	46	1.95
1088	67	2.42
1360	91	2.77
4-Methoxy-4-methyl-2-pentanone (0.028 <i>M</i>) and H ₂ SO ₄ (0.050 <i>M</i>) at 30°		
1	16	0.667
1088	28	0.416
	<i>k</i> _f / <i>k</i> _r	<i>K</i> , forward
1	1.62	1.49
1088	2.39	2.42

and reverse activation volumes point to a transition state containing two methoxy moieties and analogous in structure to 1, 2, or 3.



Addition of Ammonia. The kinetic data for this reaction are given in Table I. The volumes of activation were -14 ml/mole in water and -22 ml/mole in methanol. The volume of reaction, measured dilatometrically, was -9 ml/mole.

The variation of activation volume with solvent polarity indicates a polar transition state.



A dissection of the activation volume into separate components for solvent and reactant molecules may be attempted with the knowledge that the partial molar volumes of a variety of univalent electrolytes are 18–20 ml smaller in methanol or ethanol than in water.¹¹ If the relation between volume and polarization is assumed to be linear, the charge separation is 0.42 e; and if parabolic, 0.65 e. Since the volumes of ionization of acids and bases in water are about 25 ml/mole, the solvent component for our reaction in water would amount to $25 \times \frac{8}{10} = 10$ ml, leaving 4 ml to be accounted for by contraction of the reactants along the carbon-nitrogen bond axis. Recalling that the volume of reaction is -9 ml/mole, we may infer that the new bond of the transition state is approximately half-formed on both the geometrical and electrical scales.

Addition of Thiophenol. Thiophenoxide ion is the nucleophile for this addition, and reaction mixtures consisted of solutions of mesityl oxide, thiophenol, and sodium methoxide or hydroxide in the molar proportions 4:5:1. The kinetic data are given in Table I. The volume of activation was -20 ml/mole in methanol

(11) S. D. Hamann and S. C. Lim, *Australian J. Chem.*, 7, 329 (1954).

19 ml/mole in a mixture of ethanol-water (55:45 v/v). A change in the amount of solvent electrolyte might have been expected since a negative charge is being transferred from the thiophenoxide ion to the carbonyl oxygen and therefore becomes somewhat reduced. Since no significant change was observed, we ascribe the entire 19–20 ml to the formation of the carbon-sulfur bond. The volume of reaction observed in the dilatometer was –22 ml/mole, and it is probable that the transition state lies very close to product in the reaction coordinate. If this is so, it is understandable that the activation volume showed no change with solvent.

Experimental Section

Materials. Mesityl oxide and diacetone alcohol were prepared by the method of Vogel.¹² Mesityl oxide was distilled in the range 100–105°C (648 mm). The methyl ether of diacetone alcohol was prepared by the method of Lorette¹³ using Dowex 50 as an acidic resin catalyst. Ammonia solution in methanol was prepared by heating a concentrated solution of ammonium hydroxide over calcium oxide and into methanol. The thiophenol was Eastman White Label grade. The solvent was Van Waters and Rogers 99.8% grade, and the ethanol was U.S.P. reagent quality.

Dilatometry. The over-all volume changes were measured with a dilatometer of 17.5 ml capacity with a capillary of 1 mm. The dilatometer was weighed before and after the reaction period to ensure that volume changes were not caused by evaporative loss. The rates of mixing of mesityl oxide and diacetone alcohol were determined by measuring the densities of the pure components and the density of the mixture. Concentrations used were the same as those used in the determination of the volume of activation. Volumes of mixing are somewhat dependent on concentration.

Methods of Kinetic Measurement. Addition of water, methanol, or ammonia were followed by the disappearance of mesityl oxide as determined spectrophotometrically⁴ employing the ion peak at 243 mμ for which $\epsilon = 1.10 \times 10^4$. A Beckman DU spectrophotometer, using a hydrogen lamp as an ultraviolet source, was employed for absorbance measurements. Rate constants for the addition of water were determined from a plot of the logarithm of concentration of mesityl oxide against time. Both forward and reverse rate constants for the addition of ammonia were determined from the expressions

$$K = k_f/k_r \quad (2)$$

$$\ln(c_0 - c_\infty)/(c - c_\infty) = k_f[c_0 t/(c_0 - c_\infty)] \quad (3)$$

which is the solution of the rate equation

$$dc/dt = -k_f c - k_r(c_0 - c) \quad (4)$$

c_0 = initial concentration of mesityl oxide, c_∞ = equilibrium concentration of mesityl oxide, and c = concentration of mesityl oxide at time t . Equilibrium constants at various pressures were determined from the ratio of the percentage of mesityl oxide converted to the percentage remaining.

Second-order rate constants for the addition of ammonia were determined from the expression

$$1/(b - a) \ln [a(b - x)/b(a - x)] = kt \quad (5)$$

which is the solution of the rate equation

$$dx/dt = k(a - x)(b - x) \quad (6)$$

where x = decrease in concentration of mesityl oxide, a = initial concentration of mesityl oxide, and b = initial concentration of ammonia. Kinetic data for this addition were obtained from solutions that had reacted up to 40% completion. The reverse reaction was disregarded due to the high percentage conversion (88%) at equilibrium.

Rate constants for the addition of thiophenol were determined from a plot of the logarithm of concentration of mesityl oxide against time. The mesityl oxide concentration was obtained from the relation

$$c_{mo} = c_{mo}^0 - (c_{SH}^0 - c_{SH}) \quad (7)$$

where c_{SH}^0 is the initial titratable thiophenol (includes thiophenoxide) concentration and c_{SH} is the titratable thiophenol at time t .

Titration was done potentiometrically with a Beckman Zero-matic pH meter, using a silver electrode, against a standard silver nitrate solution. The initial mesityl oxide concentration was determined spectrophotometrically. The rate constant obtained is pseudo first order and includes the thiophenoxide concentration term which remains constant

$$d(c_{SH})/dt = kc_{mo}c_{SH} \quad (8)$$

$$= k'c_{mo} \quad (9)$$

Sampling Technique. The sampling technique was basically the same for all the addition reactions. Aliquots totalling 5 ml were pipetted into a 6-ml, narrow-necked test tube, and mercury was added so that the solution filled the test tube. The tube was then inverted into a larger test tube; the two tubes were sealed by adding more mercury, and the larger one was filled with water and placed in the pressure vessel. After a suitable reaction time, usually longer than 3 hr, a 3-ml aliquot was removed for analysis. Considerable dilution was necessary for the determination of mesityl oxide concentrations spectrophotometrically owing to its very large extinction coefficient at 243 mμ. Dilutions were adjusted so that absorbance measurements of around 0.500 were obtained.

Experimental Error. The error in the volume of activation is due almost entirely to the uncertainty in the term $\ln k_p/k_i$. From duplicate rate measurements this uncertainty is from 4 to 8% and hence activation volumes obtained are accurate within the range of ± 1.0 to ± 1.6 ml/mole. Temperatures were controlled to within 0.05°C and pressures within 7 atm. Uncertainty in the reaction time was rendered negligible by having sufficiently long reaction times, usually from 3 to 4 hr. From duplicate measurements the uncertainty in the over-all volume changes is about 5%.

Calculation of Activation Volumes. The logarithm of the ratio of the rate constant at pressure to the rate constant at 1 atm (k_p/k_i) was plotted against pressure, and the best straight line was drawn through the origin and the other points. The slope was used to evaluate the activation volume according to the equation

$$RT(\partial \ln k/\partial P)_T = -\Delta V^\ddagger \quad (10)$$

None of the plots had any obvious curvature, and this seems surprising in only one case, the addition of ammonia with methanol as solvent. Ion-producing reactions in organic solvents often show curvature at pressures as low as 1000 atm.⁴

Acknowledgment. The authors are indebted to the National Science Foundation which supported this work through Grant GP-1718.

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J. B. Lorette, *J. Org. Chem.*, **23**, 937 (1958).

Mechanisms of Ester Hydrolysis in Aqueous Sulfuric Acids¹Keith Yates and Robert A. McClelland²*Contribution from the Department of Chemistry, University of Toronto, Toronto 5, Ontario, Canada. Received November 3, 1966*

Abstract: The rates of acid-catalyzed hydrolysis of methyl, *n*-propyl, isopropyl, *sec*-butyl, benzyl, phenyl, *p*-nitrophenyl, and *p*-chlorophenyl acetates have been investigated over a wide range of acidity (10–90% aqueous H₂SO₄) by means of spectrophotometric methods. First-order kinetics were obtained in every case, and the rate constants show one of three types of acid dependence, varying with ester structure: (i) a rate maximum at intermediate acidities followed by very slow hydrolysis in very concentrated acids; (ii) a rate maximum at intermediate acidities followed by a sharp increase in rate in very concentrated acids; and (iii) a continuous increase in hydrolysis rate with increasing acid concentration, becoming very rapid even at moderate acidities. These different rate-acidity dependences have been treated uniformly as a function of H_0 and the water activity to yield reaction parameters which are explicable in terms of a change in mechanism at some intermediate acidity for each ester, either from A_{Ac}2 to A_{Al}1 or from A_{Ac}2 to A_{Ac}1, depending strongly on ester structure.

The kinetic response of ester hydrolysis to changes in acidity has been investigated mainly in the dilute acid region where the information to be gained about detailed mechanisms is quite limited. This is chiefly because one important reaction variable, the water concentration (or activity), remains effectively constant. More detailed mechanistic information has come from the classical O¹⁸-exchange studies of Bender³ and others. This work was also confined to the dilute acid region, and while extremely valuable, this approach does not always permit unequivocal decisions about reaction mechanisms. Although a few ester hydrolyses have been studied in more concentrated acids,^{4,5} no systematic investigation of the dependence of hydrolysis rate on acid concentration has yet been made for esters. We therefore thought it of interest to investigate the variation of hydrolysis rate for simple esters over as wide a range of acid concentrations as possible, in the hope of obtaining further detailed information about the various possible mechanisms and under what conditions they occur. Of the four mechanisms possible for acid catalysis, namely the A_{Ac}1, A_{Ac}2, A_{Al}1, and A_{Al}2 mechanisms,⁶ it is generally believed that apart from a few special cases, all ordinary esters hydrolyze by the A_{Ac}2 pathway. The few clearly recognized exceptions such as *t*-butyl esters and mesitoates which are believed to hydrolyze by the A_{Al}1 and A_{Ac}1 mechanisms, respectively,⁷ occur because of special structural factors in the ester. It is therefore of interest to investigate to what extent combinations of changes in structure, acidity, and water activity can lead to different mechanisms of hydrolysis even for ordinary esters.

Results and Discussion

The esters chosen for study were all acetates, so that the effect of varying one structural parameter at a time

could be investigated. These were the methyl, propyl, isopropyl, *sec*-butyl, benzyl, phenyl, *p*-chlorophenyl, and *p*-nitrophenyl esters. Ethyl acetate was not investigated since rate data covering the entire range of sulfuric acid concentrations have been reported for this ester. The rate of hydrolysis of each was measured at 25° in aqueous sulfuric acid solutions covering as wide a range as possible. The acid used was limited in some cases by high reaction viscosities or by sulfonation reactions in the more concentrated region. Simple first-order kinetics were obtained in every case, acid concentration being effectively constant during each run, and the pseudo-first-order rate constants obtained for all eight acetates are listed in Table I. Each rate constant is the mean of at least two, and sometimes three or four independent determinations. It can be seen from these results that several of the esters exhibit local rate maxima at intermediate acid concentrations (50–60% H₂SO₄), similar to those previously reported¹¹ for amide hydrolysis occurring at much higher acid strengths. The rate dependence on acid concentration is quite different for the various types of ester; can be seen clearly by plotting rate profiles of k_1 vs. % H₂SO₄ as shown in Figure 1. Literature values^{9,10} for the hydrolysis of acetate have been included in Figure 1 for comparison. The rate-acidity profiles obtained clearly belong to one of three types. Type i is characterized by a steady increase in rate with acid concentration, passing through a maximum at about 50–60% acid, followed by a rate decrease almost to zero by 80% acid and a final modest rate increase in the 85–100% range. Very similar behavior of this type is obtained for the three primary alkyl esters, as shown in Figure 1. Type ii behavior, shown by the secondary alkyl and benzyl esters, exhibits a rate maximum similar to type i at about 50–55% acid, but this is followed by a very sharp increase in rate well before the rate has approached zero. The acid region in which this sharp rate increase occurs depends markedly on the structure of the ester. Type iii differs from the previous two in having a

(1) Presented at the 49th Canadian Chemical Conference, June 1966, Saskatoon, Canada.

(2) Holder of a National Research Council Studentship.

(3) M. L. Bender, *J. Am. Chem. Soc.*, **75**, 5986 (1953); M. L. Bender, R. D. Ginger, and J. P. Uink, *ibid.*, **80**, 1044 (1958).

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(9) R. P. Bell, A. L. Dowding, and J. A. Noble, *J. Chem. Soc.* (1955).

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(11) J. T. Edward and S. C. R. Meacock, *ibid.*, 2000 (1957).

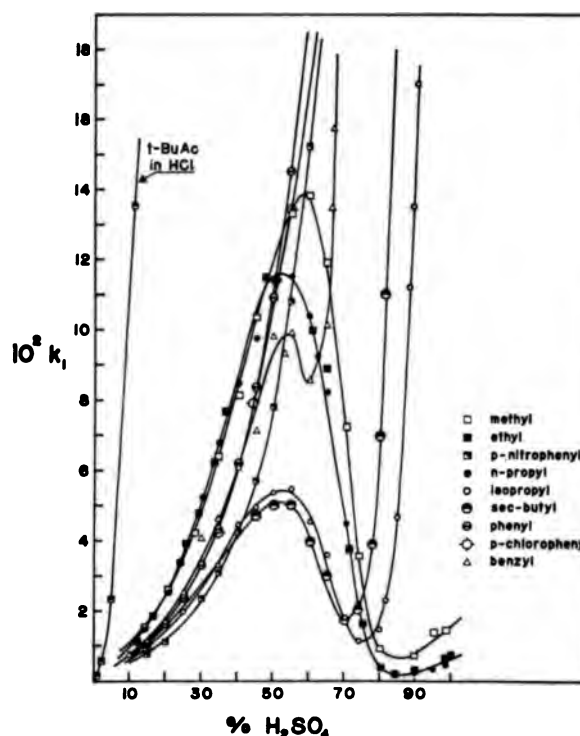
Table I. Ester Hydrolysis Rates in Sulfuric Acids at 25°

% H ₂ SO ₄	10 ³ k ₁ ^a	% H ₂ SO ₄	10 ³ k ₁	% H ₂ SO ₄	10 ³ k ₁
Methyl acetate		<i>n</i> -Propyl acetate		Isopropyl acetate	
14.1	1.50	14.1	1.47	14.1	0.890
20.7	2.61	20.7	2.52	25.3	1.99
28.3	4.22	30.2	5.23	34.8	3.30
34.8	6.41	34.8	6.78	40.4	4.21
40.4	8.14	40.4	8.47	45.4	4.96
45.4	10.4	45.4	9.76	50.2	5.38
50.2	11.4	50.2	11.4	55.2	5.48
55.2	13.3	55.2	11.5	60.4	4.54
60.4	13.8	60.4	10.4	65.2	3.60
65.2	11.9	65.2	8.23	70.4	1.80
70.4	7.25	70.4	4.48	74.1	1.14
74.1	3.83	74.1	2.20	80.0	1.48
80.0	0.931	89.7	0.205	81.7	2.30
		95.0	0.323	84.7	4.69
		98.6	0.450	88.2	11.2
				89.7	13.5
				90.8	17.0
<i>sec</i> -Butyl acetate		Benzyl acetate		Phenyl acetate	
14.1	0.964	10.1	0.740	15.1	1.08
45.4	4.72	25.3	2.52	20.1	1.62
50.2	5.00	30.2	4.04	25.3	2.38
55.2	5.02	34.8	4.61	30.2	3.30
60.4	3.96	40.4	6.08	34.8	4.34
65.2	2.99	45.4	7.13	40.4	6.20
70.4	1.71	50.2	9.81	45.4	8.36
74.1	2.03	52.8	9.30	50.2	10.9
77.7	3.90	55.2	9.91	55.2	14.5
80.0	7.00	60.4	8.52	60.4	19.2
81.7	11.00	62.5	9.24	65.2	22.6
84.7	23.6	65.2	10.1	70.4	27.2
88.2	63.2	66.8	13.7	74.1	29.3
		67.3	15.7		
		69.0	22.3		
<i>p</i> -Chlorophenyl Acetate		<i>p</i> -Nitrophenyl acetate			
15.1	0.922	15.1	0.751		
34.8	4.25	20.1	1.12		
45.4	7.90	25.3	1.52		
55.2	13.4	30.2	2.36		
65.2	22.7	34.8	3.09		
70.4	27.3	40.4	4.27		
74.1	38.2	45.4	5.71		
		50.2	7.81		
		55.2	10.8		
		60.4	15.2		
		65.2	21.3		
		70.4	36.1		
		74.1	70.5		
		75.3	93.3		
		77.7	161		
		78.5	158		
		80.0	222		

^a Pseudo-first-order rate constants in l. mole⁻¹ min⁻¹.

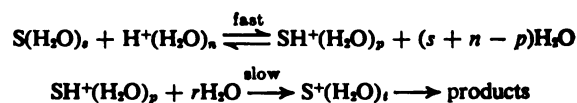
servable rate maximum, the rate increasing monotonically with acid concentration until the reaction is too rapid to follow by conventional methods even at moderate acidities. The three phenyl esters exhibit this type of behavior as shown in Figure 1, as well as *t*-butyl acetate. The reported data based on hydrolysis in HCl solutions¹² has been plotted for the *t*-butyl ester since as yet we have not been able to obtain satisfactory or reproducible results for any tertiary alkyl esters in sulfuric acid, partly because of their high reactivities and partly because of solubility problems.

It seems clear from the above diversity of behavior that all these esters cannot be reacting by the same mechanism, and further that changes in mechanism are

(12) P. Saloman, *Suomen Kemistilehti*, B32, 145 (1959).Figure 1. Rate-acidity dependence for the hydrolysis of acetates in aqueous sulfuric acid at 25° (k_1 is the pseudo-first-order rate constant in min⁻¹).

occurring for individual esters at different acidities. This raises three questions. First, can all of these rate profiles be explained in a way consistent with the types of mechanism previously mentioned? Second, can all these different rate-acidity dependences be treated quantitatively by some uniform approach, and finally can this be used to obtain any detailed information about the possible transition states?

We have shown previously¹³ that rates of organic reactions in concentrated acids can be treated quantitatively as a function of the acidity and water activity of the reaction medium by an approach which is essentially a modification of the Bunnett hydration parameter treatment.^{4,14} The modification involves basing the acidity of the reaction medium on an acidity function which is strictly appropriate to the type of substrate whose mechanism is being considered. For example, if we write the general rate scheme for ester hydrolysis in terms of fully hydrated species as



the following simple relationship between rate, acidity, and water activity can be derived from transition-state theory

$$\log k_1 + H_S = r \log a_{\text{H}_2\text{O}} + (\text{constant}) \quad (1)$$

(where k_1 is the pseudo-first-order rate constant) providing H_S is an acidity function based on the ionization of indicators which are esters of the type whose hydrolysis reaction is being considered. The approxima-

(13) K. Yates and J. B. Stevens, *Can. J. Chem.*, 43, 529 (1965); K. Yates and J. C. Riordan, *ibid.*, 43, 2328 (1965).

(14) J. F. Bunnett, *J. Am. Chem. Soc.*, 83, 4968, 4973, 4978 (1961).

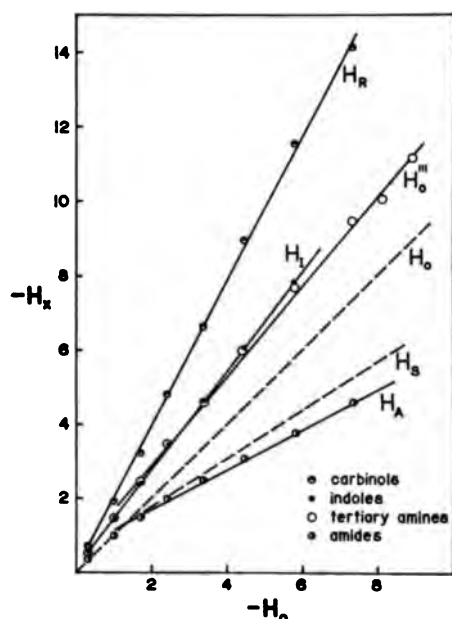


Figure 2. Approximate linear dependence of H_x acidity functions on the Hammett acidity function H_0 .

tions and assumptions involved in obtaining eq 1 are then much less drastic than in the Bunnett hydration parameter treatment^{4,14} and have been discussed previously.¹² If eq 1 is valid for ester hydrolysis, plots of $(\log k_1 + H_S)$ should be linear in $\log a_{H_2O}$ with a slope r which would give information about the involvement of water in the rate-determining step, and hence about the mechanism.

An equation like (1) has been found to give linear plots with uniform slopes for a number of amide hydrolyses¹³ for which an amide-based acidity function is available¹⁵ but as yet no ester-based acidity function such as H_S has been established. It would clearly be tedious and in some cases difficult if not impossible to establish an acidity scale strictly appropriate to each substrate type which is of interest, but fortunately this is not necessary, at least for acetate esters. Theoretically, the relationship between measured ionization ratios for esters and some suitable function H_S is given by

$$\log [SH^+]/[S] = -H_S + pK_{SH^+}$$

We have measured ionization ratios spectrophotometrically for several acetates whose rates of hydrolysis are not too fast in the acid range of interest and find that these closely obey the linear relationship

$$\log [SH^+]/[S] = -mH_0 + (\text{constant})$$

using available¹⁶ H_0 data. The slopes m are approximately 0.62 for simple acetates, which correspond closely to Lane's reported⁵ value of 0.65 for the indicator slope of ethyl acetate. Therefore, we can use available H_0 data to approximate to H_S by means of the relationship $H_S = mH_0 + (\text{constant})$ and thus modify eq 1 to give

$$\log k_1 + mH_0 = r \log a_{H_2O} + (\text{constant}) \quad (2)$$

(15) K. Yates, J. B. Stevens, and A. R. Katritzky, *Can. J. Chem.*, **42**, 1957 (1964).

(16) M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).

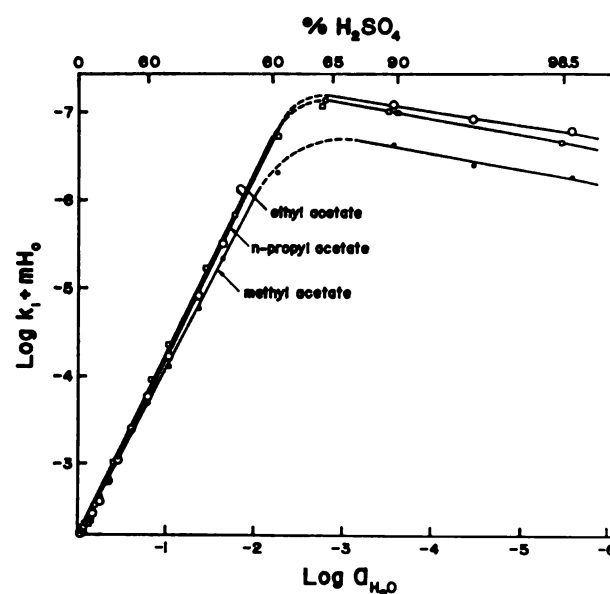


Figure 3. $\log k_1 + mH_0$ vs. $\log a_{H_2O}$ for methyl, ethyl, and n -propyl acetates.

That this is a valid approximation to H_S can be shown by plotting all available acidity functions for sulfuric acid, namely the H_R ,¹⁷ H_A ,¹⁵ H_0'' ,¹⁸ and H_1 ,¹⁹ functions, against the H_0 function. Over a very wide range of acidity (more than eight logarithmic units) each of these functions is linear in H_0 as shown in Figure 2, and, therefore, from the measured ionization behavior of the esters it is reasonable to conclude that the H_S function will vary with acid concentration approximately as shown in Figure 2.

We have tested the relationship in eq 2 using all of the rate data listed in Table I along with independently measured values of H_0 , m , and $\log a_{H_2O}$.²⁰ This is shown in Figure 3 for methyl, ethyl, and n -propyl acetates. Excellent linearity is obtained over a very wide range (0–80% acid) with an almost identical slope ($r = 2.1$) for the ethyl and n -propyl esters and a very similar slope ($r = 1.92$) for methyl acetate. In each case, a break occurs at about 80–85% acid, followed by an equally linear relationship, but with a small negative slope ($r \approx -0.02$) which extends to very high acidities²¹ or very low water activities. The same treatment of the data for the secondary alkyl acetates is shown in Figure 4. Again a linear relationship with $r = 2.1$ is found for each ester over almost as wide a range of acid (0–70%) followed by a change to a different linear dependence with negative slope in the high acidity region. However, the break occurs earlier, and the final negative slope is steeper ($r = -0.6$) for the secondary esters than for the primary. Very similar behavior to that of the

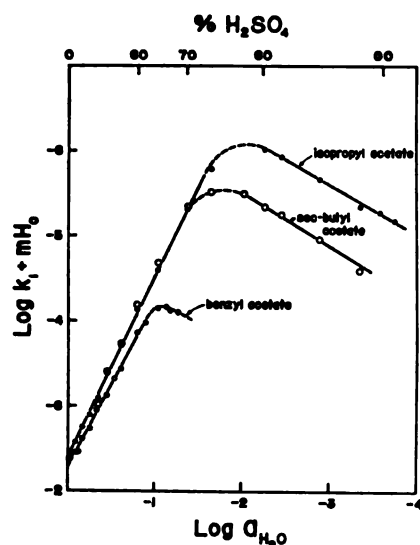
(17) N. C. Deno, J. J. Jaruszelski, and A. Schriesheim, *ibid.*, **77**, 3044 (1955).

(18) E. M. Arnett and G. W. Mach, *ibid.*, **86**, 2671 (1964).

(19) R. L. Hinman and J. Lang, *ibid.*, **86**, 3796 (1964).

(20) W. F. Giauque, E. W. Hornung, J. E. Kunzler, and T. R. Rubin, *ibid.*, **82**, 62 (1960).

(21) At the higher acidities the fraction of total ester protonated becomes significant and the function plotted against $\log a_{H_2O}$ is actually $\log (h_0^m/h_0^{m'} + K_{SH^+}^m)$. Values of $K_{SH^+}^m$ have been estimated from spectrophotometric measurements for methyl, n -propyl, and isopropyl acetates. Since these and the previously reported⁴ value for ethyl acetate show little variation with structure and the slopes r are not sensitive to small changes in $K_{SH^+}^m$ a value of $K_{SH^+}^m = -7.2$ was adopted for the other esters.



Log $k_1 + mH_0$ vs. $\log a_{H_2O}$ for isopropyl, *sec*-butyl, and benzyl acetates.

For esters is obtained for benzyl acetate, also shown in Figure 4. The initial slope is about the same ($r \approx 2.0$), but the break occurs even earlier, at 10% acid. There are insufficient data to obtain a slope for benzyl acetate, but comparison with the data for the secondary acetates shows this is very similar in its water activity dependence. The data for the three phenyl esters are plotted in Figure 5. This time the initial linear portion is 0–50% acid) but again with initial slope approx 2, followed by a fairly wide change-over 50–70%, and finally a small negative slope (0.2) for *p*-nitrophenyl acetate at higher acidities. A substituted phenyl ester cannot be studied at low acidities because of sulfonation. Thus, each ester obeys eq 2 with a large positive slope initially, then changes over a wide range of acidity. This is followed by a marked change in water activity dependence at some higher acidity and presumably a new mechanism. Since the position and type of

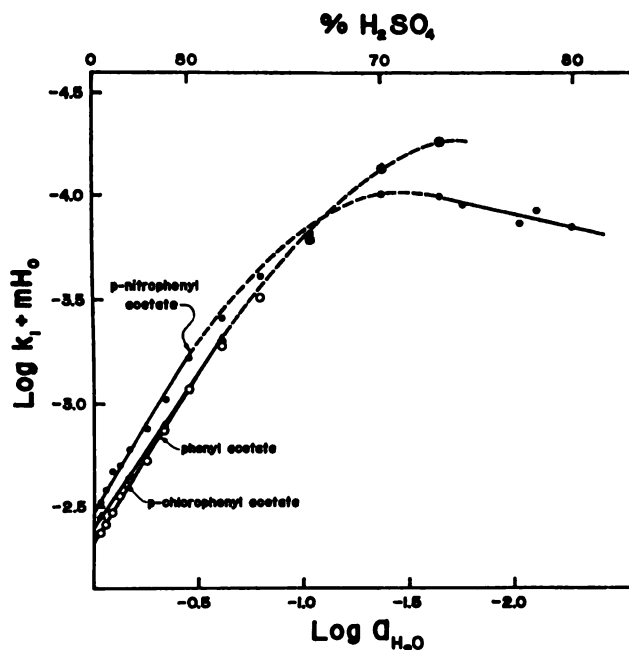


Figure 5. Log $k_1 + mH_0$ vs. $\log a_{H_2O}$ for phenyl, *p*-chlorophenyl, and *p*-nitrophenyl acetates.

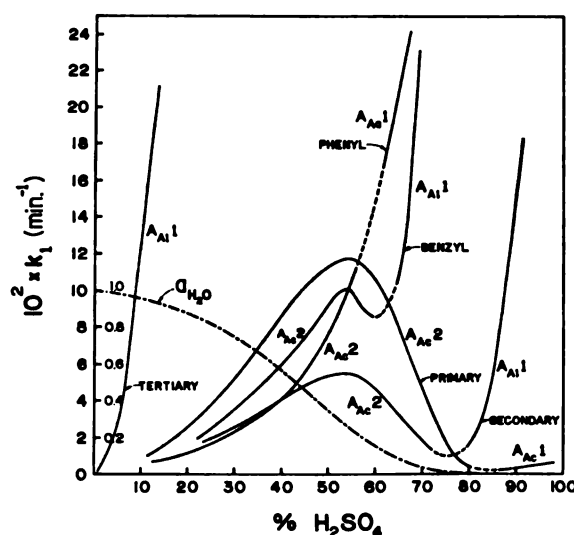


Figure 6. Schematic representation of typical rate-acidity dependences for primary, secondary, tertiary, benzyl, and phenyl acetate hydrolyses.

r Values for Ester Hydrolysis in Sulfuric Acid

Acetate	r value	Acid range, % H_2SO_4	c^a	σ_p^b	n^c	Mechanism
Alkyl	1.92	0–80	0.9997	0.026	13	$A_{Ac}2$
	-0.2	>80	3	$A_{Ac}1$
	2.10	0–80	0.9995	0.04	19	$A_{Ac}2$
	-0.18	>85	0.9999	0.004	5	$A_{Ac}1$
	2.06	0–80	0.9998	0.024	12	$A_{Ac}2$
	-0.2	>85	3	$A_{Ac}1$
	2.11	0–75	0.9994	0.037	11	$A_{Ac}2$
	-0.57	>80	0.998	0.024	6	$A_{Ac}1$
	2.18	0–70	0.9992	0.040	7	$A_{Ac}2$
	-0.66	>75	0.997	0.027	5	$A_{Ac}1$
	1.9	0–60	0.996	0.035	11	$A_{Ac}2$
	≈ -0.5	>65	3	$A_{Ac}1$
	1.6	0–50	0.998	0.016	8	$A_{Ac}2$
	<0	>70	$A_{Ac}1$
	1.6	0–50	0.996	0.055	8	$A_{Ac}2$
Benzyl	≈ -0.2	>70	0.893	0.055	5	$A_{Ac}1$
Phenyl	1.5	0–55	0.999	0.014	4	$A_{Ac}2$

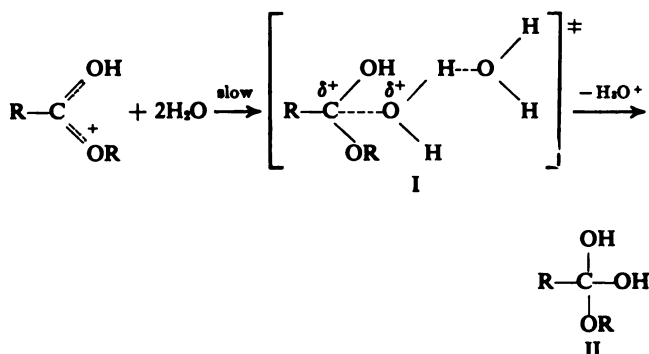
^a Squares correlation coefficient. ^b Standard deviation on $\log a_{H_2O}$ axis. ^c Number of points.

change is not the same in every case, the new mechanism operating at high acidities is different for the primary alkyl and phenyl esters from that for the secondary alkyl and benzyl esters. However, the close similarity of the water activity dependence for all esters at low acidities strongly suggests that the same mechanism is operating in all cases. However, one clear exception to this kind of behavior is shown, not surprisingly, by *t*-butyl acetate. The limited data available for HCl solutions show that the water activity dependence for this ester is decidedly negative even in the most dilute acids. The few points available for this ester give $r \approx -1.5$.

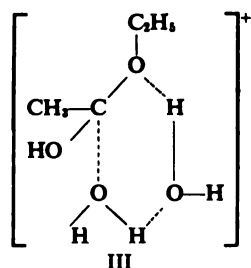
The calculated hydration parameters are summarized in Table II. The least-squares correlation coefficients and σ_p values show that the statistical fit of the data to eq 2 is surprisingly good. This indicates strongly that

the assumptions and approximations involved in the present hydration parameter treatment are reasonably valid. The concentration ranges over which linearity is obtained are also surprisingly wide, particularly since average hydration numbers for all species involved must be steadily decreasing as the water available for hydration is decreasing with acid concentration.

The values of r obtained in different acid regions can be reasonably interpreted in terms of hydrolysis mechanism as follows. Regions where $r \approx 2$ (low acidities for all esters except *t*-butyl) correspond to hydrolysis by an $A_{Ac}2$ type of mechanism in which a protonated ester molecule is attacked in the rate-determining step by two water molecules, one acting as a nucleophile and the second assisting in dispersing the positive charge developing on oxygen in the transition state I as progress is made toward the tetrahedral intermediate II



The second water molecule is then in a position to accept a proton in the formation of the intermediate II. Lane has previously suggested⁸ that two water molecules are involved in the transition state for ethyl acetate hydrolysis, but possibly in a cyclic structure III rather than that shown in I, but there appears to be no compelling reason to prefer either structure. On the basis of theoretical calculations of medium effects on



hydrolysis rates Laidler²² has concluded that for simple esters the transition state contains a molecule of ester, a hydronium ion, and a water molecule. This is consistent with either I or III in that over-all two water molecules plus a proton plus ester are involved. However, Laidler suggests a transition-state structure which differs in detail from either of the above.

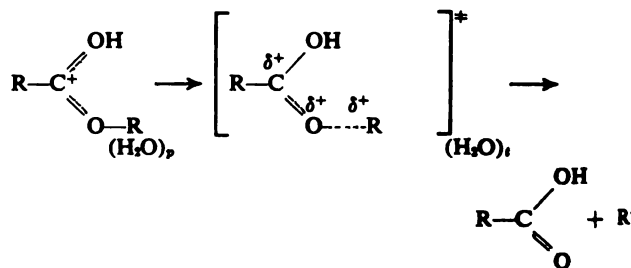
Regions where r becomes negative but is fairly close to zero (i.e., $r \approx -0.2$) correspond to changes from the $A_{Ac}2$ to the $A_{Ac}1$ mechanism, in which ester conjugate acid undergoes unimolecular fission to acylium ion and alcohol. Water is essentially not involved in the rate-determining step, hence the water activity dependence is effectively zero.²³ This behavior occurs for the

(22) K. J. Laidler and P. A. Landskroener, *Trans. Faraday Soc.*, **52**, 200 (1956).

(23) That r is not actually zero probably reflects the fact that σ_{H_2O} slopes in the higher acid regions cannot be interpreted as quanti-

primary alkyl and phenyl esters. Although the methyl, ethyl, *n*-propyl, phenyl, and *p*-nitrophenyl esters must all form the same acylium ion if they react *via* the $A_{Ac}1$ mechanism the change in water activity dependence occurs much earlier for the three phenyl esters. This is reasonable since cleavage to form acylium ion would be assisted more by the electron-withdrawing phenyl groups than by alkyl groups, so that this new mechanism can occur before the available water has been as drastically depleted as in the very high acid concentrations required before the primary alkyl acetates change mechanism. In agreement with this is the fact that at low acidities the rates of hydrolysis are in the order phenyl > *p*-chlorophenyl > *p*-nitrophenyl, but by about 75% acid (where $A_{Ac}1$ predominates) this order is exactly reversed. Although the data are limited, the log σ values for the phenyl esters give reasonably good linearity with σ in each of the acid ranges studied. Below 55% acid the ρ value is close to -0.2 in each of several acids, but above 70% acid it becomes $+0.5$. This change in both the sign and magnitude of ρ is consistent with a changeover from an $A_{Ac}2$ to $A_{Ac}1$ type of mechanism.

Regions where r is negative but significantly less than zero ($r \sim -0.5$) also correspond to a "unimolecular" fission of protonated ester, but by the $A_{Al}1$ mechanism. The strong negative water activity dependence indicates that water is actually being released in the rate-determining step, which is reasonable for decomposition of a strongly hydrated ester conjugate acid to give a weakly hydrated carbonium ion, especially since *t*-butyl acetate is known to hydrolyze $A_{Al}1$ and also has a substantial negative water activity dependence in HCl. It has already been pointed out²⁴ that r values obtained in very concentrated acids cannot be interpreted too quantitatively but it seems reasonable that $t < p$ for a reaction leading to a carbonium ion and a neutral molecule.



This behavior is shown by the isopropyl, *sec*-butyl, and benzyl esters in the higher acid regions. The regions where r becomes negative for these esters are also consistent with the expected order of stability of the carbonium ions formed in $A_{Al}1$ hydrolysis, i.e., *t*-butyl (dilute) > benzyl (65%) > *sec*-butyl (75%) > isopropyl (80%).

That the sign of r should actually change in going from an $A_{Ac}2$ to an $A_{Al}1$ or $A_{Ac}1$ mechanism is in general agreement with Whalley's²⁴ conclusions based on the pressure dependence of hydrolysis rates. For A_2 type hydrolyses, ΔV^{\ddagger} is found to be significantly negative, whereas for A_1 type hydrolyses ΔV^{\ddagger} is either zero or has a small positive value.

tatively as those for lower acidities since the approximations inherent in eq 2 will be less valid at higher acidities.

(24) E. Whalley, *Trans. Faraday Soc.*, **55**, 798 (1959); A. R. Osborn and E. Whalley, *Can. J. Chem.*, **39**, 1094 (1961).

reasons for the characteristic rate-acidity plot obtained for various types of ester can now be related in terms of structure, acidity, and water. These are shown schematically in Figure 6 for *tert*-, secondary, tertiary, benzyl, and phenyl esters. The water activity variation of the medium superimposed on the rate variation is also shown. Primary alkyl esters show an initial rate increase due to protonation of an increasing fraction of ester, until reduction of available water slows the "bimolecular" process. Eventually the rate decreases as $a_{\text{H}_2\text{O}} \rightarrow 0$, until at extremely high acidities acylium ions can be formed. Despite the fact that the mechanism does not require water, this final rate decrease is modest owing to the difficulty of forming a tertiary acylium ion. Secondary alkyl esters show an initial rate increase passing through a maximum at intermediate acidities for similar reasons. However, as $a_{\text{H}_2\text{O}} \rightarrow 0$ and $V \rightarrow 0$ a new mechanism can occur which does not require available water. As this unimolecular ion mechanism predominates the rate increases sharply since secondary carbonium ions are easier to form than acylium ions. For tertiary alkyl esters the rate rises rapidly with acidity even in the intermediate acid region due to the ease of formation of carbonium ions. The benzyl ester resembles the secondary alkyl type, except that the mechanism changes from $A_{AC}2$ to $A_{AC}1$ earlier because of the intermediate stability of benzyl carbonium ion. The phenyl ester is somewhat unusual in showing no rate maximum at intermediate acidity, after an initial rate increase resembling those for primary and secondary esters. Since the rate continues to increase sharply at very low values of $a_{\text{H}_2\text{O}}$ a unimolecular mechanism must be taking over. Since phenyl carbonium ion is extremely unlikely, the new mechanism must be $A_{AC}1$. The reason this occurs as low as 70% sulfuric acid has been discussed previously. In conclusion it seems clear that even simple esters can hydrolyze by a variety of mechanisms and that extreme acidities are not necessary before $A_{AC}1$ type mechanisms can occur. The present quantitative treatment of ester hydrolysis rates appears promising. It would be interesting to apply this treatment to other ester hydrolysis reactions whose detailed mechanisms are not well understood. The r values could then be established as a useful indicator of mechanism, in addition to those already available from O^{18} -exchange studies, kinetic isotope effects, and stereochemical studies, particularly since taken individually these criteria do not always allow unambiguous conclusions to be drawn.

Experimental Section

Materials. Commercially available acetates were either distilled directly before use or recrystallized from methanol-water. Sulfuric acids below 95% (w/w) were prepared by diluting CIL grade acid (95% min) and more concentrated acids by this acid with Fisher reagent fuming (30%) acid. Acid concentrations were determined by titrating weighed samples with standard base. The H_0 values of these solutions were determined by interpolation from a graph of the data of Jorgenson et al.¹⁶

Methods. The method chosen for each ester depended on the ultraviolet absorption characteristics of the ester itself and the acidity of the acid solution of interest. In some cases both methods were used.

For *tert*-, *n*-propyl, isopropyl, and *sec*-butyl acetates in sulfuric acid 25%, and for phenyl, *p*-chlorophenyl, and *p*-nitro-

phenyl acetates in all acids, the change in ultraviolet absorption was measured using a Perkin-Elmer Model 350 spectrophotometer with either repeated scanning attachment or external recorder. The wavelength range 182–195 $m\mu$ (1-mm cells, N_2 purging) was used for the alkyl acetates and the range 260–280 $m\mu$ (1-cm cells) for the phenyl acetates. This method could not be used below 200 $m\mu$ for solutions in the low acidity range because of the background absorption due to hydrogen sulfate ion.¹⁶ The cell compartment was thermostated at $25 \pm 0.2^\circ$. Concentrations of ester used depended on solubility and extinction coefficient and were generally in the range 0.02–0.2 *M* for the alkyl and 10^{-3} to 10^{-4} *M* for the phenyl esters. Excellent linear plots of $\log A$ vs. time were obtained in all cases (correlation coefficients ≥ 0.999), and the pseudo-first-order rate constants obtained using different wavelengths near the maximum for a given ester were in good agreement. The results of a typical run using this technique are given in Table III.

Table III. Kinetic Data for the Hydrolysis of Isopropyl Acetate at 25° ; Sulfuric Acid Concentration, 65.2%; Initial Ester Concentration, 0.238 *M*.

Time, min	A_t^a	$A_t - A_\infty$	$\log \frac{(A_t - A_\infty)}{A_\infty + 1}$
0	1.700	1.360	1.134
2	1.594	1.254	1.098
4	1.504	1.164	1.066
6	1.398	1.058	1.024
8	1.312	0.972	0.988
10	1.268	0.928	0.968
12	1.204	0.864	0.937
14	1.150	0.810	0.909
16	1.072	0.732	0.865
18	1.016	0.676	0.830
20	0.970	0.630	0.799
22	0.932	0.592	0.772
24	0.900	0.560	0.748
26	0.868	0.528	0.723
28	0.828	0.480	0.681
30	0.790	0.450	0.653
32	0.750	0.410	0.613
34	0.720	0.380	0.580
36	0.686	0.346	0.539
90	0.370		
130	0.342		
190	0.340		
$A_\infty = 0.340$		$k_1 = 3.69 \times 10^{-3} \text{ min}^{-1}$	

^a Absorbance measured at 191 $m\mu$ using 1-mm cells.

For benzyl acetate, and for the alkyl acetates in acids below 25% and *n*-propyl acetate above 85% acid, the following modification of the method of Jaques¹⁰ was used. Sulfuric acid (50 ml) of known concentration and ester (0.02–0.04 ml) were mixed in a reaction vessel thermostated at $25.0 \pm 0.1^\circ$. At suitable time intervals, 5-ml samples were withdrawn and poured onto crushed ice. These were then neutralized, first with concentrated, then with 0.1 *N* sodium hydroxide to exactly pH 7. This neutral solution was made up to 100 ml with distilled water and a 20-ml aliquot added to 10 ml of 2 *M* hydroxylamine hydrochloride and 10 ml of 2.5 *N* sodium hydroxide. After 10 min, 5 ml of 5.6 *N* HCl was added followed by an excess of 15% ferric chloride in 0.2 *N* HCl. The optical density of this solution at 540 $m\mu$ was measured within 2 on a Bausch and Lomb Model 505 spectrophotometer using 10-cm cells. Accurate pH control (1.0–1.4) is required in the above procedure to prevent hydrolysis of the ferric chloride complex of the acethydroxamic acid formed from unreacted ester. This method also gave good linear plots of $\log (\text{ester})$ vs. time from which the pseudo-first-order rate constants were obtained.

pK Determinations. The indicator behavior of methyl, *n*-propyl, and isopropyl acetates was investigated by measuring the zero-time extinction coefficient at 190 $m\mu$ as a function of sulfuric acid concentration. The data were treated by standard methods and for methyl acetate fitted the equation $\log [BH^+]/[B] = 0.63(-H_0 -$

(25) J. T. Edward and I. C. Wang, *Can. J. Chem.*, **43**, 2867 (1965).

Table IV

% H ₂ SO ₄	-H ₀	ϵ_{obsd}^a	$\epsilon_{\text{calcd}}^b$
15.1	0.67	79	75
30.2	1.73	89	90
40.4	2.44	94	101
50.2	3.40	115	117
55.2	3.94	127	128
60.4	4.51	146	141
65.2	5.10	167	162
67.3	5.40	186	177
70.4	5.86	221	210
72.6	6.18	245	241
74.1	6.40	279	270
75.3	6.60	294	297
78.5	7.11	367	373
80.0	7.34	424	410
81.7	7.61	446	450
84.7	8.08	535	510
88.2	8.65	567	554
89.7	8.90	577	566
94.5	9.75	585	588
98.6	10.5	595	595

^a Zero-time extinction coefficient measured at 190 m μ . ^b Calculated from the equation $\log [\text{BH}^+]/[\text{B}] = 0.62(-H_0 - 7.16)$ with $\epsilon_{\text{B}} = 65$, $\epsilon_{\text{BH}^+} = 598$, $g_{\text{B}} = -14.7$, $g_{\text{BH}^+} = 0$.³⁴

7.25), and for *n*-propyl acetate the equation $\log [\text{BH}^+]/[\text{B}] = 0.62(-H_0 - 7.18)$. A typical set of experimental data for *n*-propyl acetate is given in Table IV. This was treated by a previously described³⁴ method to obtain the best fit of the experimental points

to a calculated curve based on the equation $\log [\text{BH}^+]/[\text{B}] = m(-H_0 - pK)$. The above method of obtaining *m* values was preferred over the more conventional logarithmic plots for two reasons. First, the $\log [\text{BH}^+]/[\text{B}]$ vs. *H*₀ plots only utilize data obtained within a narrow range, usually 1.5–2.0 *H*₀ units either side of *pK*, whereas the previously described kinetic treatment using *m* involves data obtained over a much wider acidity range (15–98% sulfuric acid). Second, both the linearity and slopes of these log plots can be influenced by medium effects on the spectra of the base and conjugate acid forms. The present method reduces the seriousness of this possibility by correcting for medium effects. Unfortunately the rate of hydrolysis of isopropyl acetate is too high in acids above 90% to obtain reliable zero-time extinction coefficients. However, below this acidity, plots of $\log \epsilon$ for isopropyl and *n*-propyl acetates against *H*₀ are strikingly similar, and it is reasonable to assume that the ionization behavior of isopropyl acetate closely resembles that of the *n*-propyl ester. Lane,⁸ using a similar method, found the ionization behavior of ethyl acetate in sulfuric acid followed the equation $\log [\text{BH}^+]/[\text{B}] = 0.65(-H_0 - 6.93)$. The close similarity of the indicator slopes and “*pK*” values for methyl, *n*-propyl, and ethyl acetates indicates that the protonation behavior of acetate esters is reasonably independent of structure. For the other acetates studied no reliable protonation data could be obtained either because of too rapid hydrolysis or because sulfonation interfered at the high acidities required to measure ϵ_{BH^+} . Therefore, in cases where no indicator slope could be measured, a value of *m* = 0.62 was assumed, and an approximate *pK* of -7.2 was used to correct for fraction protonated, where necessary.³¹

Acknowledgment. We are grateful to the National Research Council of Canada for continued financial support, and for the award of a studentship to R. A. M.

(26) A. R. Katritzky, A. J. Waring, and K. Yates, *Tetrahedron*, **19**, 465 (1963).

Stable Carbonium Ions. XXXIV.¹ The 1-Methylcyclopentyl Cation²

George A. Olah, J. Martin Bollinger,^{3a} Chris A. Cupas, and Joachim Lukas^{3b}

Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. Received February 10, 1967

Abstract: 1-Methyl-1-chlorocyclopentane, cyclopentylcarbonyl chloride, and cyclohexyl fluoride (chloride, bromide) in SbF₅-SO₂ solutions at -60° gave a stable solution of the 1-methylcyclopentyl cation. The same ion is also formed when 1-methylcyclopentanol or cyclohexanol were dissolved in FSO₃H-SbF₅ solutions. 1-Methylcyclopentene and cyclohexene are protonated in HF-SbF₅-SO₂ or FSO₃H-SbF₅-SO₂ solution to the 1-methylcyclopentyl cation, which is also formed by hydride abstraction from methylcyclopentane and cyclohexane in FSO₃H-SbF₅ solution. The structure of the 1-methylcyclopentyl cation was investigated based on its nmr spectrum.

The acid-catalyzed isomerization of methylcyclopentane and cyclohexane has long been recognized and studied and has provided much useful information concerning the carbonium ion chain mechanism for hydrocarbon isomerization.^{4,5} In terms of product

stability, cyclohexane is favored. The equilibrium mixture at 25° consists of 77% cyclohexane and 23% methylcyclopentane.⁶ In terms of carbonium ion stability, however, the tertiary methylcyclopentyl cation I should be favored over the secondary cyclohexyl cation II. No good estimate is available concerning either the relative energy differences between these two

(1) Part XXXIII: G. A. Olah and J. M. Bollinger, *J. Am. Chem. Soc.*, in press.

(2) For a preliminary report see G. A. Olah and M. W. Meyer in "Friedel-Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 645.

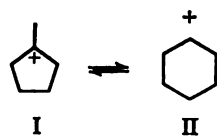
(3) (a) National Science Foundation Postdoctoral Research Investigator, 1966–1967. (b) National Institutes of Health Postdoctoral Research Investigator, 1966–1967.

(4) C. D. Nenitzescu and I. P. Cantuniari, *Ber.*, **66**, 1097 (1933).

(5) For reviews see (a) H. Pines and N. E. Hoffman, "Friedel-Crafts and Related Reactions," Vol. II, Part 2, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 28; (b) F. E. Condon

and P. H. Emmett, Ed., "Catalysis," Vol. VI, Reinhold Publishing Corp., New York, N. Y. 1958, Chapter 2.

(6) A. L. Glasebrook and W. G. Lovell, *J. Am. Chem. Soc.*, **61**, 1717 (1939), reported in accordance with ref 2 that the equilibrium mixture at 25° consists of 77% cyclohexane and 23% methylcyclopentane. D. P. Stevenson and J. H. Morgan, *ibid.*, **70**, 2773 (1948), found the equilibrium favors cyclohexane at lower temperatures, the amount of methylcyclopentane increasing with temperature.



the activation energy necessary for their interconversion.

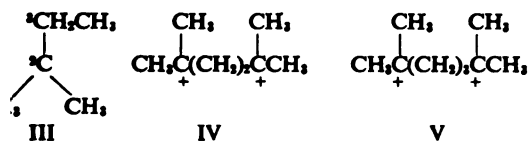
In the course of the investigation of stable carbonium acidic solvent systems like SbF_5 or $\text{SbF}_5\text{-FSO}_3\text{H}$ it is of interest to attempt the observation of the carbonium ions formed from both 1-methylcyclopentyl and cyclohexyl precursors. We briefly reported on the formation of 1-methylcyclopentyl cation I in 1963,² and would like now to present in detail our observations regarding this ion.⁸ As ion I was observed to be formed from a variety of precursors in strong acid, its investigation also proved interesting with respect to applying a variety of methods in its generation.

Results and Discussion

In 1-chloro-1-methylcyclopentane (1) was dissolved in $\text{SbF}_5\text{-SO}_2$ solution at -60° a stable solution of ion I was obtained. Ion I was also obtained from cyclohexyl carbonyl chloride (2) or cyclohexyl chloride (fluoride, bromide) in the same solvent at -60° . The primary cyclopentylcarbonyl cation and the secondary cyclohexyl cation thus rearrange with great ease at -60° to the tertiary ion I which is the only one observed by nmr spectroscopy.

In $\text{FSO}_3\text{H-SbF}_5$ as the acid medium, 1-methylcyclopentanol-1 (4) and cyclohexanol (5) gave also ion I. 1-Methylcyclopentene-1 (6) and cyclohexene (7) were also protonated in $\text{HF-SbF}_5\text{-SO}_2$ or $\text{FSO}_3\text{H-SbF}_5\text{-SO}_2$ at -60° to give I. Furthermore, we observed that the extremely strong acid $\text{FSO}_3\text{H-SbF}_5$ is able to affect hydride ion abstraction from 1-methylcyclopentane (8) or cyclohexane (9) to form ion I.⁹ Table I summarizes the different precursors and pathways leading to ion I.

The pmr spectrum of the methylcyclopentyl cation at -60° is shown in Figure 2. The substantially deshielded methyl (-3.98 ppm) and α -methylene (-4.50 ppm) protons adjacent to the positive charge show the anticipated deshielding.¹⁰ Particularly noticeable is the long-range coupling ($J_{\text{H-H}} = 4.0$ cps) of the methylene and methyl hydrogens through the sp^2 -hybridized center of ion I. Similar long-range coupling is also observed in simple alkylcarbonium ions. Thus



as in previous papers of this series.

M. Brouwer and E. L. Mackor [*Proc. Chem. Soc.*, 147 (1964)] observed the methylcyclopentyl cation and claimed, based on line broadening, that above -20° the methyl group shifts along the ring. We do not concur with this explanation and feel that line broadening is caused by other reasons.

The application of $\text{FSO}_3\text{H-SbF}_5$ as a hydride-abstracting medium for the formation of carbonium ions from hydrocarbons is a general method: see Olah and J. Lukas, *J. Am. Chem. Soc.*, **89**, 2227 (1967).

The positions of the methyl and methylene groups adjacent to the positive charge are at 4.50 and 4.93 ppm: G. A. Olah, E. B. C. Evans, W. S. Tolgyesi, J. S. McIntyre, and I. J. Bastien, *J. Am. Chem. Soc.*, **86**, 1360 (1964).

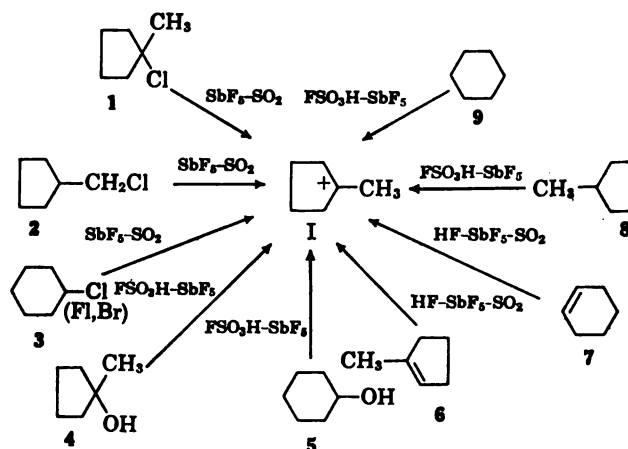


Figure 1.

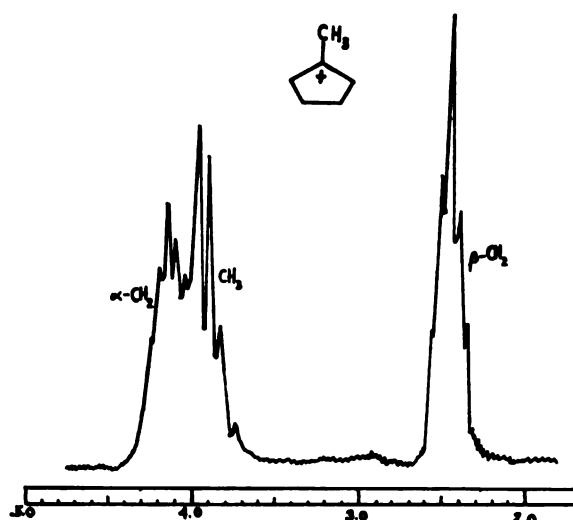


Figure 2.

in the dimethylethylcarbonium ion (*t*-amyl cation) (III), $J_{\text{H-H}} = 5.0$ cps,¹⁰ while for the dications IV and V, $J_{\text{H-H}} = 3.0$ and 4.0 cps, respectively.¹¹ The β -methylene protons at -2.47 ppm show also the anticipated deshielding. Finally, quenching ion I in methanol at -70° gave a high yield (80%) of 1-methylcyclopentyl methyl ether¹² with smaller amounts of methylcyclopentene.

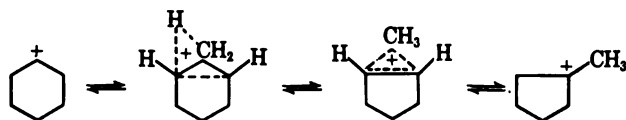
The fact that, starting from either 1-methylcyclopentyl or cyclohexyl precursors even at -60° , we were able to observe only the 1-methylcyclopentyl cation indicates that rearrangement of any initially formed cyclohexyl cation occurs too rapidly to be detected by nmr, at least under the experimental conditions used in the present work. Although the exact mechanistic details of this rearrangement are not yet known, we favor a mechanism not involving the intermediacy of a primary carbonium ion, which would represent a substantially high energy barrier. A rearrangement mechanism similar to the one proposed by Nenitzescu,¹³ involving

(11) J. M. Bollinger, C. A. Cupas, K. J. Friday, M. L. Woolfe, and G. A. Olah, *ibid.*, **89**, 156 (1967).

(12) G. A. Lutz, A. E. Bearse, J. F. Leonard, and F. P. Croxton, *ibid.*, **70**, 4139 (1948).

(13) C. D. Nenitzescu in "Carbonium Ions," G. A. Olah and P. von R. Schleyer, Ed., Interscience Publishers, Inc., New York, N. Y., in press.

a protonated cyclopropane intermediate, merits consideration.



Experimental Section

All compounds with the exception of 1-chloromethylcyclopentane and 1-methylcyclopentyl methyl ether were commercially available. 1-Chloro-1-methylcyclopentane was prepared by the procedure of Merrwein and Mühlendyk.¹⁴ 1-Methylcyclopentyl methyl ether was prepared according to the method of Lutz, *et al.*¹⁵

Nmr Spectra. The nmr spectra were obtained on a Varian Associates Model A56-60A spectrometer equipped with a variable-temperature probe. All spectra were run at -60° . The chemical shifts are recorded in parts per million relative to external TMS.

Preparation of Solutions of 1-Methylcyclopentyl Cation. a. From Halides. A saturated solution of antimony pentafluoride in sulfur dioxide was prepared (at -10°). Portions (2 ml) of this solution were cooled to -78° , causing some antimony pentafluoride to crystallize from solution. To this suspension was added

with stirring approximately 0.2 g of the appropriate 1-methylcyclopentyl or cyclohexyl halide. Slight warming was required to complete the ionization, whereupon a homogeneous solution resulted with only slight traces of color. Ion concentrations were around 10%.

b. From Alcohols. The precursor alcohol (1-methyl-1-cyclopentanol or cyclohexanol) in SO_2 was cooled to -60° and added to a vigorously stirred 1:1 molar mixture of FSO_3H and SbF_5 at -60° . Generally an excess of SO_2 was used to prepare the solution which was then concentrated by pumping off SO_2 to give an approximately 8–10% concentration of the carbonium ion solution.

c. From Cycloalkanes. The cycloalkane (1-methylcyclopentane, cyclohexane) and a tenfold (weight) excess of acid (1:1 FSO_3H - SbF_5) were vigorously stirred at room temperature until they formed a homogeneous colorless mixture.

d. From Cycloalkenes (1-Methylcyclopentene and Cyclohexene). A cold (-60°) solution of the cycloalkene in SO_2 was added slowly with stirring to a cold solution of HF - SbF_5 and FSO_3H - SbF_5 in SO_2 . Excess SO_2 was pumped off in order to obtain a $\sim 10\%$ solution of the methylcyclopentyl cation.

Quenching the methylcyclopentyl cation in a suspension of methanol and potassium carbonate at -78° gave an 81% yield of 1-methylcyclopentene according to comparison with authentic samples.

Acknowledgment. Support of this work by grants of the National Science Foundation and the Petroleum Research Fund administered by the American Chemical Society is gratefully acknowledged.

(14) H. Meerwein and M. Mühlendyk, *Ann.*, **405**, 171 (1964).

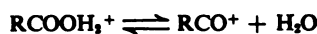
Stable Carbonium Ions. XXXVIII.¹ Alkenyloxocarbonium Ions

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Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. Received December 21, 1966

Abstract: An investigation of the alkenoyl fluoride-antimony pentafluoride complexes has been carried out. Acryloyl-, methacryloyl-, crotonoyl-, tigloyl-, β,β -dimethylacryloyl-, and cinnamoyl fluoride all form complexes with antimony pentafluoride, which based on infrared and nmr investigations are alkenyloxocarbonium ions.

No investigation of the complex formation of alkenoyl halides with Lewis acid halides has been reported in the literature. Deno, Pittman, and Wisotsky³ investigated the behavior of crotonic, 2-methylcrotonic (tiglic), 3-methylcrotonic, and 2,4-hexadienoic (sorbic) acid in sulfuric acid and oleum. It was suggested, based on nmr studies, that an equilibrium exists between the oxocarbonium ions and protonated acids.



In continuation of our previous work⁴ on oxocarbonium ions it was of interest to attempt the preparation of alkenyloxocarbonium ion complexes ($\text{RC}^+=\text{O}$, R = unsaturated).

(1) Part XXXVII: G. A. Olah, R. D. Chambers, and M. B. Comisarow, *J. Am. Chem. Soc.*, **89**, 1268 (1967).

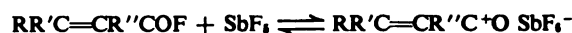
(2) National Science Foundation Predoctoral Research Investigator, 1965–1967.

(3) N. C. Deno, C. U. Pittman, Jr., and J. Wisotsky, *J. Am. Chem. Soc.*, **86**, 4370 (1964).

(4) (a) G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *ibid.*, **84**, 2733 (1962); (b) G. A. Olah, *Rev. Chim., Acad. Rep. Populaire Roumaine*, **7**, 1139 (1962); (c) G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffatt, I. J. Bastien, and E. B. Baker, *J. Am. Chem. Soc.*, **85**, 1328 (1963); (d) G. A. Olah and M. B. Comisarow, *ibid.*, **88**, 3313, 4442 (1966).

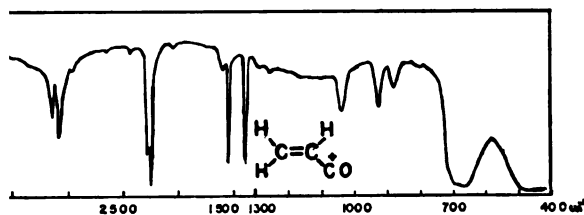
Results and Discussion

Stable alkenyloxocarbonium ion complexes were obtained by treating alkenoyl fluorides with antimony pentafluoride ("fluoride method" of oxocarbonium ion formation⁴).



The necessary alkenoyl fluorides were prepared from the corresponding acyl chlorides and anhydrous hydrogen fluoride except for acryloyl fluoride, methacryloyl fluoride, and crotonoyl fluoride, which were prepared from the corresponding acids and benzoyl fluoride. Yields were generally better than 90%. Table I summarizes the boiling points of the alkenoyl fluorides. Their purity, based on nmr and infrared spectra, was better than 98%.

The alkenyloxocarbonium ion complexes were prepared by mixing cold 1,1,2-trifluoroethane (Freon 113) solutions of the corresponding alkenoyl fluorides with Freon 113 solutions of antimony pentafluoride. The complexes separate as liquids at room temperature except for the cinnamoyl complex which crystallizes (mp 75°). They are all brown in color except for the cinnamoyl complex which is bright red.



1.

stored in the absence of moisture the complexes are found to be stable indefinitely.

Alkenyl Fluorides

Fluoride	Bp, °C (mm)
Acryloyl	34 ^a
Methacryloyl	56–57 ^b
Crotonoyl	80–82 ^a
Tigloyl	63–64 (180)
β,β -Dimethylacryloyl	66 (188)
Cinnamoyl	108 (12) ^d

^a 34.5°. ^b B. W. Howk and R. A. Jacobson [U. S. Patent 2,800,000; *Chem. Abstr.*, 42, 4794 (1948)] report 56.5–58°. ^c F. J. Langer [*Ber.*, 91, 2553 (1958)] report 81–82° (745 mm). ^d 108° (12 mm).

Infrared Investigations. The liquid complexes were prepared as neat films between Irtran-2 plates using the standard techniques for exclusion of moisture. The solid cinnamoyl complex was examined as a Fluorac 1 mull.

Infrared investigations show that all of the complexes are exclusively oxocarbenium ions ($\text{RC}^+=\text{O}$) as indicated by the absence of carbonyl absorption and the presence of an absorption band (around 2240 cm^{-1}) characteristic of oxocarbenium ions.⁴ The infrared absorption data are summarized in Table II.

II. Infrared Absorption of Alkenyl Fluoride-Antimony Fluoride Complexes (cm^{-1})

	Acyl fluoride		Oxocarbenium ion	
	ν_{CO}	$\nu_{\text{C}=\text{C}}$	$\nu_{\text{C}^+=\text{O}}$	$\nu_{\text{C}=\text{C}}$
Acryloyl	1825	1635	2250	1555
Methacryloyl	1815	1645	2240	1590
Crotonoyl	1815	1655	2240	1580
Tigloyl	1800	1650	2230	1580
β,β -Dimethylacryloyl	1800	1645	2220	1555
Cinnamoyl	1805	1640	2210	1550

The $\text{C}^+=\text{O}$ stretching frequency is generally close to 2240 cm^{-1} , which is lower than the $\text{C}^+=\text{O}$ stretching frequency found in saturated alkyl oxocarbenium ions⁴ and close to the stretching frequency of the phenyloxocarbenium ion (2212 cm^{-1}). This is undoubtedly due to conjugation with the adjacent double bond. As found previously for other oxocarbenium ions^{4d} the absence of carbonyl absorption bands is dependent on the purity of the complexes. Addition of water to the complexes diminishes the intensity of the 2240- cm^{-1} band and causes a concomitant appearance of a band at 1600 cm^{-1} . The spectrum of the acryloyl complex is shown in Figure 1 as representative of the infrared spectra of the alkenyloxocarbenium ions.

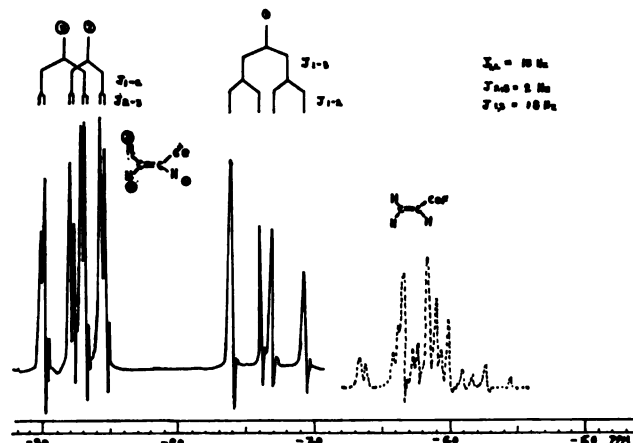


Figure 2.

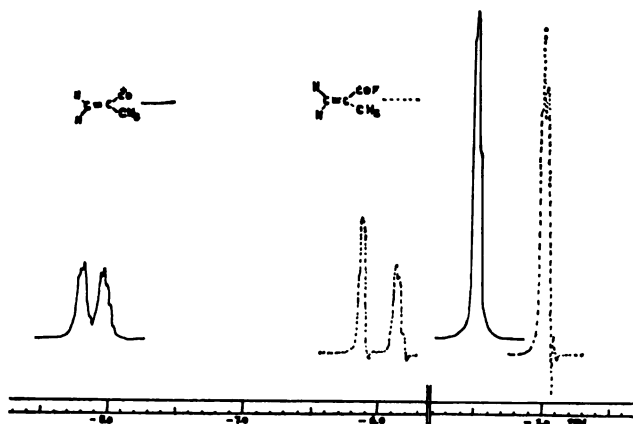
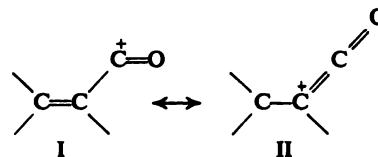
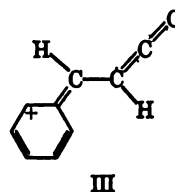


Figure 3.

Nmr Investigations. The pmr spectra of the alkenyl-oxocarbenium hexafluoroantimonate complexes and the starting acyl fluorides as solution in SO_2 at -40 to -60° are shown in Figures 2–7. First-order techniques were used for the analysis of all of the spectra except that of acryloyl fluoride.⁵ The data are summarized in Table III. They clearly indicate the oxocarbenium ion nature of the investigated complexes. The deshielding ($\Delta\delta$ values) of the methyl protons β to the $\text{C}^+=\text{O}$ group is greater than that of the α -methyl protons, indicating substantial contributions from the resonance forms I and II. Comparison of $\Delta\delta$ values



indicates that the proton *cis* to the $\text{C}^+=\text{O}$ group in the cinnamoyl complex is deshielded less than the same proton in the other complexes indicating a further strong contribution from resonance form III.



III

(5) (a) The authors wish to thank Professor Axel Bothner-By for communication of the analysis of the acryloyl fluoride spectrum prior to publication. (b) D. F. Koster, *J. Am. Chem. Soc.*, 88, 5062 (1966).

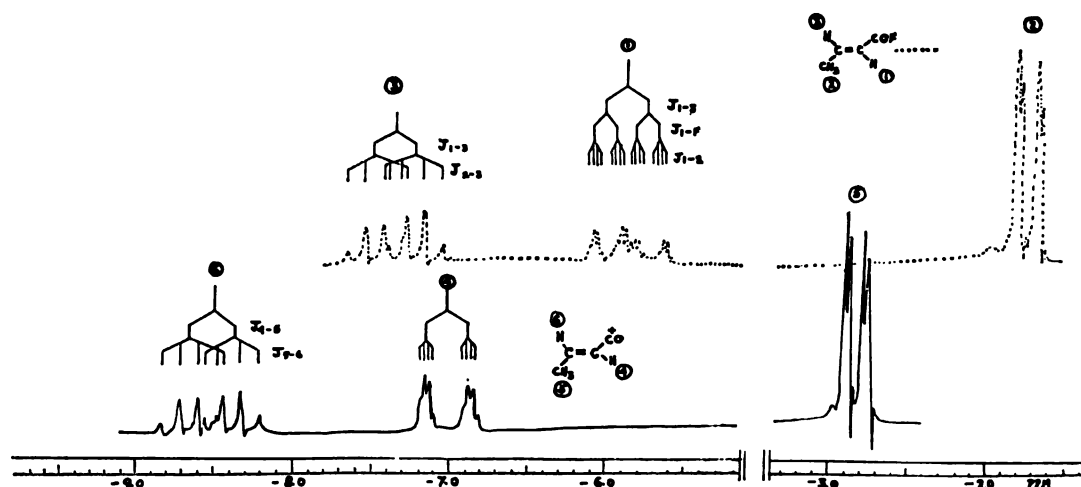


Figure 4.

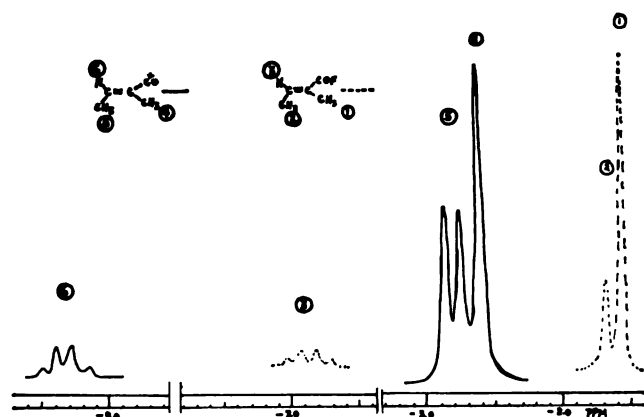


Figure 5.

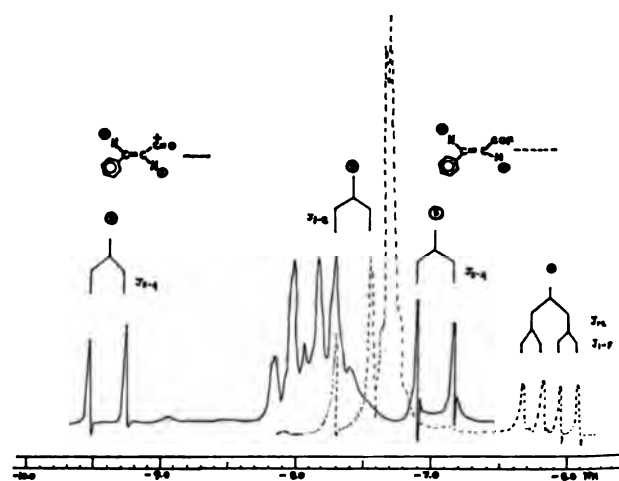


Figure 7.

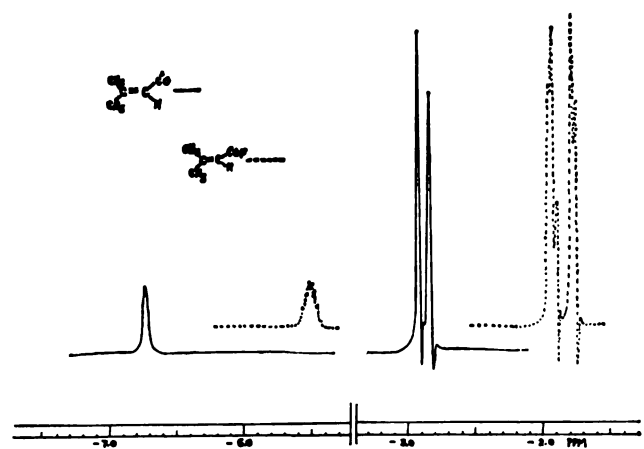


Figure 6.

Addition of small amounts of water to the nmr samples results in the appearance of new resonances at higher field than the oxocarbenium ion peaks but at lower field than the starting acyl fluorides peaks. These can be assigned to the donor:acceptor complexes.^{4d,6}

The alkenyloxocarbenium hexafluoroantimonate complexes could also be examined as neat liquids at

(6) NOTE ADDED IN PROOF. The protonation of alkenoic acids in $\text{FSO}_3\text{H-SbF}_5$ solution and their dehydration to alkenyloxocarbenium ions is being investigated with Dr. M. Calin and will be reported. This work indicates that the donor-acceptor complex RC(F)=O-SbF_5 is most likely the O-protonated acid RCO_2H_2^+ .

Table III. Nuclear Magnetic Proton Resonance Shifts of Alkenyloxocarbenium Ions

		$\begin{array}{c} \beta_{\text{cis}} \\ \beta_{\text{trans}} \end{array} > \text{C} = \text{C} < \overset{+}{\text{CO}}_{\alpha}$		
		Fluoride in SO_2	δ , ppm Oxocarbenium	
			In SO_2	Neat
Acryloyl	α	-5.88 ^a	-7.33	-7.70
	β -cis	-6.26 ^a	-8.85	-9.22
	β -trans	-5.79 ^a	-8.60	-9.05
Methacryloyl	α -CH ₃	-1.16	-2.73	-3.12
	β -cis	-6.13	-8.45	-8.70
	β -trans	-5.89	-8.17	-8.53
Crotonyl	α	-5.65	-7.00	-7.31
	β -cis	-7.12	-9.50	-9.88
	β -trans-CH ₃	-1.61	-2.83	-3.35
Tigloyl	α -CH ₃	-1.55	-2.62	-3.04
	β -cis	-6.88	-9.33	-9.60
	trans-CH ₃	-1.61	-2.82	-3.32
β,β -Dimethyl- acryloyl	α	-5.50	-6.72	-7.05
	cis-CH ₃	-1.93	-2.92	-3.42
	trans-CH ₃	-1.78	-2.83	-3.33
Cinnamoyl	α	-6.11	-6.96	...
	β -cis	-7.57	-9.40	...
	Ring H	-7.27	≈ 7.90	...

^a These values were obtained from ref 5b by adding 0.1 from the chemical shifts in CFCl_3 ; +0.1 ppm is a typical solvent shift from CFCl_3 (internal TMS) to SO_2 (external TMS): Olah and Comisarow, unpublished data.

room temperature (with the exception of the cinnamoyl complex) and their spectra were very similar to the solution spectra except for the solvent shift. The resolution of the neat spectra was slightly lower due to the higher viscosity of the neat complexes as compared with their SO_2 solutions.

The F^{19} spectra of the complexes shows no C-F resonances, only antimony-fluorine peaks at around $\phi + 100$ (parts per million from external CFCl_3).

Experimental Section

Acryloyl, methacryloyl, and crotonoyl fluorides were prepared from the acids and benzoyl fluoride using the published procedure for cyclopropanecarbonyl fluoride.^{4a} Tigloyl, β,β -dimethylacryloyl, and cinnamoyl fluorides were prepared from the corre-

sponding chlorides and anhydrous hydrogen fluoride using the published procedure for preparing cyclobutanecarbonyl fluoride.^{4a}

The preparation of the alkenyloxocarbenium ion complexes from alkenoyl fluorides and antimony pentafluoride in 1,1,2-trifluoroethane solution was carried out according to methods previously described to prepare other types of oxocarbenium complexes.^{4a-d}

The techniques of infrared and nmr studies were also analogous to those described previously. Infrared spectra were obtained on a Beckman Model IR 10 spectrophotometer and a PE 337 spectrophotometer. Nmr spectra were obtained on Varian Associates Model HA-60-IL and A56-60A spectrometers equipped with variable-temperature probes. All chemical shifts are relative to external TMS (H^1) or CCl_3F (F^{19}) as references (capillary tubes).

Acknowledgment. Generous support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

Carbodiimide-Sulfoxide Reactions. VI.¹ Syntheses of 2'- and 3'-Ketouridines

A. F. Cook² and J. G. Moffatt

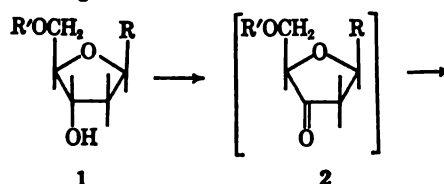
Contribution No. 46 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California. Received January 23, 1967

Abstract: Oxidation of 2',5'-di-O-trityluridine by the dimethyl sulfoxide-dicyclohexylcarbodiimide method gave crystalline 2',5'-di-O-trityl-3'-ketouridine in good yield. Treatment with hydrogen chloride in chloroform then gave free 3'-ketouridine. In a similar way oxidation of 3',5'-di-O-trityluridine gave 3',5'-di-O-trityl-2'-ketouridine which was detritylated to free 2'-ketouridine. These oxidations could also be performed using dimethyl sulfoxide together with acetic anhydride or phosphorus pentoxide. The uridine ketones were very labile toward alkali, being cleaved to uracil. Borohydride reduction of the free or tritylated 2'-ketone led predominantly to the formation of products with the arabinose configuration while similar reduction of the 3'-ketones gave mixtures of the corresponding xylosides and ribosides in a ratio of 2:1. Attempts to alkylate the ditrityl 3'-ketone with Grignard reagents, methyllithium, or diazomethane have not as yet been successful. Nuclear magnetic resonance spectra data are presented for the various compounds.

An extremely mild, yet efficient, oxidation of alcohols through their reaction with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) has been developed in this laboratory.³ Since the oxidation proceeds at room temperature, and under essentially neutral conditions (e.g., using pyridinium trifluoroacetate as the proton source), it has found considerable application when dealing with sensitive compounds.⁴ A particular merit lies in the oxidation of primary alcohols exclusively to the aldehyde stage,³ and this property has permitted the oxidation of the 5'-hydroxyl group of protected nucleosides to give the corresponding nucleoside 5'-aldehydes.^{2a,5}

Our earlier observations^{2b} showed that the reaction of deoxynucleosides, such as thymidine, substituted at the 5' position by phosphate, acetyl, or *p*-nitrobenzoyl groups (1, R = thymine, R' = PO_2H_2 , Ac, *p*-nitrobenzoyl) with DMSO and DCC in the presence of an-

hydrous orthophosphoric acid led to the rapid and complete cleavage of the N-glycosidic bond with release of thymine. Such a degradation undoubtedly proceeds *via* oxidation to the 5'-substituted 3'-ketonucleoside 2 which then undergoes β elimination of the heterocyclic base. The elimination step was apparently extremely rapid and no sign of the intermediate ketones 2 could be detected chromatographically. Similar results have been encountered by others during attempted oxidation of the 3'-hydroxyl group of protected deoxynucleosides with manganese dioxide,⁶ chromium trioxide in pyridine,⁷ or platinum and oxygen under forcing conditions.⁸



R + sugar fragments

(1) For part V see M. G. Burdon and J. G. Moffatt, submitted for publication.

(2) Syntex Postdoctoral Fellow, 1964-1966.

(3) (a) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963); (b) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965); (c) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 3670 (1965).

(4) See, e.g., (a) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965); (b) B. R. Baker and D. H. Busa, *ibid.*, **30**, 2304 (1965); (c) A. G. Brook and J. B. Pierce, *ibid.*, **30**, 2566 (1965).

(5) A detailed account of these studies is in preparation by G. H. Jones and J. G. Moffatt.

(6) A. S. Jones, R. T. Walker, and A. R. Williamson, *J. Chem. Soc.*, 6033 (1963).

(7) A. S. Jones, A. R. Williamson, and M. Winkley, *Carbohydrate Res.*, **1**, 187 (1965).

(8) Personal communication from Dr. G. M. Tener of the University of British Columbia.

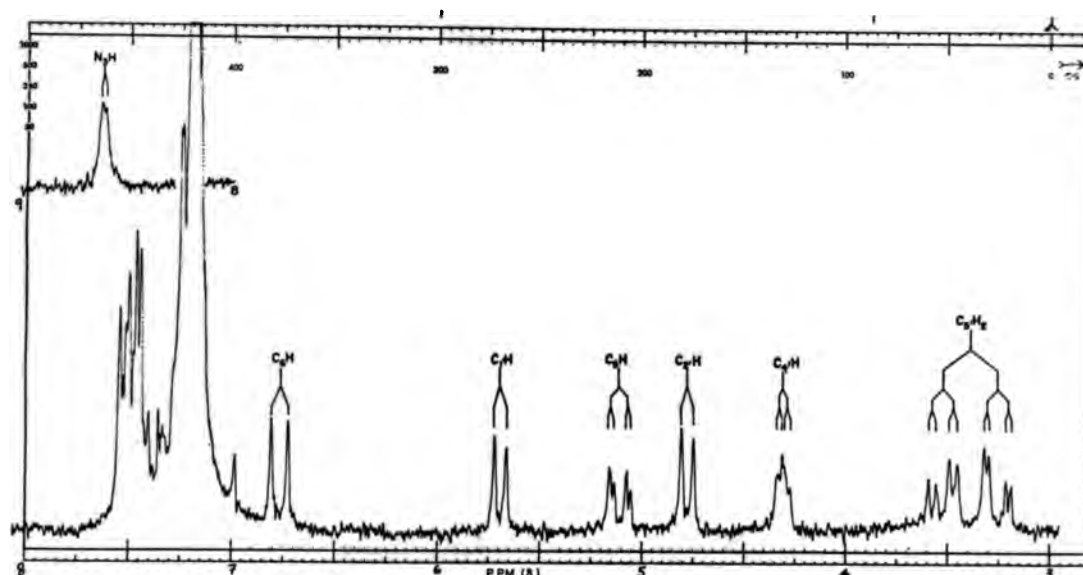
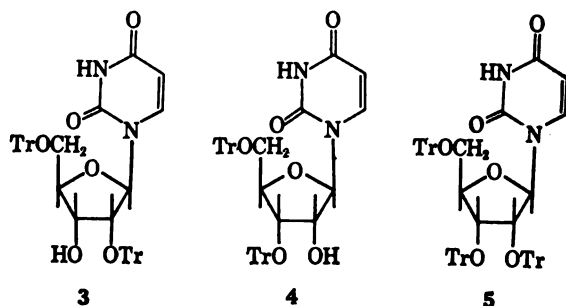


Figure 1. Nuclear magnetic resonance spectrum of 2',5'-di-O-trityl-3'-ketouridine in deuteriochloroform at 100 Mc.

In this paper we describe the successful oxidation of some doubly blocked uridine derivatives and the isolation of free 2'- and 3'-ketouridines.

The starting materials in this work were the well-known 2',5'-di-O-trityluridine (3) and 3',5'-di-O-trityluridine (4) which were obtained in yields of 39 and 19% by reaction of uridine with excess triphenylmethyl chloride in pyridine at 100° essentially according to Yung and Fox^{9a} and Žemlička.^{9b} Much of the 2',5'-ditrityl compound could be directly isolated by crystallization and the 3',5'-ditrityl isomer was obtained by chromatography of the mother liquors on a silicic acid column. In addition to these two products a small amount (2%) of the previously undescribed 2',3',5'-tri-O-trityluridine (5) was obtained in crystalline form and its structure was confirmed by elemental analysis and nuclear magnetic resonance spectroscopy. The presence of the third trityl group on a sugar hydroxyl rather than on N₃ of the uracil ring was shown by the ultraviolet spectrum which was typically that of a uridine derivative [λ_{\max} 261 m μ (ϵ 9990)]. In addition, the nmr spectrum of 5 showed an interesting, and previously undescribed, coupling (J = 2 cps) of the N₃ and C₅ protons of the uracil ring. This effect, which was readily confirmed by spin-decoupling studies, was also noted with 3 and 4 as well as with the tritylated ketonucleosides to be described below.



Treatment of 3 with DMSO and DCC in the presence of pyridinium trifluoroacetate at room temperature led

- (9) (a) N. C. Yung and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961);
(b) J. Žemlička, *Collection Czech. Chem. Commun.*, **29**, 1734 (1964).

to the smooth formation of a new, less polar product together with a little unreacted 3, as demonstrated by thin layer chromatography. Direct crystallization from methanol gave a 46% yield of pure 2',5'-ditrityl-3'-ketouridine (6) and preparative thin layer chromatography of the mother liquors on 1-mm glass plates coated with a 1.3-mm layer of silicic acid gave a further 20% yield of the pure product. The compound had an ultraviolet spectrum typical of uridine derivatives [λ_{\max} 261 m μ (ϵ 9600)] and had an infrared spectrum similar to that of 3 except for the presence of an additional carbonyl band at 1775 cm⁻¹. Under nonaqueous conditions the product exists in the keto form as shown by its elemental analysis and its nmr spectrum. The latter is particularly revealing since the keto group effectively insulates the protons at C_{4'} and C_{5'} and thus leads to a spectrum in which the protons are clearly resolved and readily analyzed. The 100-Mc spectrum of 6 is shown as Figure 1 and all assignments have been confirmed by spin-decoupling studies. Figure 1 clearly shows the previously mentioned coupling of C₅H and N₃H of the uracil ring, these protons occurring as a doublet of doublets ($J_{5,6}$ = 8 cps; $J_{5,3}$ = 2 cps) at δ 5.11 and a doublet (J = 2 cps) at δ 8.63, respectively. Irradiation at δ 8.63 results in the collapse of the C₅ proton to a doublet ($J_{5,6}$ = 8 cps) and irradiation at δ 5.11 reduces the N₃H to a singlet. The nonequivalence of the methylene protons is also striking, these protons appearing as a pair of quartets centered at δ 3.24 ($J_{4',5'a}$ = 10 cps, $J_{4',5'b}$ = 2.2 cps) and δ 3.51 (J_{gem} = 10 cps, $J_{4',5'b}$ = 5.2 cps). The C_{4'}H occurs as a quartet at δ 4.30 and irradiation at this point reduces the methylene protons to a pair of geminally coupled doublets (J = 10 cps). Similarly, irradiation at δ 4.30 collapses C_{4'}H to a singlet at δ 4.30. The C_{1'} and C_{2'} protons occur as simple doublets at δ 5.69 and δ 5.85 ($J_{1',2'}$ = 6 cps) and irradiation of either collapses them to a singlet. Addition of D₂O to the sample caused

(10) H. Halpaap, *Chem. Ing. Tech.*, **35**, 488 (1963).

(11) Carbonyl absorptions in the 1770-cm⁻¹ region are known for other ketofuranosides. See, e.g., K. Onodera, S. Hirano, and K. Kashimura, *J. Am. Chem. Soc.*, **87**, 465 (1965).

of the N_3H for deuterium and eliminated the α with C_5H which then became a doublet.

We also examined the oxidation of 3 by the delayed DMSO-phosphorus pentoxide¹¹ and acetic anhydride¹² methods and found them to be unsuitable. These methods offer the distinct advantage of giving only water-soluble by-products, eliminating the necessity of removing dicyclohexyl phosphorane. Using the phosphorus pentoxide method the starting alcohol 3 essentially disappeared. 70% yield of the ketone 6 could be obtained by crystallization. A further 15% yield could be obtained by preparative thin layer chromatography of the eluents and the remaining material appeared largely degraded to uracil which was identified in the aqueous extracts. A similar situation obtained in the DMSO-acetic anhydride reaction which gave an reaction mixture from which a 45% yield could be obtained by crystallization.

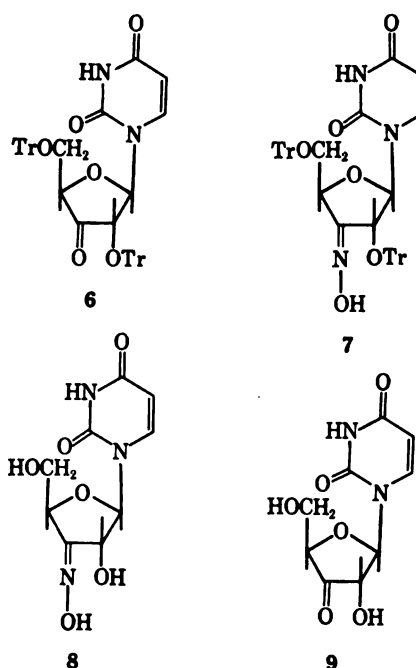
We were unable to isolate either a 2,4-dinitrothiazine or a tosylhydrazone derivative of 6 and the oxime 7 could be obtained readily in 65% yield. Repeated attempts to reduce this oxime to a 3'-deoxynucleoside with hydrogen and palladium, as yet, been unsuccessful and treatment with aluminum hydride led to extensive degradation of the molecule. Treatment of 7 with 20% hydrogen chloride in chloroform at 0° successfully removed the trityl groups giving the free 3'-ketouridine (8) which gave the expected nmr spectrum. It appeared to be unstable, becoming discolored on exposure to air and decomposing upon attempted distillation. Palladium-catalyzed hydrogenation of 8 gave only unchanged starting material.

Reaction of the ditrityl ketone 6 with 2 equivalents of hydrogen chloride in chloroform at 0° gave smooth detritylation and precipitation of 3'-ketouridine (9) in quantitative yield. Elemental analysis of this material showed it to be the anhydrous form rather than the hydrate. On paper chromatography in borate buffer at pH 6.0,¹⁴ however, it had a mobility of 1.2 times that of uridine and was roughly comparable to that of lyxofuranosyl uracil. This suggests hydration of the ketone in aqueous solution leading to a product that can form both the 3',5'-borate complexes. Paper chromatography on bisulfite impregnated paper markedly increased the mobility of the ketone relative to uridine, being comparable to that of uridine 5'-aldehyde.

The ditrityl ketone 6 and the free ketone 9, as glycosylamines, are extremely sensitive to acidic conditions and readily undergo β elimination of the uracil moiety. Free 3'-ketouridine is especially unstable and is instantaneously cleaved to uracil in aqueous solution at room temperature during attempted isolation. The free ketone had λ_{max} 286 m μ typical of uracil. The free ketone, showed a broad maximum at 337 m μ .

Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4215 (1965).

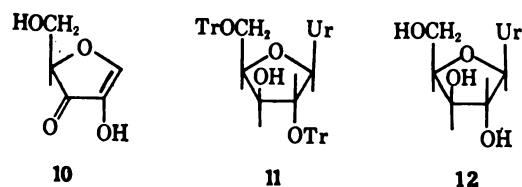
This problem can also be circumvented by using diethylcarbodiimide in DMSO, the resulting diethylurea being water soluble; and J. G. Moffatt, unpublished observations. Codrington, R. Fecher, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 560 (1960).



which is not present in uracil. The latter peak is presumably due to an unsaturated sugar fragment such as 10, resulting from the elimination reaction. Attempts to prepare a quinoxaline derivative of 10 by addition of *o*-phenylenediamine failed, but uracil was identified in the alkaline mixture by paper chromatography. Rapid elimination of uracil also seemed to occur at pH 9.8, but was more difficult to follow since uracil and uridine have rather similar spectra below pH 10.5. The ditrityl 3'-ketone 6 was much more stable toward alkali than was 9 and the rate of release of uracil could be readily followed in 0.1 *N* methanolic sodium hydroxide by the increase in ultraviolet absorption at 285 m μ relative to that at 260 m μ . In this case only a very weak absorption at 330 m μ resulted and by plotting the ratio of optical densities at 285 and 260 m μ a half-time of 7 min was determined for 6 under these conditions. This increased stability due to the presence of the 2'- and 5'-trityl groups is perhaps a consequence of steric distortion of the furanose ring into a conformation less amenable to β elimination. It may be noted that attempted oxidation of 5'-O-tritylthymidine (1, R = thymine, R' = trityl) with either DMSO-DCC in the presence of pyridinium trifluoroacetate or with DMSO-acetic anhydride led only to thymine and to considerable amounts of triphenylcarbinol without detectable accumulation of the intermediate ketone (2, R = thymine, R' = trityl). The presence of bulky substituents at both C₂ and C₅ thus appears to be a prerequisite for successful oxidation.

Reduction of the ditrityl ketone 6 with sodium borohydride in ethanol was rapid and separation of the products by preparative thin layer chromatography and crystallization gave a 59% yield of 1-(2,5-di-O-trityl-beta-D-xylofuranosyl)uracil (11) and 31% of 2',5'-di-O-trityluridine (3) in crystalline form. Both products had physical constants identical to those described by Yung and Fox.^{9a} Detritylation of the crude reduction mixture by treatment with hot 80% acetic acid gave a mixture of uridine and 1-(beta-D-xylofuranosyl)uracil (12) which were cleanly separated by borate

electrophoresis.¹⁴ Quantitative estimation of the eluted spots by ultraviolet absorption showed that borohydride reduction of 6 gave 66% of the xylosyl derivative (11) and 34% of the ribose epimer 3. This result indicates that the trityl ether at C_{2'} offers less steric hindrance to approach by the reducing agent than does the uracil ring and the 5'-trityl group on the β face of the ribose ring. Borohydride reduction of free 3'-ketouridine (9) in aqueous ethanol was also studied and quantitative estimation of the two products by borate electrophoresis showed 1-(β -D-xylofuranosyl)uracil (12) and uridine to be present in 69 and 31% yields, respectively. The similarity of these results to those with the ditrityl ketone once again emphasizes the predominant directive influence of the uracil ring in the reduction process.

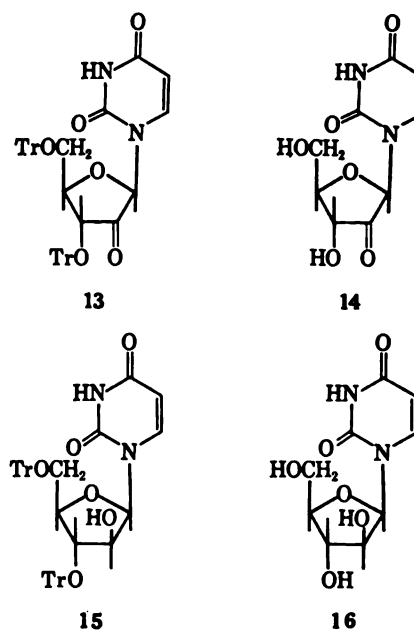


The oxidation of 3',5'-di-O-trityluridine (4) has also been accomplished. Thus treatment with DMSO-DCC in the presence of pyridinium trifluoroacetate gave some unreacted 4 together with the major product, 3',5'-di-O-trityl-2'-ketouridine (13), which was isolated in pure form in 63% yield by preparative thin layer chromatography. In spite of repeated efforts we have been unable to obtain this product in crystalline form. Its structure, however, is certain from its elemental analysis and nmr spectrum, the latter clearly showing the C_{1'} proton as a sharp singlet at δ 5.79, and the C_{3'}-H as a doublet ($J_{2',3'} = 4$ cps) at δ 4.40. Coupling between C₅H and N₃H ($J_{5,6} = 2$ cps) was again apparent but, unlike 6, the 5'-methylene protons were equivalent and appeared as a doublet ($J_{5',4'} = 4$ cps) at δ 2.91.

Oxidation of 4 with DMSO-phosphorus pentoxide at 65° was also successful and gave a 52% yield of only slightly impure 13 by precipitation from the crude, extracted reaction mixture without chromatography. Once again an appreciable amount of uracil was found in the aqueous extracts. In a similar way oxidation of 4 by DMSO-acetic anhydride gave a 56% yield of slightly impure 13 by precipitation without chromatography.

Treatment of the ditrityl ketone 13 with 2 equiv of anhydrous hydrogen chloride in chloroform at 0° led to the precipitation of chromatographically and analytically pure 2'-ketouridine (14) in 72% yield. The nmr spectrum of 14 was completely compatible with the assigned structure, the C_{1'}-H once again appearing as a sharp singlet at δ 5.42, and the C_{3'}-H as a doublet ($J = 9$ cps) at δ 7.30, both confirming the absence of a proton at C_{2'}. For convenience a tabulation of 100-Mc nmr assignments for a number of the uridine nucleosides described in this paper is given in Table I and all have been confirmed by spin-decoupling studies. A crystalline 2,4-dinitrophenylhydrazone of 2'-ketouridine was readily prepared using the extremely useful method of Parrick and Rasburn¹⁵ with DMSO as solvent. The reduction of both the ditrityl 2'-ketone 13 and the free 2'-ketone 14 has been examined using sodium borohydride in ethanol and gave results quite similar

to those with the 3'-keto compounds. Thus reduction of 13 gave predominantly 1-(3,5-di-O-trityl- β -D-arabinofuranosyl)uracil¹⁶ (15) and lesser amounts of 3',5'-di-O-trityluridine (4) which were isolated in yields of 57 and 11% by preparative thin layer chromatography. Removal of the trityl groups from these compounds gave 1-(β -D-arabinofuranosyl)uracil (16) and uridine, which were identified by comparison with authentic samples using borate electrophoresis and paper chromatography. Direct acid hydrolysis of the borohydride reduction mixture followed by borate electrophoresis showed that the products were the arabinosyl and the ribosyl derivatives in yields of 82 and 18%, respectively. In a similar way, reduction of free 2'-ketouridine (14) followed by quantitative borate electrophoresis showed the products to be arabinosyluracil (16) and uridine in yields of 90 and 10%. The predominant directive influence of the uracil ring on the reduction process is once again evident, the greater stereoselectivity being a consequence of the closer proximity of the heterocyclic base and the keto group. The reduction of 2'- and 3'-ketouridines with tritiated sodium borohydride provides a convenient synthesis of the specifically 2'-tritiated arabinosyluracil and uridine and 3'-tritiated xylosyluracil and uridine, and these results will be reported elsewhere.¹⁷



The action of alkali on the 2'-ketouridines has also been studied and, as with 3'-ketouridine, it was shown that essentially instantaneous elimination of uracil took place in either 0.01 N sodium hydroxide or in pH 10.8 buffer. Thus while 14 had the typical ultraviolet spectrum of uridine under neutral conditions the spectrum of a freshly prepared solution at pH 10.8 showed a maximum at 286 m μ typical of uracil and a second maximum at 337 m μ similar to that found with 3'-ketouridine. Uracil could be identified by paper chromatography and the other elimination product has not been studied further. A similar alkaline instability of the ditrityl 2'-ketone 13 was also observed and uracil could be readily identified by thin layer and

(15) J. Parrick and J. W. Rasburn, *Can. J. Chem.*, **43**, 3453 (1965).

(16) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 564 (1964).

(17) A. F. Cook, G. H. Jones, and J. G. Moffatt, in preparation.

L. Nmr Spectra of Uridine Nucleosides at 100 Mc^{a,b}

Compd	C ₅ H	C ₅ H	N ₃ H	C _{1'} H	C _{2'} H	C _{3'} H	C _{4'} H	C _{5'} H
Trityl- uridine (3)	5.10 (q) $J_{5,6} = 8$ cps $J_{5,8} = 2$ cps	7.66 (d) $J_{5,6} = 8$ cps	9.60 (d) $J_{3,5} = 2$ cps	6.57 (d) $J_{1',3'} = 7.5$ cps	4.49 (q) $J_{1',3'} = 7.5$ cps $J_{2',3'} = 4.5$ cps	2.77 (d) $J_{2',3'} = 4.5$ cps	3.96 (s)	3.13 (s)
Trityl- uridine (4)	5.25 (q) $J_{5,6} = 8$ cps $J_{5,8} = 2$ cps	7.56 (d) $J = 8$ cps	8.93 (d) $J_{3,5} = 2$ cps	6.00 (d) $J_{1',3'} = 5$ cps	3.70 (m)	4.30 (q) $J_{2',3'} = 4$ (5) cps $J_{3',4'} = 5$ (4) cps	3.70 (m)	3.35 (q) $J_{gem} = 10$ cps $J_{4',5'b} = 10$ cps 3.00 (q) $J_{gem} = 10$ cps $J_{4',5'a} = 3$ cps 2.61 (q) $J_{gem} = 11$ cps $J_{4',5'b} = 1.5$ cps 2.27 (q) $J_{gem} = 11$ cps $J_{4',5'a} = <1$ cps
Trityl- uridine (5)	4.85 (q) $J_{5,6} = 8$ cps $J_{5,8} = 2$ cps	... ^d	8.38 (d) $J_{3,5} = 2$ cps	... ^d	4.63 (q) $J_{1',3'} = 8$ cps $J_{2',3'} = 4$ cps	3.52 (d) $J_{2',3'} = 4$ cps $J_{3',4'} = <1$ cps	3.96 (broad s)	3.51 (q) $J_{gem} = 10$ cps $J_{4',5'b} = 4.2$ cps 3.24 (q) $J_{gem} = 10$ cps $J_{4',5'a} = 2.2$ cps 2.91 (d) $J_{4',5'} = 4$ cps
Trityl- ketouridine	5.11 (q) $J_{5,6} = 8$ cps $J_{5,8} = 2$ cps	6.77 (d) $J_{5,6} = 8$ cps	8.63 (d) $J_{3,5} = 2$ cps	5.69 (d) $J_{1',3'} = 6$ cps	4.78 (d) $J_{1',3'} = 6$ cps	...	4.30 (q) $J_{4',5'a} = 2.2$ cps $J_{4',5'b} = 4.2$ cps	3.51 (q) $J_{gem} = 10$ cps $J_{4',5'b} = 4.2$ cps 3.24 (q) $J_{gem} = 10$ cps $J_{4',5'a} = 2.2$ cps
Trityl- ketouridine	5.34 (q) $J_{5,6} = 8$ cps $J_{5,8} = 2$ cps	... ^d	8.88 (d) ^e $J_{3,5} = 2$ cps	7.57 (s)	...	4.40 (d) $J_{2',3'} = 4$ cps	4.04 (q) $J_{3',4'} = 4$ cps $J_{4',5'} = 4$ cps	2.91 (d) $J_{4',5'} = 4$ cps
ouridine	5.76 (q) $J_{5,6} = 8$ cps $J_{5,8} = 0.5$ cps	7.89 (d) $J_{5,6} = 8$ cps	11.42 (broad s)	6.05 (d) $J_{1',3'} = 8$ cps	4.24 (d) $J_{1',3'} = 8$ cps	...	4.22 (t) $J_{4',5'} = 3$ cps	3.63 (d) $J_{4',5'} = 3$ cps
ouridine	5.64 (q) $J_{5,6} = 8$ cps $J_{5,8} = 2$ cps	7.72 (d) $J_{5,6} = 2$ cps	11.49 (d) $J_{3,5} = 2$ cps	5.42 (s)	...	7.30 (d) $J_{2',3'} = 9$ cps	3.40-3.90 (m)	3.40-3.90 (m)
Trityl- syluracil	5.52 (q) $J_{5,6} = 8$ cps $J_{5,8} = 2$ cps	... ^d	8.91 (d) ^e $J_{3,5} = 2$ cps	6.10 (d) $J_{1',3'} = 2$ cps	4.11 (d) $J_{1',3'} = 2$ cps	3.18 (d) $J_{2',3'} = 3$ cps	4.05 (m)	3.46 (q) $J_{gem} = 11$ cps $J_{4',5'b} = 4.5$ cps 3.32 (q) $J_{gem} = 11$ cps $J_{4',5'a} = 5$ cps 3.29 (q) $J_{gem} = 10$ cps $J_{4',5'b} = 2$ cps 3.01 (q) $J_{gem} = 10$ cps $J_{4',5'a} = 4$ cps
Trityl- inosyl- il (15)	5.44 (q) $J_{5,6} = 8$ cps $J_{5,8} = 2$ cps	7.49 (d) $J_{5,6} = 8$ cps	9.02 (d) ^e $J_{3,5} = 2$ cps	6.12 (d) $J_{1',3'} = 3$ cps	3.70 (m)	3.96 (m)	3.90 (m)	3.42 (m) $J_{4',5'} = 2$ cps
2',5'- tylxylo- racil	5.59 (d) $J_{5,6} = 8$ cps	... ^d	N ₃ -Me at 3.31 (s)	6.09 (d) $J_{1',3'} = 2$ cps	4.12 (d) $J_{1',3'} = 2$ cps	3.27 (m)	4.06 (m)	
2',5'- tyluridine	5.12 (d) $J_{5,6} = 8$ cps	5.62 (d) $J_{5,6} = 8$ cps	N ₃ -Me at 3.40 (s)	6.59 (d) $J_{1',3'} = 8$ cps	4.49 (q) $J_{1',3'} = 8$ cps $J_{2',3'} = 5$ cps	2.84 (d) $J_{2',3'} = 5$ cps $J_{3',4'} = 0$	3.96 (broad s)	3.10 (d)

^a Spectra in deuteriochloroform unless otherwise noted. ^b (s) = singlet, (d) = doublet, (t) = triplet, (q) = quartet (m) = multiplet. ^c Tetraiodomethyl sulfoxide. No hydroxyl coupling was evident. ^d In trityl envelope. ^e Some further undefined coupling ($J = 0.5$ also present).

chromatography. Determination of the rate of imination by examination of ultraviolet spectral changes was, however, rendered impossible by the formation of an orange color and broad absorption below 270 m μ . When the alkaline treatment was on a larger scale the appearance of the orange color accompanied by the separation of a cream-colored solid. From this material it was possible to isolate a crystalline compound identified as bis(triphenylmethyl) uridine¹⁸ by physical constants, elemental analyses, and spectral data. The mechanism by which this uridine is formed remains obscure but its formation is markedly reduced by conducting the alkaline treatment under nitrogen. In addition to uracil, enylcarbinol was the only other major product

M. Gomberg, *Ber.*, 33, 3155 (1900).

identified in the methanol-soluble fractions from the alkaline reaction mixture.

A number of attempts have been made to alkylate the carbonyl group of 2',5'-di-O-trityl-3'-ketouridine so as to prepare branched chain nucleosides such as 3'-C-methyluridine (17).¹⁹ In general, however, reactions of 6 with methyl Grignard reagents in ether, tetrahydrofuran, monoglyme, or tetrahydrothiophene²⁰ under a variety of conditions led to no observable products. In most cases some precipitation resulted upon addition of the Grignard reagent but the lack of

(19) The analogous 2'-C-methyladenosine and 3'-C-methyladenosine have been recently described by other routes. See E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmerman, and F. W. Holly, *J. Am. Chem. Soc.*, 88, 4524 (1966), and E. Walton, F. W. Holly, and R. F. Nutt, Abstract 37C of the Winter Meeting of the American Chemical Society, Phoenix, Ariz., Jan 1966.

(20) A. A. Scala and E. I. Becker, *J. Org. Chem.*, 30, 3491 (1965).

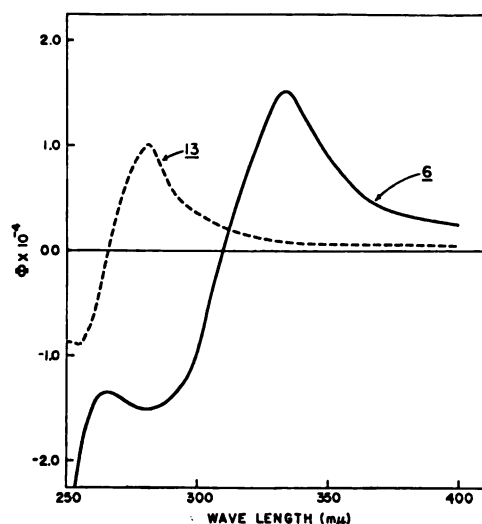
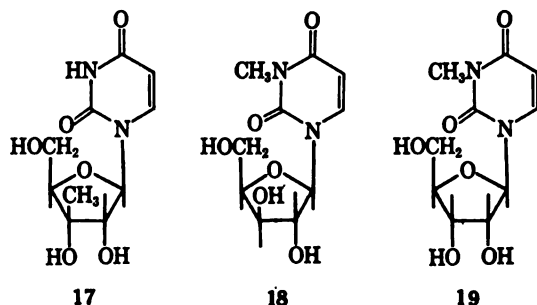


Figure 2. Optical rotatory dispersion spectra of 2',5'-di-O-trityl-3'-ketouridine (6) —, and of 3',5'-di-O-trityl-2'-ketouridine (13) ---, in methanol.

any alkylation was confirmed by thin layer chromatographic identification of unreacted starting material and by borohydride reduction to the previously described xyloside 11 and riboside 3. As yet no successful methylation has been achieved using methyl lithium in ether, tetrahydrofuran, or monoglyme. Under these conditions extensive decomposition of the ketone, and of 2',5'-ditrityluridine itself, was apparent.

An attempt was also made to react 6 and 13 with diazomethane, a reaction that has been successfully applied to alkylation of protected keto sugars.²¹ Methylation at N₃ of the uracil ring was, of course, an expected side reaction.²² After storage of 6 with an excess of diazomethane in ether thin layer chromatography indicated the presence of one major product and several minor ones. The major product was isolated, treated with sodium borohydride, and then detritylated with acetic acid giving two products. These were identified by both paper chromatography and borate electrophoresis as N₃-methyl-1-(β-D-xylofuranosyl)uracil (18) and N₃-methyluridine (19), authentic samples of which were prepared by the action of diazomethane on 2',5'-di-O-trityl-1-(β-D-xylofuranosyl)uracil (11) and 2',5'-di-O-trityluridine (3), respectively, followed by acid hydrolysis. Thus while N-methylation readily occurred, alkylation of the keto group cannot have taken place to more than a minor degree.



- (21) (a) W. G. Overend and N. R. Williams, *J. Chem. Soc.*, 3446 (1965); (b) J. J. K. Novák and F. Šorm, *Collection Czech. Chem. Commun.*, 30, 3303 (1965).
(22) J. A. Haines, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 1406 (1964).

Further work will, however, be necessary in order to fully explore the possibility of using 2'- and 3'-keto-nucleosides as synthetic intermediates.

A final point of interest concerns a comparison of the optical rotatory dispersion (ORD) spectra of the 2'- and 3'-ketouridine derivatives 6 and 13 which are shown in Figure 2. It can be seen from Figure 2 that the 2'-ketone (13) has a positive Cotton effect (molecular amplitude 191) with a zero rotation at 265 mμ similar to that of uridine²³ or 2',5'-ditrityluridine. The 3'-ketone 6, however, shows a positive Cotton effect (amplitude 307) displaced toward longer wavelengths and showing zero rotation at 310 mμ. A second maximum is also present at lower wavelengths and is more pronounced when dioxane is used as the solvent. The position of this Cotton effect indicates its relationship to the n-π* transition of the carbonyl group rather than to the uracil ring. A similar effect is noted in the optical rotatory dispersion curves of the detritylated 2'- and 3'-ketouridines (14 and 9) which showed zero rotations at 265 and 302 mμ, respectively.

Further work on the synthesis of other ketonucleosides is in progress and will be reported at a later date.

Experimental Section

Methods. Thin layer chromatography was carried out on 0.25-mm layers of Merck silica gel GF, and the products were visualized by ultraviolet absorption or by spraying with a 5% solution of ammonium molybdate in 10% sulfuric acid followed by brief heating at 150°. Preparative thin layer chromatography was done on 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF and column chromatography on Merck silica with 0.05–0.20-mm particles. Nuclear magnetic resonance spectra were obtained using solutions in deuteriochloroform (unless otherwise stated) and either a Varian A-60 or HA-100 spectrometer. Mass spectra were determined using an Atlas CH-4 spectrometer with a direct inlet system. Ultraviolet spectra were determined using a Cary Model 15 instrument and infrared spectra were obtained from potassium bromide pellets on a Perkin-Elmer Model 237 instrument. Optical rotatory dispersion spectra were obtained using a Jasco Model ORD/UV-5 instrument. Instrumental analyses were performed by the staff of the Analytical Laboratory of Syntex Research. We are particularly grateful to Mr. J. Murphy and to Drs. T. Toubé and L. Tokes for their painstaking assistance with nmr and mass spectrometry respectively. Elemental analyses were obtained from Dr. A. Bernhardt, Mulheim, Germany.

Tritylation of Uridine. Uridine (15 g, 61.5 mmoles) and triphenylmethyl chloride (51.4 g, 183 mmoles) were stored overnight in pyridine (150 ml) and then heated at 100° for 4 hr. The light brown solution was poured into vigorously stirred ice water, and the gummy precipitate was dissolved in chloroform, washed with cadmium chloride solution and then with water, dried over sodium sulfate, and evaporated to a yellow syrup. Crystallization from benzene-ether gave 13.6 g (30%) of 2',5'-di-O-trityluridine (3) which was homogeneous by thin layer chromatography using chloroform-ethyl acetate (1:1) and had mp 217–220° (lit. mp 224–225°²⁴ and 215–220°²⁵); λ_{max}^{dioxane} 261 mμ (ε 9100). The nmr spectrum in deuteriochloroform is recorded in Table I.

Chromatography of the combined mother liquors²⁴ on 1200 g of silicic acid using chloroform-ethyl acetate (1:1) gave a small amount (2%) of 2',3',5'-tri-O-trityluridine (5) of mp 286–288° from ethyl acetate after final purification by preparative thin layer chromatography using chloroform-ethyl acetate (10:1); λ_{max}^{dioxane} 261 mμ (ε 9990); [α]_D²⁵ -37.5° (c 0.1, chloroform). The nmr spectrum is recorded in Table I.

Anal. Calcd for C₄₆H₄₄N₂O₈: C, 81.65; H, 5.57; N, 2.89; O, 9.90. Found: C, 81.53; H, 5.74; N, 3.06; O, 10.15.

- (23) T. L. V. Ulbricht, J. P. Jennings, M. M. Scopes, and W. Klyne, *Tetrahedron Letters*, 695 (1964).

(24) The tritryluridine was actually found almost exclusively in the mother liquors from recrystallization of the second and third crops of 2',5'-ditrityluridine.

tylation with 80% acetic acid at 100° for 1 hr gave crystalline

Continued elution gave a further 3.8 g of crystalline trityluridine (total yield 39%) followed by 8.4 g (19%) of topographically homogeneous but apparently amorphous *O*-trityluridine (4) with $\lambda_{\text{max}}^{\text{dioxane}}$ 261 m μ (ϵ 9540) and $[\alpha]_D^{25}$ (c 0.1, chloroform). See Table I for the nmr spectral

Di-*O*-trityl-3'-ketouridine (6). (a) By the DMSO-DCC. 2',5'-Di-*O*-trityluridine (3.02 g, 4 mmoles) was dissolved in a mixture of anhydrous DMSO²⁸ (15 ml) and benzene (15 ml) in the presence of dicyclohexylcarbodiimide (2.48 g, 12 mmoles) and pyridine (32 ml, 4 mmoles). Trifluoroacetic acid (0.16 ml, 2 mmoles) was added, and the mixture was stored overnight at room temperature. Oxalic acid (1.3 g, 12 mmoles) was then added to destroy DCC and after 30 min, chloroform (50 ml) and water (50 ml) were added and dicyclohexylurea was removed by filtration. The chloroform layer was rapidly extracted twice with 1 *N* sodium carbonate and then with water. It was then dried over sodium sulfate and evaporated leaving a residual froth which was dissolved in methanol, seeded,²⁹ and allowed to slowly cool giving 1.40 g of 2',5'-di-*O*-trityl-3'-ketouridine (6) of mp 146–148° and undepressed upon recrystallization, $\lambda_{\text{max}}^{\text{methanol}}$ 261 m μ (ϵ 9600); $[\alpha]_D^{25}$ (c 0.1, chloroform). The nmr and optical rotatory dispersion spectra are shown as Figures 1 and 2 and are discussed in

Calcld for C₄₇H₃₉N₅O₈: C, 77.67; H, 5.27; N, 3.85. Found: C, 77.54; H, 5.17; N, 4.02; O, 13.01.

Mother liquors were evaporated leaving 1.8 g of a syrup that was chromatographed on four 20 × 100 cm preparative thin layer plates using chloroform-ethyl acetate (10:1) which separated 2',5'-ditrityluridine from the faster moving ketone. The faster band was eluted with acetone giving 890 mg of the homoketone which was crystallized from methanol giving 620 mg (total yield 2.02 g, 66%) of pure material.

Using DMSO-Phosphorus Pentoxide.¹¹ Phosphorus pentoxide (1.74 g, 12 mmoles) was added slowly to anhydrous dimethyl sulfoxide (75 ml). After the mixture cooled 2',5'-di-*O*-trityluridine (3.02 g, 4 mmoles) was added, and the mixture was stirred at 60° for 1 hr. Ether (200 ml) was added, and the solution was extracted three times with 5% aqueous sodium bicarbonate and then with water.

After drying with sodium sulfate and evaporating the solvent, 6.33 g of a solid froth remained and was directly crystallized from methanol with slow cooling giving 3.08 g (42%) of the ketone 6 in two crops. The mother liquors were then chromatographed on 200 g of silicic acid using chloroform-ethyl acetate giving a further 1.08 g of pure product (total yield 57%) upon recrystallization from methanol. The product was identical to that from the DMSO-DCC reaction.

Using DMSO-Acetic Anhydride.¹² 2',5'-Ditrityluridine (3.02 g, 4 mmoles) was dissolved in DMSO (65 ml) and acetic anhydride (20 ml) and stored overnight at room temperature. The acetic anhydride was then evaporated *in vacuo* leaving a residue which was dissolved in ether, extracted three times with 5% aqueous sodium bicarbonate, then with water, and dried over sodium sulfate.

After evaporation of the solvent the residue was crystallized from methanol giving 3.18 g (44%) of the pure ketone 6, mp 146–148°.

2',5'-Di-*O*-trityl-3'-oximinouridine (7). 2',5'-Di-*O*-trityl-3'-ketouridine (6, 1.01 g) was dissolved in pyridine (20 ml) together with hydroxylamine hydrochloride (1.02 g), and the mixture was stirred at 60° for 2.5 hr at which time thin layer chromatography using chloroform-ethyl acetate (6:1) showed the disappearance of the starting material and formation of a somewhat slower product. The solvent was then evaporated to dryness, and the residue was extracted with chloroform. After extraction with aqueous cadmium chloride and then water, the solution was dried with sodium sulfate and evaporated leaving 1.32 g of a white froth which was crystallized from ethanol giving 0.67 g (65%) of the pure oxime 7, mp 170–172°; $\lambda_{\text{max}}^{\text{dioxane}}$ 260 m μ (ϵ 9900); $[\alpha]_D^{25}$ +38.2° (c 0.1, chloroform).

Calcld for C₄₇H₃₉N₅O₈: C, 76.11; H, 5.26; N, 5.67. Found: C, 75.94; H, 5.26; N, 5.80.

ORD spectrum in dioxane showed a positive Cotton effect with a maximum at 282 m μ (molecular rotation +27,000°), zero at 260 m μ , and a shoulder at 245 m μ (molecular rotation +10,000°).

Distilled and stored over Linde Molecular Sieve Type 4A.

Initial seeds were obtained by crystallization of material from a reaction that was purified by preparative thin layer chromatography using chloroform-ethyl acetate (8:1).

–23,500°). The nmr spectrum in DMSO-*d*₆ showed the oximino hydrogen as a singlet at δ 11.77.

Attempted reduction of 7 with hydrogen and palladium on barium sulfate²⁷ in ethyl acetate was unsuccessful and using lithium aluminum hydride in tetrahydrofuran there was extensive loss of ultraviolet-absorbing materials.

3'-Ketouridine (9). 2',5'-Ditrityl-3'-ketouridine (1.228 g, 1.69 mmoles) was dissolved in dry chloroform (20 ml) and cooled to 0°. A freshly standardized solution of hydrogen chloride in chloroform (9.3 ml of 0.40 *N*, 3.72 mmoles) was then added dropwise with stirring over 20 min, and the mixture was stirred for 1 hr more. The resulting white precipitate was then collected by centrifugation, washed six times with 25-ml portions of ether, and dried *in vacuo* over potassium hydroxide giving 404 mg (99%) of 3'-ketouridine as an amorphous white solid that was not obtained crystalline but melted at 130–138°.

Anal. Calcd for C₉H₁₀N₂O₆: C, 44.63; H, 4.16; N, 11.57. Found: C, 44.76; H, 4.32; N, 11.51.

The product was homogeneous by thin layer chromatography with chloroform-methanol (4:1) having an *R_f* identical with that of uracil, and on paper using *n*-butyl alcohol-acetic acid-water (5:2:3) where it had *R_f* 0.41, just faster than uridine. Using the same solvent system with paper previously impregnated with sodium bisulfite it had a very low *R_f* while uracil moved normally. On paper electrophoresis¹⁴ in 1 *M* boric acid adjusted to pH 6.0 using 1000 v for 4 hr 9 had a mobility of 1.2 relative to uridine while uracil remained on the origin; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 261 m μ (ϵ 9400); $[\alpha]_D^{25}$ +71.2° (c 0.1, water).

The ORD spectrum in water showed a positive Cotton effect with a maximum at 316 m μ (molecular rotation +4400°), zero rotation at 292 m μ , and a minimum at 251 m μ (molecular rotation –8420°).

Borohydride Reduction of 6 and 9. (a) 2',5'-Di-*O*-trityl-3'-ketouridine was dissolved in ethanol (15 ml) and sodium borohydride (286 mg) was added. After 1 hr at room temperature the solution was partitioned between chloroform and water, and the chloroform solution was washed three times with water, dried over sodium sulfate, and evaporated to dryness. Crystallization from benzene-ether gave a first crop (55 mg) of pure 2',5'-di-*O*-trityluridine, mp 219–221°, undepressed on admixture with an authentic sample. The infrared spectra were also identical. The mother liquors were then chromatographed on three 20 × 100 cm preparative thin layer plates using carbon tetrachloride-acetone (4:1) which clearly resolved two bands. Elution of the faster band with acetone gave a further 35 mg of 2',5'-ditrityluridine after crystallization from ether (total yield 31%). The slower band gave, after elution with acetone, 210 mg of a crystalline residue which was recrystallized from ethanol giving 170 mg of pure 1-(2,5-di-*O*-trityl- β -D-xylofuranosyl)uracil, mp 150–154° (lit.²⁶ mp 151.5–153.5°). The nmr spectrum indicated the presence of 1 mole of ethanol of crystallization rather than one-half mole as described previously;²⁶ $\lambda_{\text{max}}^{\text{dioxane}}$ 258 m μ (ϵ 11,760); $[\alpha]_D^{25}$ +49.6° (c 0.1, chloroform). The ORD spectrum in methanol showed a positive Cotton effect with a maximum at 276 m μ (molecular rotation +20,100°), zero rotation at 272 m μ , and a minimum at 242 m μ (molecular rotation –20,100°).

A small portion (11 mg) of the crude reduction mixture was also treated with 80% acetic acid (1 ml) at 100° for 1 hr, evaporated to dryness, and examined by electrophoresis in pH 6.0 borate buffer at 1000 v for 4 hr. Elution of the two resulting spots which had mobilities of 1.0 and 0.67 relative to uridine showed the reduction to give 34% uridine and 66% 1- β -D-xylofuranosyluracil (12).²⁸

(b) 3'-Ketouridine (7.2 mg) was dissolved in water (1 ml) together with sodium borohydride (8 mg). After 30 min the solution was neutralized with Dowex 50 (H⁺) resin and directly examined by borate electrophoresis. Quantitative elution of the resulting spots with 0.1 *N* hydrochloric acid showed the products to be 31% uridine and 69% xylosyluracil.

Action of Alkali on 6 and 9. (a) 2',5'-Di-*O*-trityl-3'-ketouridine was dissolved in methanol at a concentration of 106.3 μ g/ml and diluted with an equal volume of 0.2 *N* methanolic sodium hydroxide. The ultraviolet spectrum of the solution was recorded at intervals over 2 hr, and the course of the reaction was followed by the ratio of absorbance at 285 and 260 m μ . The initial 285:260 ratio was 0.17 and the final value was 1.40. The half-time of the reaction was 7 min, and the product was identified as uracil by paper and thin layer chromatography.

(27) R. Kuhn and H. J. Hass, *Angew. Chem.*, **67**, 785 (1955).

(28) We are grateful to Dr. J. J. Fox for an authentic sample of 12.

(b) An aqueous solution of 3'-ketouridine in water at a concentration of 20.20 $\mu\text{g/ml}$ (λ_{max} 262 $\text{m}\mu$) was diluted with an equal volume of 0.05 *M* carbonate buffer (pH 10.8). Within 2 min the spectrum showed the complete disappearance of the 262- $\text{m}\mu$ peak with formation of two new maxima at 286 and 336 $\text{m}\mu$ of roughly equal intensities. Paper chromatographic examination of a more concentrated solution showed a strong spot identical with uracil.

3',5'-Di-O-trityl-2'-ketouridine (13). (a) Using DMSO-DCC. 3',5'-Di-O-trityluridine (728 mg, 1 mmole) was dissolved in a mixture of DMSO (10 ml) and benzene (10 ml) containing DCC (0.62 g, 3 mmoles) and pyridine (0.075 ml, 1 mmole). Trifluoroacetic acid (0.04 ml, 0.5 mmole) was added and after 16 hr at room temperature oxalic acid (0.38 g, 3 mmoles) was added. After 30 min the mixture was diluted with chloroform (50 ml), filtered, and extracted with aqueous sodium bicarbonate, followed by water. The chloroform solution was dried over sodium sulfate and evaporated *in vacuo* leaving 1.02 g of a white froth that was separated by preparative thin layer chromatography on three 20 \times 100 cm plates using two consecutive developments with chloroform-ethyl acetate (9:1). The slower band was eluted with acetone giving 217 mg (30%) of unreacted 3',5'-ditrityluridine while the faster band gave 455 mg (63%) of chromatographically homogeneous 3',5'-di-O-trityl-2'-ketouridine which we have been unable to crystallize but which melted at 130–135°; $\lambda_{\text{max}}^{\text{MeOH}}$ 260 $\text{m}\mu$ (ϵ 10,900); $[\alpha]_{\text{D}}^{25} +30.8^\circ$ (*c* 0.1, chloroform).

Anal. Calcd for $\text{C}_{47}\text{H}_{40}\text{N}_4\text{O}_8$: C, 77.67; H, 5.27; N, 3.85. Found: C, 77.77; H, 5.50; N, 3.91.

The ORD spectrum is shown in Figure 2, and significant features of the nmr spectrum are discussed in the text. The carbonyl group appeared in the infrared spectrum at 1785 cm^{-1} (KBr) and at 1790 cm^{-1} (CCl_4).

(b) Using DMSO-Phosphorus Pentoxide. 3',5'-Di-O-trityluridine (3.85 g, 5.3 mmoles) was added to a solution of phosphorus pentoxide (0.90 g, 6.3 mmoles as P_2O_5) in DMSO (25 ml), and the solution was heated for 1 hr at 65°. It was then diluted with ether, washed with aqueous sodium bicarbonate, dried, and evaporated leaving an off-white froth (2.77 g) which contained several minor by-products in addition to 13. This was dissolved in ether and precipitated with hexane giving 1.99 g (52%) of 13 of sufficient purity for most purposes. Completely pure product could be obtained by preparative thin layer chromatography.

(c) Using DMSO-Acetic Anhydride. 3',5'-Di-O-trityluridine (1.46 g, 2 mmoles) was treated overnight at room temperature with a mixture of DMSO (10 ml) and acetic anhydride (4 ml). The acetic anhydride was largely evaporated *in vacuo*, and the residue was dissolved in ether and extracted twice with aqueous sodium bicarbonate and then with water. Evaporation of the solvent left 1.39 g of a froth which was dissolved in ether and precipitated with hexane giving 858 mg (56%) of 13 containing only minor impurities. Detritylation of the nonprecipitated fraction gave a complex mixture of products that was not studied further.

2'-Ketouridine (14). 3',5'-Di-O-trityl-2'-ketouridine (597 mg, 0.82 mmole) was dissolved in dry chloroform (20 ml) and cooled to 0°. A solution of hydrogen chloride in chloroform (8 ml of 0.23 *N*, 1.84 mmoles) was added dropwise over 15 min and stirring was continued for a further 30 min. The precipitated solid was collected by centrifugation and washed six times with 25-ml portions of ether. The white residue was then dried *in vacuo* over potassium hydroxide giving 144 mg (72%) of 2'-ketouridine (mp 186–189°) which ran as a single spot just ahead of uridine on borate electrophoresis and as a somewhat elongated spot between uridine and uracil on thin layer chromatography using chloroform-methanol (4:1); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 261 $\text{m}\mu$ (ϵ 9600); $[\alpha]_{\text{D}}^{25} +43.7^\circ$ (*c* 0.1, water).

Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_6$: C, 44.63; H, 4.16; N, 11.57. Found: C, 44.48; H, 4.31; N, 11.51.

The ORD spectrum in water showed a positive Cotton effect with a maximum at 274 $\text{m}\mu$ (molecular rotation +11,200°), zero rotation at 248 $\text{m}\mu$, and a minimum at 234 $\text{m}\mu$ (molecular rotation –3900°).

Reaction¹⁵ of 14 (27 mg) with 2,4-dinitrophenylhydrazine (20 mg) and concentrated hydrochloric acid (10 μl) in DMSO (1 ml) at room temperature for 2 hr gave the crystalline 2,4-dinitrophenylhydrazone, mp 174–177° from ethanol; $\lambda_{\text{max}}^{\text{MeOH}}$ 355 $\text{m}\mu$ (ϵ 21,400), 254 $\text{m}\mu$ (ϵ 18,700); $\lambda_{\text{max}}^{\text{N}_2\text{NaOH}}$ 437 $\text{m}\mu$ (ϵ 18,400), 250 $\text{m}\mu$ (ϵ 16,300), if taken immediately. On standing the 437- $\text{m}\mu$ peak slowly disappears and is replaced by peaks at 336 and 285 $\text{m}\mu$ (uracil?).

Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_6\text{O}_8$: C, 42.64; H, 3.34; N, 19.90. Found: C, 42.68; H, 3.33; N, 19.00.

Borohydride Reduction of 13 and 14. (a) 3',5'-Di-O-trityl-2'-ketouridine (13, 339 mg) was treated at room temperature for 1 hr with sodium borohydride (300 mg) in ethanol (10 ml). The

mixture was then partitioned between chloroform and water the organic phase was washed with water, dried, and evaporated leaving 340 mg of a white froth. Most of this (300 mg) was matographed on three 20 \times 100 cm silica plates using successive developments with carbon tetrachloride-acetone which cleanly separated two very close bands. The faster was eluted with acetone giving 33 mg (11%) of 3',5'-ditrityluridine which was identical with an authentic sample by thin layer chromatography and by its infrared spectrum. Elution of the slower gave 172 mg (57%) of chromatographically homogeneous di-O-trityl- β -D-arabinofuranosyluracil (15)¹⁶ which melted at 130° but could not be obtained crystalline; $\lambda_{\text{max}}^{\text{MeOH}}$ 261 $\text{m}\mu$ (ϵ 10,900); $[\alpha]_{\text{D}}^{25} +11.1^\circ$ (*c* 0.1, chloroform).

Anal. Calcd for $\text{C}_{47}\text{H}_{40}\text{N}_4\text{O}_8$: C, 77.47; H, 5.49; N, 3.93. Found: C, 76.73; H, 5.82; N, 3.93.

The ORD spectrum in dioxane showed a positive Cotton effect with a maximum at 280 $\text{m}\mu$ (molecular rotation +9900°) rotation at 272 $\text{m}\mu$, and a minimum at 252 $\text{m}\mu$ (molecular rotation –18,400°). The nmr spectrum is recorded in Table I.

Detritylation of a small portion of the crude reduction product was effected by treatment with 80% acetic acid at 100° for 2 hr, and after removal of triphenylmethanol by chloroform extraction the products were separated by borate electrophoresis. Qualitative elution of the spots showed the products to be 18% uracil and 82% 1-(β -D-arabinofuranosyl)uracil (12).

(b) 2'-Ketouridine (6 mg) was treated for 30 min at room temperature with 7 mg of sodium borohydride in 80% ethanol. The material was then passed through a small column of 100 μ (H+) resin, evaporated to dryness, and evaporated four times with small portions of methanol. Borate electrophoresis and titative elution of the spots showed the products to be 10% uracil and 90% 1-(β -D-arabinofuranosyl)uracil.

Action of Alkali on 13. 3',5'-Di-O-trityl-2'-ketouridine (1.46 g) was dissolved in methanol (3.6 ml) and 1 *N* methanolic sodium hydroxide (0.4 ml) was added. Within a minute the solution turned yellow and then orange and a precipitate separated. After 10 min the mixture was cooled in ice, and the solid was collected by centrifugation. The precipitate was washed four times with methanol and dried *in vacuo* leaving a cream solid (23 mg) contained about 4 mg of uracil (ultraviolet and chromatographic) and no triphenylmethanol. The solid was washed with chloroform, and the soluble portion was evaporated leaving 12 mg of crystalline bis(triphenylmethyl) peroxide that was recrystallized from chloroform-methanol and had mp 186–188° (lit.¹⁸ mp 186–188°). The nmr spectrum showed only aromatic protons and the spectrum (at 15 ev) showed intense peaks at *m/e* 259 (Ph, relative intensity 100%) and *m/e* 243 (relative intensity 73%, P).

Anal. Calcd for $\text{C}_{38}\text{H}_{30}\text{O}_4$: C, 88.00; H, 5.83. Found: C, 88.28; H, 5.62.

The methanol-soluble fraction from the alkaline reaction contained triphenylmethanol and uracil as shown by thin layer and paper chromatography.

Action of Diazomethane on 13. 2',5'-Di-O-trityl-3'-ketouridine (400 mg) was treated overnight in ether (10 ml) with an excess of diazomethane. Thin layer chromatography showed the presence of one major product and several minor ones. The major product was isolated by preparative thin layer chromatography using two developments with chloroform-benzene (1:1) giving a chromatographically homogeneous product that contained some aliphatic impurities by nmr spectroscopy. This product had $\lambda_{\text{max}}^{\text{MeOH}}$ 261 $\text{m}\mu$ which gradually changed to a broad maximum at 265–270 $\text{m}\mu$ in alkali during 10–15 min. Treatment of this product with sodium borohydride followed by detritylation with 80% acetic acid at 100° for 30 min gave a mixture of 1-(β -D-xylofuranosyl)uracil (see below) and *N*-methyluridine (roughly 1:1) which were readily separated by paper chromatography using *n*-propyl alcohol-concentrated ammonium hydroxide-water (4:1) (*R*_f's 0.75 and 0.70, respectively), in *n*-butyl alcohol-acetic acid (5:2:3) (*R*_f's 0.64 and 0.59), or by borate electrophoresis (mobilities of 1.03 and 0.80 relative to uridine). In all cases the products behaved identically with authentic samples.

2',5'-Di-O-trityl-*N*-methyluridine. 2',5'-Di-O-trityluridine (1.46 g) was stored overnight in a mixture of chloroform (2 ml) and ether (4 ml) containing an excess of diazomethane. The mixture was then evaporated leaving a crystalline residue that was recrystallized from ether giving 2',5'-di-O-trityl-*N*-methyluridine (10 mg) mp 243–245°; $\lambda_{\text{max}}^{\text{MeOH}}$ 262 $\text{m}\mu$ (ϵ 7940), unchanged in alkali; $[\alpha]_{\text{D}}^{25} +90^\circ$ (*c* 0.1, chloroform).

Anal. Calcd for $\text{C}_{48}\text{H}_{46}\text{N}_4\text{O}_8$: C, 77.60; H, 5.70; N, 3.91. Found: C, 77.84; H, 5.62; N, 3.91.

ORD spectrum showed a positive Cotton effect with a maximum at 276 $m\mu$ (molecular rotation $+28,500^\circ$), zero rotation at λ_c , and a minimum at 232 $m\mu$ (molecular rotation $-40,500^\circ$). Table I for the nmr spectrum.

Hydrolysis with 80% acetic acid at 100° for 30 min gave N-methyluridine (19) that was chromatographically identical with the major product from the action of diazomethane on uridine.

5-Di-O-trityl- β -D-xylofuranosyl)-N-methyluracil. 1-(2,5-Di-O-trityl- β -D-xylofuranosyl)uracil (11, 57 mg) was treated overnight with a mixture of chloroform (1 ml), methanol (1 ml), and ether (2 ml) in the presence of an excess of diazomethane. Evaporation of the solvent left a solid residue (63 mg) which was homogeneous by thin layer chromatography using chloroform-ethyl acetate (20:1). Crystallization from ether gave 43 mg of 1-(2,5-di-O-trityl- β -D-xylofuranosyl)-N-methyluracil, mp $244-246^\circ$; λ_{max}^{MeOH} 260 $m\mu$ (ϵ 9900), unchanged in alkali, $[\alpha]_D^{25} +51.9^\circ$ (c 0.1, chloroform).

Anal. Calcd for $C_{48}H_{48}N_2O_{10}$: C, 77.60; H, 5.70; N, 3.77. Found: C, 77.39; H, 5.64; N, 3.73.

The ORD spectrum in methanol showed a positive Cotton effect with a maximum at 273 $m\mu$ (molecular rotation $+14,900^\circ$), zero rotation at 256 $m\mu$, and a minimum at 236 $m\mu$ (molecular rotation $-17,200^\circ$). The mass spectrum (15 ev) showed an intense peak at m/e 126 corresponding to N-methyluracil.

Detritylation with 80% acetic acid at 100° for 30 min gave 1-(β -D-xylofuranosyl)-N-methyluracil which ran as a single spot on paper chromatograms and on borate electrophoresis but was not isolated in crystalline form.

An Electron Spin Resonance Study of the Radical Cations of Some *p*-Dialkoxybenzenes

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Abstract: The electron spin resonance spectra of some *p*-dialkoxybenzene cation radicals in aluminum chloride-nitromethane have been investigated. The spectra can be interpreted by assuming *cis-trans* isomerism. The temperature dependence of the β -proton splitting constants, observed for the larger alkoxy compounds (ethoxy upwards), is explained by assuming hindered rotation of the alkoxy side chain.

In a continuation of earlier work,^{1,2} the cation radicals of some *p*-dialkoxybenzenes have been studied. The aim was to investigate how larger alkyl groups might affect properties such as *g* values, spin densities, conformations, and the free energy difference between conformations. These systems also illustrate some of the advantages of the aluminum chloride-nitromethane system for producing cation radicals.

Experimental Section

Hydroquinone, *p*-dimethoxybenzene, *p*-diethoxybenzene, and butoxybenzene were commercially available samples, which were recrystallized several times. The other *p*-dialkoxybenzenes were prepared by the Williamson reaction^{3,4} and purified by standard methods.

Sulfuric acid was best grade commercially available 98% free acid. Dideuterosulfuric acid was a commercially available sample (Fluka). Sulfuric acid spectra were determined in a 1M solution, ca. 0.04 ml of which was placed in a glass reaction tube which was then inserted in the spectrometer cavity. Nitromethane and aluminum chloride (anhydrous) were Fisher reagent grade. Nitromethane was dried (CaH_2) and deoxygenated by drying (H_2SO_4 , Al_2O_3) nitrogen gas through the solution, and by degassing under vacuum. Radical formation was carried out (cf. ref 5) in an inverted U tube (diameter ca. 8 mm), one arm of which was filled with aluminum chloride and the other with *p*-benzene (ca. 20 and 5 mg, respectively). The U tube was connected to a vacuum line (ca. 0.5 mm) and nitromethane (ca. 10 mm) was distilled into the mixture. The reaction proceeded at room temperature, and the solution was subsequently transferred under vacuum to a capillary tube (diameter ca. 1 mm) which was directly to one arm of the U tube. The capillary tube was

then placed in the esr cavity. If necessary, concentrations were varied by distilling solvent from one arm to the other.

Esr spectra were determined on a JES-3BX spectrometer at 100-kc/sec modulation using a field-selector unit. *g* values were obtained in a dual cavity with reference to Fremy's salt which was used as a secondary standard being first calibrated against the spectrum of anthracene (positive ion) for which an accurate *g* value (2.002565 ± 0.000006) is available.⁶ The magnetic field was calibrated with both Fremy's salt ($a_N = 13.07$ gauss)⁷ and an nmr probe, and values of the splitting constants are believed accurate to $\pm 0.5\%$ (for splitting constants >1 gauss). The magnetic field was swept in both directions, and the first derivative spectra of the energy absorption were recorded in the relevant figures. Radical concentrations were estimated by overmodulating the signal and comparing it, under similar conditions, with a standard diphenylpicrylhydrazyl (DPPH) sample.

Spectra were simulated on an IBM 7040 computer, with a modified program kindly supplied by Dr. Lawrence C. Snyder of the Bell Telephone Laboratories.⁸ The output data from the IBM 7040, in the form of punched cards, were plotted via an IBM 1710 computer. Approximate splitting constants were obtained directly from the observed spectra, usually by careful inspection of the wings. Sometimes, however, such direct measurement is not possible, and it is necessary to estimate splitting constants by measuring the total width of the spectrum. It is these values which are then slightly altered, within the experimental error, until a good simulated spectrum is obtained. Molecular orbital calculations were carried out by the self-consistent-field method of McLachlan⁹ on an IBM 7040 computer, with a program kindly supplied by Dr. J. M. Fritsch¹⁰ of the University of Kansas.

Results and Discussion

***p*-Dihydroxybenzene.** The spectrum of the cation radical of hydroquinone in aluminum chloride-nitro-

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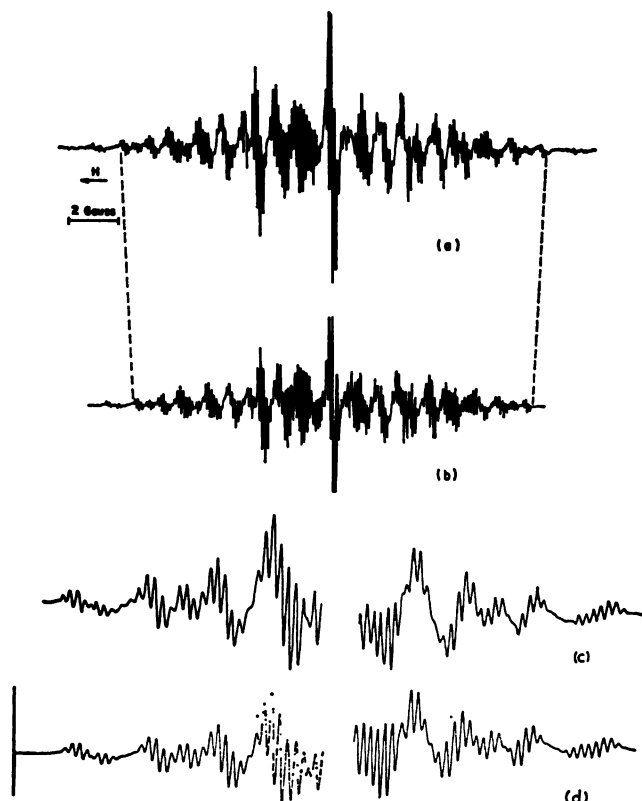


Figure 1. (a) The observed esr spectrum of the *p*-diethoxybenzene cation radical at -49° ; (b) a computed spectrum using the parameters given in the text; (c) the experimental wing lines using increased amplification; and (d) the computed wing lines.

methane has previously been interpreted in terms of *cis-trans* isomerism.² Table I shows the temperature dependence of the splitting constants, indicating significant changes for the hydroxy splittings. A similar trend has been observed for other *p*-dihydroxy-substituted benzenes.¹¹

Table I. Variation of Splitting Constants with Temperature for the Hydroquinone Cation Radical in Aluminum Chloride-Nitromethane

Temp, °C	Total width, ^a gauss	Sum of ring splittings, ^b gauss	Hydroxy splittings, ^c gauss
-103 (Semisolid)	15.726	9.040	3.343
-68	15.632	9.026	3.303
-55	15.596	8.998	3.299
-51	15.566	8.972	3.297
-32	15.567	9.000	3.283
-16.5	15.515	8.988	3.263
-5	15.464	8.988	3.238
+2.5	15.474	8.986	3.244
+14	15.479	8.990	3.245
+28	15.422	8.990	3.216

^a Estimated experimental error = ± 0.08 ; *i.e.*, significant trend.

^b Estimated experimental error = ± 0.05 ; *i.e.*, no significant trend.

^c Estimated experimental error = ± 0.02 ; *i.e.*, significant trend.

p-Dimethoxybenzene. The spectrum of the cation radical of this compound, previously investigated in sulfuric acid,¹ has been further studied in aluminum chloride-nitromethane. Splitting constants under var-

(11) P. D. Sullivan, unpublished information.

Table II. Variation of Splitting Constants with Temperature for the *p*-Dimethoxybenzene Cation Radical

Splitting constants, gauss		Aluminum chloride-nitromethane			Ca. 50% CCl ₄ added	
		-60°	-34°	-10°	-9°	Concd H ₂ SO ₄ $+20^\circ$
$a_{\text{H}}(3,5)$	T ^a	1.599	1.598	1.599	1.588	1.499
$a_{\text{H}}(3,5)$	T	2.921	2.940	2.926	2.960	2.990
Sum of ring splittings	T	9.040	9.076	9.050	9.096	8.978
a_{CH_3}	T	3.443	3.432	3.437	3.472	3.450
Total width	T	29.700	29.667	29.671	29.931	29.680
$a_{\text{H}}(6,8)$	C	1.876	1.876	1.859	1.866	1.810
$a_{\text{H}}(3,5)$	C	2.643	2.664	2.635	2.634	2.680
Sum of ring splittings	C	9.038	9.060	8.990	9.005	8.980
a_{CH_3}	C	3.286	3.280	3.289	3.334	3.330
Total width	C	28.754	28.739	28.723	29.009	28.960
$\Delta\text{CH}_3 = a_{\text{CH}_3}(\text{T}) - a_{\text{CH}_3}(\text{C})$		0.157	0.152	0.148	0.148	0.120

^a For nomenclature used in this and subsequent tables, see ref 1; also T = *trans* and C = *cis*, throughout.

ious conditions are shown in Table II; the data indicate no significant changes with temperature.

p-Diethoxybenzene. Figures 1a and 1c show the spectrum of the cation radical of *p*-diethoxybenzene in aluminum chloride-nitromethane. The spectrum can be interpreted in terms of two species A and B with splitting constants (in gauss) as follows: species A, $a_{\text{H}} = 4.104$, $a_{\text{H}} = 2.922$, $a_{\text{H}} = 1.614$, and $a_{\text{H}} = 0.152$; species B, $a_{\text{H}} = 3.802$, $a_{\text{H}} = 2.660$, $a_{\text{H}} = 1.880$, and $a_{\text{H}} = 0.152$. Figures 1b and 1d show a simulated spectrum using these parameters and assuming a line width of 73 mgauss, a displacement of centers of 35 mgauss, and an intensity ratio A:B = 56:44.

The two species are assumed to correspond to *trans* and *cis* isomers. The assignment of the species to the isomers is made by analogy with previous calculations.^{1,2} For the cation radicals of *p*-dimethoxybenzene¹ and hydroquinone,² empirical molecular orbital calculations following Stone and Maki¹² predicted that the species with the larger ratio of ring proton splitting constants is the *trans* isomer. On this basis, species A is the *trans* and B the *cis* isomer (see also later discussion). Assignments shown in Tables II-V are also based on these calculations.^{12a}

In sulfuric acid, a similar but less intense signal was observed (see Table III for parameters). In D₂SO₄, a broad five-line spectrum (intensity ratio *ca.* 1:4:6:4:1) was obtained and, since rapid exchange of the ring protons is known to occur for compounds of this type,¹ the main splittings are ascribed to the four CH₃ protons (β -protons) of the alkoxy groups. The splitting constants are, moreover, *ca.* 3.7 gauss, corresponding to the splitting constants of the four equivalent protons used in computing the spectrum shown in Figure 1b.

The temperature dependence of the spectrum (Table III) is illustrated in Figures 2a, 2b. The data show that the ring splitting constants remain approximately constant, but that the β -proton splittings vary significantly.

p-Di-*n*-propoxy-, *p*-Di-*n*-butoxy-, *p*-Di-*n*-pentoxy-, *p*-Di-*n*-hexoxy-, *p*-Di-*n*-heptoxy-, and *p*-Di-*n*-octoxybenzene. The spectra of all these cations proved to be

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(12a) NOTE ADDED IN PROOF. A recent study¹¹ of 2,3- and 2,5-dimethylhydroquinones which exist only in the *cis* and *trans* form, respectively, afforded results consistent with the present assignments.

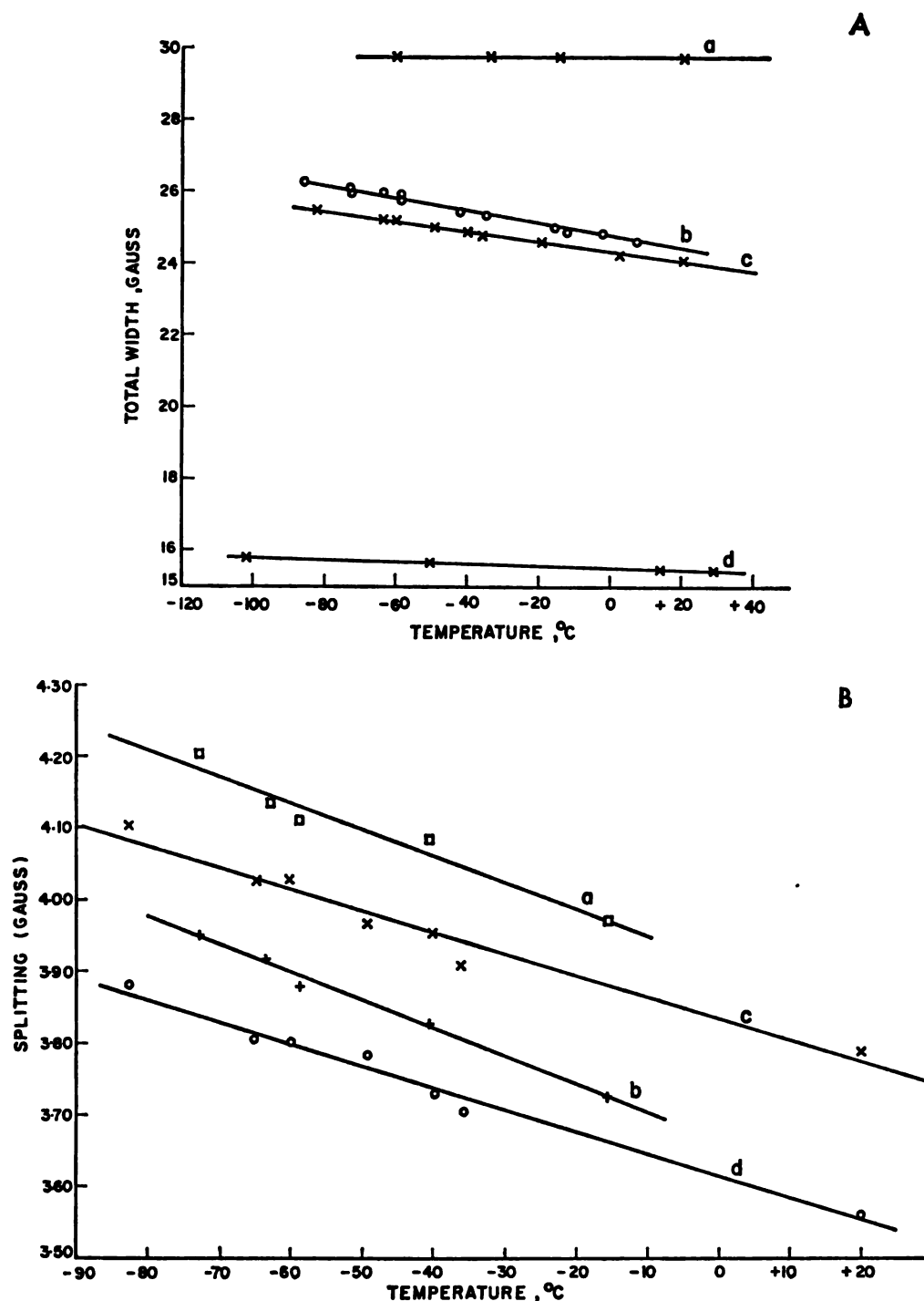


Figure 2. (A) Plots of the total width of the spectra against temperature for the cation radicals of (a) *p*-dimethoxybenzene, (b) *p*-di-*n*-butoxybenzene, (c) *p*-diethoxybenzene, (d) *p*-dihydroxybenzene. (B) Plots of the β -proton splitting constants against temperature for (a) *trans*- and (b) *cis*-*p*-di-*n*-butoxybenzene, and (c) *trans*- and (d) *cis*-*p*-diethoxybenzene, respectively.

similar under our conditions. Splitting constants are listed in Table IV. The spectrum of the *p*-di-*n*-octoxybenzene cation is shown in Figures 3a and 3c and a simulated spectrum with the following parameters is shown in Figures 3b and 3d. For species A (in gauss), $a_{4H} = 4.168$, $a_{2H} = 2.930$, $a_{1H} = 1.622$, $a_{1H} = 0.118$; for species B, $a_{4H} = 3.968$, $a_{2H} = 2.660$, $a_{1H} = 1.880$, $a_{1H} = 0.118$; a line width of 85 mgauss, a displacement of centers of 35 mgauss, and an intensity ratio A:B = 61:39 were assumed.

The temperature dependence of the splitting constants are shown in Table V and Figure 2, and again a change in the β -proton splitting constant is noted.

In sulfuric acid a weak signal is obtained, but the broadness of the lines precludes any accurate measurement of splitting constants. In D_2SO_4 , a five-line spectrum (intensity ratio *ca.* 1:4:6:4:1) with a splitting constant of *ca.* 3.7 gauss was again obtained.

***p*-Diisopropoxybenzene.** The spectrum of the cation radical of *p*-diisopropoxybenzene in sulfuric acid is shown in Figure 4b. It is not well resolved and a complete analysis has not been carried out, although the spectrum appears to consist of more than one component, consistent with the occurrence of *cis* and *trans* isomers. In D_2SO_4 , only three broad lines, with a splitting constant of 2.74 ± 0.05 gauss, are observed.

Table III. Temperature Dependence of Splitting Constants for the *p*-Diethoxybenzene Cation Radical

Splitting constants, gauss		Aluminum chloride-nitromethane							H ₂ SO ₄ , +20°
		-82.5°	-64°	-60°	-49°	-40°	-36°	-19°	
<i>a</i> _{H(a,s)}	T	1.614	1.616	1.613	1.606	1.602	1.612	x ^a	1.587
<i>a</i> _{H(s,s)}	T	2.925	2.928	2.921	2.921	2.911	2.929	x	2.885
Total ring splittings	T	9.078	9.088	9.068	9.042	9.026	9.082	x	8.944
<i>a</i> _{β-CH₂}	T	4.103	4.023	4.027	3.969	3.951	3.908	x	3.789
Total width	T	25.491	25.182	25.177	24.927	24.832	24.714	24.514	24.100
<i>a</i> _{H(s,s)}	C	1.883	1.886	1.879	1.875	1.901	1.887	x	1.812
<i>a</i> _{H(s,s)}	C	2.639	2.649	2.659	2.640	2.637	2.661	x	2.661
Total ring splittings	C	9.044	9.070	9.076	9.030	9.076	9.096	x	8.946
<i>a</i> _{β-CH₂}	C	3.883	3.807	3.801	3.786	3.730	3.704	x	3.561
Total width	C	24.618	24.337	24.337	24.176	23.995	23.913	23.688	23.190
Δ <i>CH₂</i> = <i>a</i> _{β-CH₂} (T) - <i>a</i> _{β-CH₂} (C)		0.220	0.216	0.226	0.183	0.221	0.204	0.202	0.228
γ _{CH₂}		0.154	0.153	0.148	0.146	x	0.144	x	0.131

^a x = Not measured.

and corresponding lines are also observed in sulfuric acid (cf. Figures 4a and b). By analogy with previous spectra, this splitting is assigned to the two β-protons of the alkoxy groups.

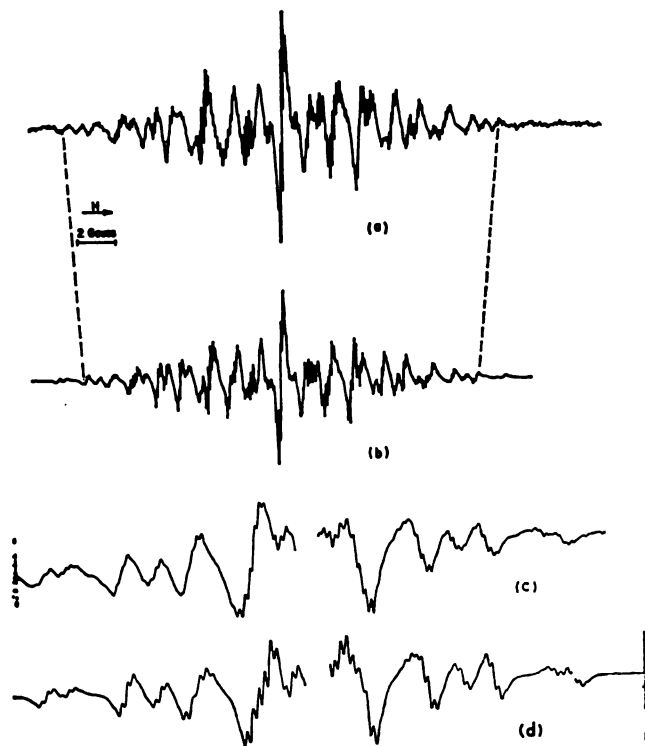


Figure 3. (a) An experimental esr spectrum of the *p*-di-*n*-octoxybenzene cation radical at -63°; (b) a computed spectrum using the parameters given in the text; (c) the experimental wing lines using increased modulation and amplification; and (d) the computed wing lines.

The temperature dependence of the splitting shows a reverse trend to that observed for the other *p*-dialkoxybenzenes; it decreases from 2.70 ± 0.05 gauss at 0° to 2.50 ± 0.05 gauss at -50° (cf. Tables III and V).

The Formation of Cation Radicals in Sulfuric Acid and Aluminum Chloride-Nitromethane. For the compounds studied, the same radicals were obtained in both systems. However, the radical concentrations in $\text{AlCl}_3\text{-CH}_3\text{NO}_2$ approximated 100%, whereas in

Table IV. Splitting Constants for the Radical Cations of *p*-Di-*n*-propoxy-, *p*-Di-*n*-butoxy-, *p*-Di-*n*-heptoxy-, and *p*-Di-*n*-octoxybenzenes in Aluminum Chloride-Nitromethane

Splitting constants, gauss		Benzene radical cations			
		<i>p</i> -Di- <i>n</i> -propoxy -58°	<i>p</i> -Di- <i>n</i> -butoxy -58°	<i>p</i> -Di- <i>n</i> -heptoxy -73°	<i>p</i> -Di- <i>n</i> -octoxy -63°
<i>a</i> _{H(a,s)}	T	1.645	1.630	1.664	1.675
<i>a</i> _{H(s,s)}	T	2.965	3.000	3.000	3.031
Total ring splittings	T	9.220	9.260	9.320	9.410
<i>a</i> _{β-CH₂}	T	4.114	4.102	4.188	4.135
Total width	T	25.675	25.670	26.074	25.950
<i>a</i> _{H(s,s)}	C	1.820	1.864	1.886	1.899
<i>a</i> _{H(s,s)}	C	2.590	2.651	2.706	2.764
Total ring splittings	C	8.820	9.030	9.184	9.326
<i>a</i> _{β-CH₂}	C	3.873	3.874	3.952	3.918
Total width	C	24.709	24.560	25.092	x
Δ <i>CH₂</i> = <i>a</i> _{β-CH₂} (T) - <i>a</i> _{β-CH₂} (C)		0.241	0.228	0.238	0.216
γ _{CH₂}		0.101	0.113	0.122	x

Table V. Temperature Dependence of Total Width and of the β-CH₂ Splittings for the Cation Radical of Some Di-*n*-alkoxybenzenes

Temp, °C	Substituents	Total width, gauss		<i>a</i> _{β-CH₂} , gauss		[<i>a</i> _{β-CH₂} (T) - <i>a</i> _{β-CH₂} (C)] = [(total width(T) - total width(C))/4]
		<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	
-86	<i>n</i> -Butoxy	26.178	25.191	x	x	0.244
-73	<i>n</i> -Butoxy	25.986	25.006	4.219	3.947	0.278
-73	<i>n</i> -Heptoxy	26.074	25.092	4.188	3.952	0.238
-66	<i>n</i> -Propoxy	25.927	24.961	x	x	0.241
-63	<i>n</i> -Octoxy	25.950	x	4.134	3.918	0.216
-58	<i>n</i> -Butoxy	25.670	24.560	4.102	3.874	0.228
-58	<i>n</i> -Heptoxy	25.902	24.878	x	x	0.256
-58	<i>n</i> -Propoxy	25.675	24.709	4.114	3.873	0.241
-42	<i>n</i> -Butoxy	25.359	24.436	4.082	3.826	0.236
-35	<i>n</i> -Butoxy	25.321	24.345	x	x	0.244
-16	<i>n</i> -Butoxy	24.960	24.022	3.971	3.723	0.248
-3.5	<i>n</i> -Butoxy	24.822	23.981	x	x	0.210
+7	<i>n</i> -Butoxy	24.568	x	x	x	x

sulfuric acid less than 1% of the compounds was converted to the radical (cf. ref 5). This low radical yield

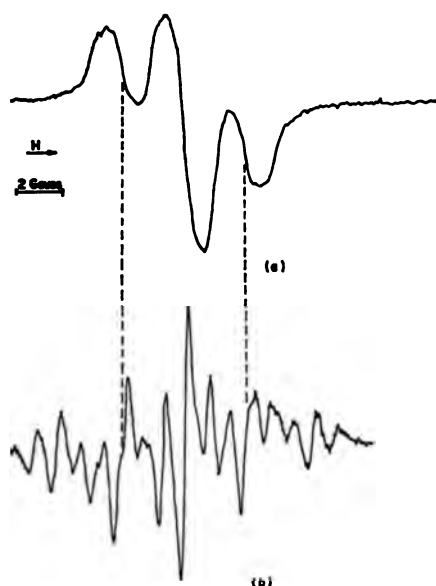


Figure 4. An ESR spectrum of *p*-diisopropoxybenzene in (a) D_2SO_4 , O_4 .

ue to a competing sulfonation reaction (un-
data from this laboratory).
but significant, changes in the splitting con-
the ring protons for the cation radicals of
xy- and *p*-diethoxybenzene were noted be-
two systems (see Tables II and III), presu-
o a solvent effect. Because of the small radi-
tration in sulfuric acid, comparisons were not
the other compounds.

s. *g* Values were determined, as described in
mental section, and are listed in Table VI.

Table VI. *g* Values of *p*-Dialkoxybenzene Cation Radicals

Isomer	Solvent	Temp, °C	<i>g</i> values
none	$AlCl_3-CH_3NO_2$	-60	2.00350 ± 0.00002
	Concd H_2SO_4	+20	2.00368 ± 0.00002
	$AlCl_3-CH_3NO_2$	-60	2.00368 ± 0.00002
	$AlCl_3-CH_3NO_2$	-60	2.00371 ± 0.00002
y	$AlCl_3-CH_3NO_2$	-60	2.00372 ± 0.00002
	$AlCl_3-CH_3NO_2$	-60	2.00370 ± 0.00001
y	$AlCl_3-CH_3NO_2$	-60	2.00368 ± 0.00003
	$AlCl_3-CH_3NO_2$	-60	2.00372 ± 0.00002
y	$AlCl_3-CH_3NO_2$	-60	2.00371 ± 0.00005
	$AlCl_3-CH_3NO_2$	-60	2.00372 ± 0.00003
xy	$AlCl_3-CH_3NO_2$	-60	2.00369 ± 0.00003

ues for the dialkoxybenzenes all fall within
 2.0037 ± 0.00006 , consistent with the pre-
ed generalization¹³ that delocalization onto
atom of an alkoxy group increases the *g* value
0.001 over the free spin value (2.0023). The
rger value, relative to the hydroquinone cation
scribed to the electronic effects of the alkyl
its.

ices between *cis* and *trans* Isomers. Assign-
d *trans* isomers as indicated previously (see
e VII), it is found that the percentage of the
1 increases with the size of the alkyl group in

C. Norman and R. J. Pritchett, *Chem. Ind. (London)*, 2040

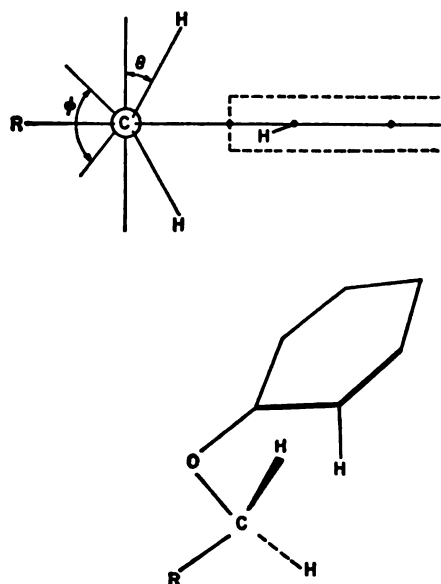


Figure 5. Schematic representation of the equilibrium conformation of *p*-di-*n*-alkoxybenzene.

the order 50, 55, 56, 61 for the radicals of hydroquinone,
p-dimethoxy-, *p*-diethoxy-, and *p*-di-*n*-propoxyben-
zenes, respectively. These percentages correspond to
a free energy difference between the isomers of 0–250
cal/mole. Such an energy difference corresponds to a
change in isomer ratio of only 3 or 4% over an 80°
range and hence is not readily detected experimentally.

Tables II, III, IV, and VII also show that differences
in β -proton splitting constants between the two isomers
increase from *ca.* 0.15 gauss (for *p*-dimethoxybenzene)
to *ca.* 0.22 gauss (for di-*n*-propoxybenzene). This may
be related to the slightly greater displacement, observed
between the centers of the two isomer spectra, for *p*-
diethoxybenzene (0.035 gauss) than for *p*-dimethoxy-
benzene (0.029 gauss).¹ Possibly, increased steric
interactions in the *cis* form cause some out-of-plane
movement in the CH_2-O bond, leading to a relatively
lower β -proton splitting constant and *g* value for the
cis isomer. Such steric interactions might also be ex-
pected to make the *trans* isomer thermodynamically
more stable, consistent with the previous assignment of
cis and *trans* isomers (see earlier discussion). The
above results are consistent with those obtained for
other related examples of *cis-trans* isomerism.^{12,14}

Conformation of the Alkoxy Groups. To explain the
temperature dependence of the β -proton splitting con-
stants, various torsional oscillations of the alkoxy side
chain are considered. Since the methoxy proton
splitting constants of the *p*-dimethoxybenzene cation
radical show no temperature dependence, and the
hydroxy protons of hydroquinone show only a small
dependence, it is probable that torsional motion about
the nuclear C–O bond can be neglected.

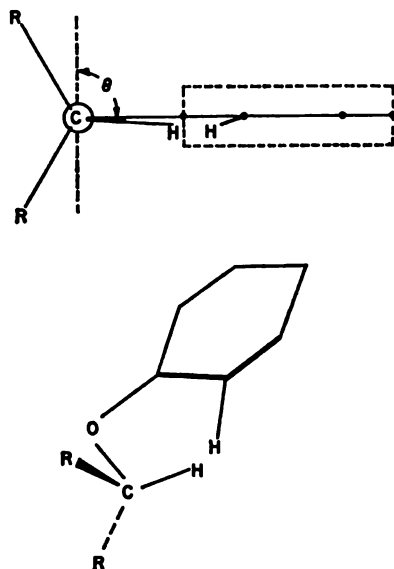
The discussion is therefore confined to the oscilla-
tions of the alkyl groups. Molecular models indicate
that for the alkyl groups, steric interactions between the
ortho ring proton and the alkyl protons may cause
hindered rotation (see Figures 5 and 6). For a methoxy
group (Figure 5; $R = H$), there will be a threefold
potential barrier to rotation about the O–C (alkyl) bond.
Experimentally, all three methoxy protons are equiva-

(14) P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.*, **37**, 2811 (1962).

Table VII. Assignment of Splitting Constants for *cis* and *trans* Isomers

Subst	<i>cis</i> isomer			<i>trans</i> isomer		
	Splitting constants, gauss	Ratio of ring splittings	Sum of ring splittings	Splitting constants, gauss	Ratio of ring splittings	Sum of ring splittings
H	$a_{H(\beta, \beta)}$ 2.351 $a_{H(\beta, \delta)}$ 2.129 a_{OH} 3.263	1.10	4.480	$a_{H(\beta, \delta)}$ 2.434 $a_{H(\beta, \beta)}$ 2.040 a_{OH} 3.263	1.19	4.474
CH ₃	$a_{H(\beta, \beta)}$ 2.644 $a_{H(\beta, \delta)}$ 1.869 a_{CH_3} 3.297	1.41	4.513	$a_{H(\beta, \delta)}$ 2.937 $a_{H(\beta, \beta)}$ 1.596 a_{CH_3} 3.446	1.84	4.533
CH ₃ CH ₂ (-62°)	$a_{H(\beta, \beta)}$ 2.647 $a_{H(\beta, \delta)}$ 1.885 $a_{\beta-CH_2}$ 3.804 $a_{\gamma-CH_3}$ 0.151	1.40	4.532	$a_{H(\beta, \delta)}$ 2.923 $a_{H(\beta, \beta)}$ 1.610 $a_{\beta-CH_2}$ 4.025 $a_{\gamma-CH_3}$ 0.151	1.81	4.533
<i>n</i> -Propoxy ↓ <i>n</i> -Octoxy (-58°)	$a_{H(\beta, \beta)}$ 2.694 $a_{H(\beta, \delta)}$ 1.840 $a_{\beta-CH_2}$ 3.886 $a_{\gamma-CH_3}$ 0.113	1.46	4.534	$a_{H(\beta, \delta)}$ 2.961 $a_{H(\beta, \beta)}$ 1.647 $a_{\beta-CH_2}$ 4.118 $a_{\gamma-CH_3}$ 0.113	1.80	4.608

lent, and, therefore, the barrier to rotation must be small. Since the CH₃ splittings are caused by a hyperconjugative mechanism, the maximum splitting will occur when the angle (θ) between the CH bond and the $p\pi$ orbitals is 0° (see Figures 5 and 6). The actual

Figure 6. Schematic representation of the equilibrium conformation of *p*-diisopropoxybenzene.

form of the dependence of the splitting constant ($a_{\beta H}$) on θ may be postulated as (cf. ref 15),

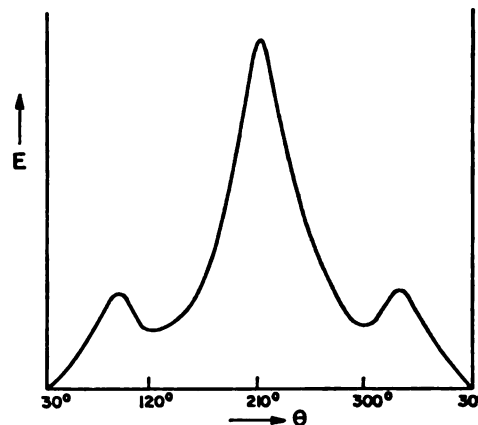
$$a_{\beta H} = (B_0 + B_2 \cos^2 \theta) \rho_0 \pi$$

where $\rho_0 \pi$ = spin density on the oxygen atom, B_0 is a small constant, and B_2 has been found to be of the order 30–45 gauss for a number of radicals. For the freely rotating methyl group, the average value of $\theta = 45^\circ$ gives $\langle \cos^2 \theta \rangle = 1/2$. Using a value of $\rho_0 \pi = 0.1758$, taken from MO calculations,^{1,16} $B_0 + B_2 = 38.5$ gauss, in reasonable agreement with earlier work. This, together with the observed sharp lines and with the absence of line-width effects expected from a non-freely rotating methyl group,¹⁷ suggests that the rotation is reasonably unhindered.

(15) M. C. R. Symons, *Advan. Phys. Org. Chem.*, **1**, 325 (1963), and references cited there.

(16) We have since improved the MO calculations in ref 1 by using a slightly different set of parameters.

For the *p*-diethoxybenzene cation radical, increased steric interactions between the β -ethyl group and the *ortho* ring protons are expected. This should lead to a potential energy diagram of the form schematically shown in Figure 7. The minimum energy conforma-

Figure 7. Schematic energy diagram for rotation about the O-C (alkyl) bond of *p*-diethoxybenzene.

tion will be that shown in Figure 5 ($R = CH_3$). If this is the actual conformation, then $2a_{\beta-CH_2}$ (diethoxy) = $3a_{\beta-CH_2}$ (dimethoxy), but experimentally $2a_{\beta-CH_2} = 8.05$ gauss and $3a_{\beta-CH_2} = 10.17$ gauss. Stone and Maki,¹⁸ in their treatment of the systems $RRCHAr\cdot$ and $RCH_2Ar\cdot$, have pictured the physical situation as one in which there is torsional oscillation about the equilibrium conformation. The form of this motion is assumed to be sinusoidal, leading to an equation for $a_{\beta-H}$ of the form¹⁸

$$a_{\beta-H} = [B_0 + B_2 \cos^2 (\theta_0 + \phi \sin 2t/\tau)] \rho_0 \pi$$

where θ = the equilibrium angle, ϕ = torsional amplitude, and τ is the period of oscillation. Provided that τ is rapid compared to the hyperfine interaction, the equation may be averaged over time. If τ is of the same order as the hyperfine interaction (ca. 7×10^{-8} sec), the lines will be broadened (see also discussion for *p*-diisopropoxybenzene).

From Figure 5, $\theta = 30^\circ$, and hence, by comparison with Figure 2 of ref 18, we can estimate that at a tem-

(17) J. H. Freed and G. K. Fraenkel, *J. Am. Chem. Soc.*, **86**, 3477 (1964).

(18) E. W. Stone and A. H. Maki, *J. Chem. Phys.*, **37**, 1326 (1962).

perature of -60° , $\phi = 50^\circ$ for the *p*-diethoxybenzene cation radical. As the temperature decreases, ϕ would be expected to decrease, leading to the observed increase in the β -proton splitting constant.

For the larger *p*-di-*n*-alkoxybenzene cation radicals, a similar temperature dependence would be expected, and is observed (see Table V). The torsional amplitude, ϕ , would be expected to decrease with increased size of the substituent, leading to an increased β -proton splitting constant, and this is observed for the *n*-propoxy compound (cf. Tables III and IV). Further lengthening of the side chain does not give rise to any significant changes, presumably because the effective size of the substituent is not altered on passing from *n*-propyl to *n*-octyl (cf. also ref 19).

Molecular models of the *p*-diisopropoxybenzene cation radical (see Figure 6; $R_1 = R_2 = \text{CH}_3$) indicate an equilibrium conformation in which $\theta \approx 90^\circ$ for the lone CH proton, suggesting $a_{\beta\text{-H}} = 0$ in the absence of torsional oscillation. Increased torsional oscillation with temperature would be expected to lead to an in-

crease in the value of $a_{\beta\text{-H}}$. Although the spectrum is not well resolved, because of line broadening, such an increase is indeed observed (see section on *p*-diisopropoxybenzene). The experimentally obtained value of $a_{\beta\text{-H}} = \text{ca. } 2.60$ is consistent with a torsional amplitude of about 57° .

The experimentally observed line-width increase of the *p*-diisopropoxybenzene cation compared with that of the other *p*-dialkoxybenzenes (ca. 250 mgauss to 70 mgauss) could be explained if the period of torsional oscillation, τ , in the isopropoxy compound was of the same order as the hyperfine splitting ($\sim 10^{-7}$ sec), thus leading to line broadening. Alternatively, it may be caused by small unresolved splittings of the $\beta\text{-CH}_3$ groups.

In the above discussion, changes because of the inductive effect of substituents have been ignored. The justification for this is based on the near-constancy of (i) the *g* values (see Table VI) and (ii) the ring proton splitting constants.

Acknowledgments. The authors are indebted to the National Research Council of Canada for a studentship (to P. D. S.) and continued financial assistance.

(19) A. Carrington and P. F. Todd, *Mol. Phys.*, **7**, 533 (1964).

Mass Spectrometry in Structural and Stereochemical Problems. CXXX.¹ A Study of Electron Impact Induced Migratory Aptitudes²

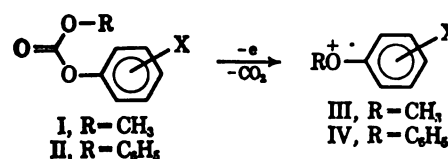
Peter Brown³ and Carl Djerassi

Contribution from the Department of Chemistry, Stanford University,
Stanford, California 94305. Received January 6, 1967

Abstract: The electron impact induced decarboxylation of aryl methyl and aryl phenyl carbonates has been investigated in some detail, using low-voltage and isotope-labeling techniques, and by studying substituent effects on the rate of loss of carbon dioxide. In the substituted-aryl methyl compounds, exclusive methyl group migration is observed, whereas in the aryl phenyl carbonates, competition between the two possible itinerant moieties is apparent, and aryl group relative migratory aptitudes can be assigned. In addition, the substituent dependence of the abundance of the CH_2OCO^+ ion from α cleavage in aryl methyl carbonates has been correlated with Hammett σ values.

Of the unimolecular processes energetically accessible to ions generated by electron impact, that of skeletal rearrangement⁴ (in compounds other than hydrocarbons) has only recently been accorded recognition as a relatively common possibility. Despite the elegant application⁵⁻⁷ of accepted physical organic techniques to simple mass spectral bond cleavages, no

similar studies on systems undergoing alkyl or aryl group migrations have as yet been reported. We therefore elected to examine in some detail the necessary requirements for methyl migration in aryl methyl carbonates⁸ ($\text{I} \rightarrow \text{III}$) and aryl *vs.* phenyl migration in aryl phenyl carbonates⁸ ($\text{II} \rightarrow \text{IV}$), each with concomitant ejection of carbon dioxide as the neutral species.



M - 44

The rearrangement reactions proved to be relatively facile, giving rise to intense peaks in the 70-ev spectra.³ Reduction of the ionizing voltage to approxi-

(8) P. Brown and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 2469 (1966).

(1) Paper CXXXIX: A. M. Duffield, W. Carpenter, and C. Djerassi, *Chem. Commun.*, 109 (1967).

(2) Financial support from the National Institutes of Health (Grant No. AM-04257) is gratefully acknowledged. The purchase of the Atlas CH-4 mass spectrometer was made possible through NASA Grant No. NaG 81-60.

(3) Postdoctoral Fellow, 1964-1966.

(4) P. Brown and C. Djerassi, *Angew. Chem. Intern. Ed. Engl.*, in press.

(5) (a) M. M. Bursay and F. W. McLafferty, *J. Am. Chem. Soc.*, **88**, 529 (1966); (b) *Ibid.*, **88**, 4484 (1966).

(6) (a) F. W. McLafferty, M. M. Bursay, and S. M. Kimball, *Ibid.*, **88**, 5022 (1966); (b) M. M. Bursay and F. W. McLafferty, *Ibid.*, **88**, 5023 (1966); (c) *Ibid.*, **89**, 1 (1967).

(7) J. L. Mateos and C. Perez, *Bol. Inst. Quim. Univ. Nat. Auton. Méx.*, **17**, 202 (1965).

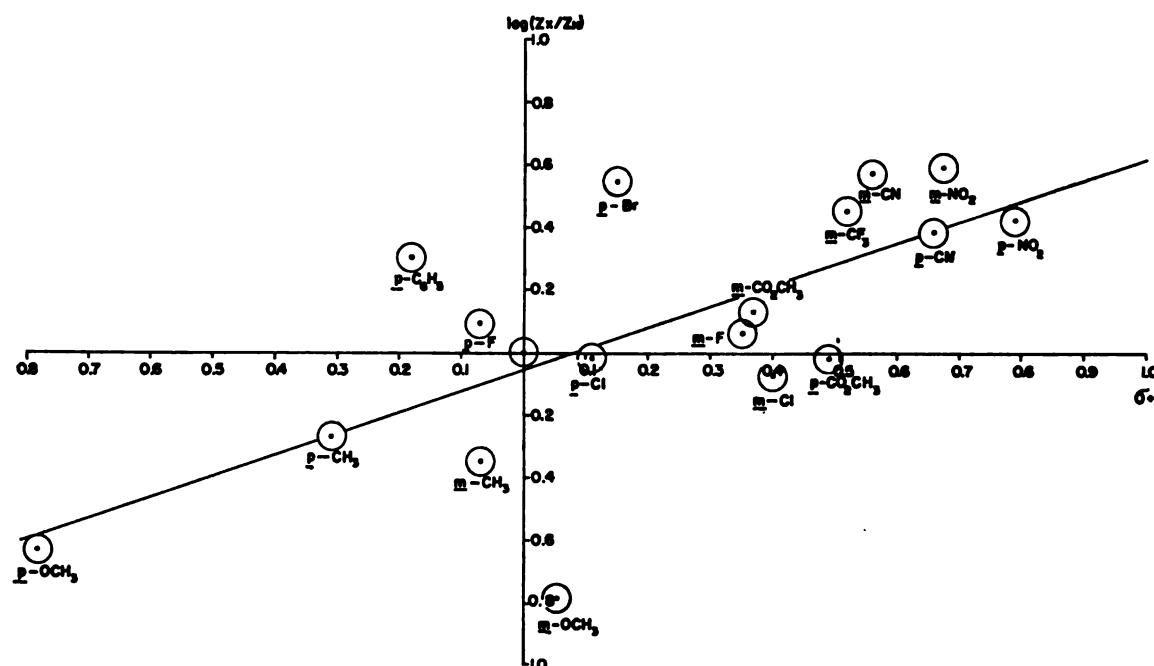


Figure 1. Correlation of the $M - 44$ ion III intensity in the 12-ev mass spectra of substituted aryl methyl carbonates I with σ^+ . Least-squares slope (ρ) = +0.67, standard deviation = 0.18.

mately 12 ev⁹ greatly simplified the spectra, the peaks due to the molecular ion and the $M - 44$ species together accounting for at least 95% of the total ionization (Σ_{40}) with compounds I, and at least 60% Σ_{40} with compounds II.¹⁰ Thus by variation of the nuclear substituents X in I and II, it was hoped to secure data pertaining to both the electronic nature of the migrating group and of the receptor site in these particular systems.

Aryl Methyl Carbonates. The results obtained in the electron impact induced¹¹ decarboxylation of substituted aryl methyl carbonates (I \rightarrow III) are presented as a Hammett^{12a,12} plot in Figure 1, using relationship 1 as modified by McLafferty^{13a} to permit kinetic evaluation of mass spectra. Thus $Z = [A]/[M]$, where [A] and [M] are the relative abundances of the peaks due to the $M - 44$ fragment (III) and the molecular ion respectively, and the subscripts X and H refer to substituted and parent compounds, respectively. In these

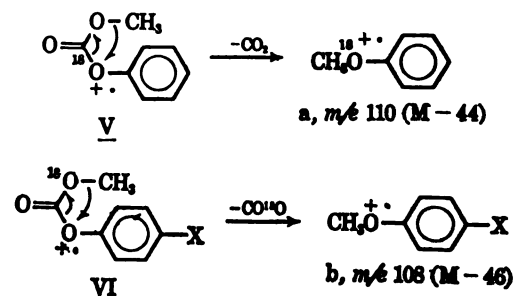
$$\log(Z_X/Z_H) = \rho\sigma \quad (1)$$

systems, the $M - 44$ species (III) have compositions dependent on the substituent X, and at normal ionizing voltages (i.e., 70 ev), further decompositions of III will also depend on the nature of X. At lower voltages, however (i.e., 12 ev), all peaks in the spectra of compounds of type I except for the $M - 44$ /molecular ion pair¹³ are absent, indicating that competing and consecutive reactions have been totally eliminated. The

relative peak heights at 12 ev were therefore employed exclusively in all calculations of relative kinetics of the rearrangement processes.

Although the correlation (Figure 1) displays considerable scatter, sufficient substituents were employed to show that a very definite trend exists. Thus in general, electron-attracting groups increase the rate of the reaction I \rightarrow III, and electron-releasing substituents depress it. Use of σ constants^{15a} did not obviously improve the quality of the fit over that obtained with σ^+ values,^{15b} and the latter appear in Figure 1.^{15c} The least-squares value of the slope ($\rho = +0.67$) was obtained by computer.

In order to elucidate further⁸ the mechanism of electron impact induced decarboxylation of compounds of type I, the ¹⁸O-labeled carbonates V and VI (X = H) were prepared. In the mass spectrum of V, the rearrangement peak moved cleanly to m/e 110 (a, $M - 44$),



whereas with VI (X = H) it remained⁸ entirely at m/e 108 (b, $M - 46$). These observations are consistent

(9) Cf. O. L. Chapman, T. H. Kinstle, and M. T. Sung, *J. Am. Chem. Soc.*, **88**, 2618 (1966).

(10) P. Natalis and J. L. Franklin, *J. Phys. Chem.*, **69**, 2943 (1965), report 10.78 ± 0.05 ev for the appearance potential of the $M - 44$ ion derived from diphenyl carbonate (II, X = H).

(11) Supported by the appropriate metastable peaks.

(12) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter 7.

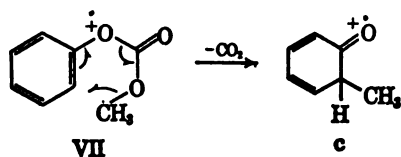
(13) With the *m*- and *p*-nitrophenyl methyl carbonates (I, X = NO₂), small peaks corresponding to $M - 16$ and $M - 30$ processes¹⁴ are still apparent even at 12 ev.

(14) J. H. Beynon, R. A. Saunders, and A. E. Williams, *Ind. Chim. Belge*, **29**, 311 (1964).

(15) (a) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 4. (b) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958). (c) A referee has pointed out that the rate terms for *meta* and *para* electron-donating substituents are nearly the same. A similar observation had been made earlier¹⁶ with substituted phenetoles, and the suggestion had been made that equilibration of substituents occurred in the molecular ion. If such a rearrangement is also operating in our compounds with electron-donating substituents, then the Hammett correlations in Figures 1, 3, and 4 would be considerably improved.

preferential charge location¹⁶ in the molecular ion ie phenoxy group, followed by exclusive methylation to the electron-deficient site. The data also out isomerizations of the molecular ion analogous those encountered¹⁷ in methyl phenyl thioncarbamates. The mass spectra of the ¹⁸O-labeled compounds VI (X = OCH₃) and VI (X = CN) were also and total loss of the heavy isotope as carbon dioxide-¹⁸O indicates that only methyl migration is ring, regardless of the electronic nature of the substituent X.

the preference for the phenoxy oxygen atom (e.g., a) over the *ortho* position of the aromatic ring → c) as the receptor site for methyl migration has already been expressed.⁸ Additional evidence against migration of a six-center transfer (VII → c) is contained



the per cent total ionization figures for the M - 44 rearrangement peak in the spectra of the isomeric 3,4-, and 2,6-dimethylphenyl methyl carbonates (VIII, and X, respectively, Table I). It is clear that there is an abnormal steric effect intervening in the case of *para*-X.¹⁸

L. Σ_{66} Values for M - 44 Species from *para*-phenyl Methyl Carbonates

		Σ_{66}
III	R ₁ = R ₂ = CH ₃ ; R ₃ = R ₄ = H	6.1
X	R ₁ = R ₄ = H; R ₂ = R ₃ = CH ₃	4.4
V	R ₁ = R ₂ = H; R ₃ = R ₄ = CH ₃	4.6

the evidence of a more compelling nature for representative M - 44 species from decarboxylation of aryl methyl carbonates I as the aryl methyl ether molecular ion was adduced by comparison of the metastable peaks observed in the mass spectra of the parent catione (I, X = H) and anisole (III, X = H). Not only the spectra of these two compounds extremely

It is assumed that electron impact can displace an electron from the neutral molecule, and that the resulting radical ion decomposes extremely rapidly to a state in which the net charge is stabilized distributed over the whole system, and that this type of molecular ion decomposes into the major ions of the mass spectrum. The best approximation of "charge localization" involves the writing of apparently favorable resonance structures of an ion, and then the formal electron deficiency to rationalize subsequent fragmentation. Thus the single electron deficiency of the molecular ion of methyl carbonate can be accommodated in more low energy resonance structures of the phenoxy rather than the methoxy portion of the molecule (I and VI are preferred formalisms). With aryl phenyl carbonates, charge distribution in the molecular ion is expected to be somewhat symmetrically disposed on either side of the carbonyl group, and sensitive to the electronic nature of aromatic substituents.

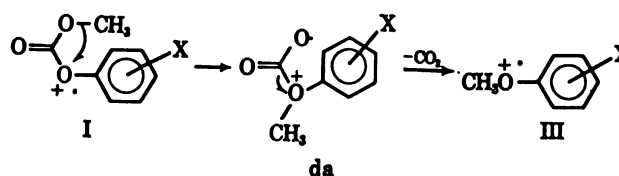
J. B. Thomson, P. Brown, and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 49 (1966).

C. P. Lewis, *Anal. Chem.*, **36**, 176 (1964), reports that 2,6-disubstitution does not deter an analogous skeletal rearrangement involving loss of carbon dioxide in ethyl N-phenylcarbamate.

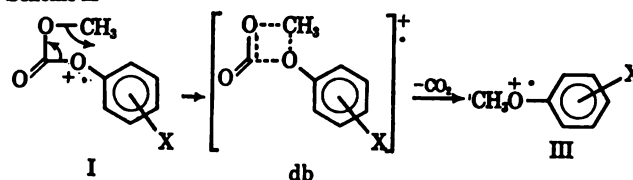
similar⁸ below *m/e* 108 (M - 44 for I, X = H) (except for the presence of an additional peak at *m/e* 59 in I, X = H, due to the CH₃OCO⁺ species), but the positions, relative intensities, and peak shapes¹⁹ of all six metastable peaks²⁰ in the anisole spectrum (Figure 2b) are faithfully reproduced in that of methyl phenyl carbonate (Figure 2a). This correspondence is demonstrated in a particularly striking fashion in Figures 2a and 2b, which show the direct record obtained by means of a logarithmic transfer recorder,²¹ operating in conjunction with an Atlas CH-4 mass spectrometer.

Two of the more plausible mechanisms consistent with the labeling results that may be entertained for the M - 44 rearrangement process are depicted in Schemes I and II.

Scheme I



Scheme II



In Scheme I, methyl radical migration to electron-deficient phenoxy oxygen (I → da) is envisaged initially, followed by homolysis of the O-CO bond and loss of carbon dioxide (da → III). If the process is concerted, i.e., methyl migration and carbon dioxide ejection occurring simultaneously, then the situation is described by Scheme II. There appear to be no authenticated precedents for 1,3-methyl radical migrations outside of mass spectrometry.²² Even 1,2-methyl radical shifts are rare,^{23,24} although 1,2 migration as a potential carbanion to an electrophilic center is much more common²⁵ (e.g., Wagner-Meerwein, Baeyer-Villiger, pinacol rearrangements).

Scheme II envisages a four-center transition state db, and accounts satisfactorily for the observed positive slope of the Hammett plot (Figure 1) by invoking a shift of the methyl group with its bonding pair of elec-

(19) T. W. Shannon and F. W. McLafferty, *J. Am. Chem. Soc.*, **88**, 5021 (1966), call attention to the fact that ions identical in structure and energy should exhibit identical decomposition reactions and, therefore, the spectra should also show the same metastable peaks, with identical peak shapes and intensities relative to the parent ion.

(20) These appear at *m/e* 80.0 (93¹/108), *m/e* 57.9 (79¹/108), *m/e* 56.4 (78¹/108), *m/e* 45.4 (65¹/93), *m/e* 33.8 (51¹/77), and *m/e* 23.4 (39¹/65). The only additional metastable peak discernible in the carbonate spectrum (Figure 2a) occurs at *m/e* 76.8 (108¹/152), and corresponds to the loss of carbon dioxide from the molecular ion.

(21) R. T. Aplin, H. Budzikiewicz, H. S. Horn, and J. Lederberg, *Anal. Chem.*, **37**, 776 (1965).

(22) A formal 1,3-methyl shift has been detected in the pyrolysis of diazoisofenchone by P. Yates and S. Danishefsky, *J. Am. Chem. Soc.*, **84**, 879 (1962), although the electronic nature of the migrating species is not known.

(23) C. Walling, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers Inc., New York, N. Y., 1963, p 416.

(24) C. McKnight and F. S. Rowland, *J. Am. Chem. Soc.*, **88**, 3179 (1966), report tritium-labeling evidence for a 1,2-methyl radical migration pathway in the reaction of triplet methylene with *trans*-2-butene.

(25) H. E. Zimmerman and A. Zweig, *J. Am. Chem. Soc.*, **83**, 1196 (1961), have provided a rationale for 1,2 shifts of methyl and phenyl groups based on MO calculations.

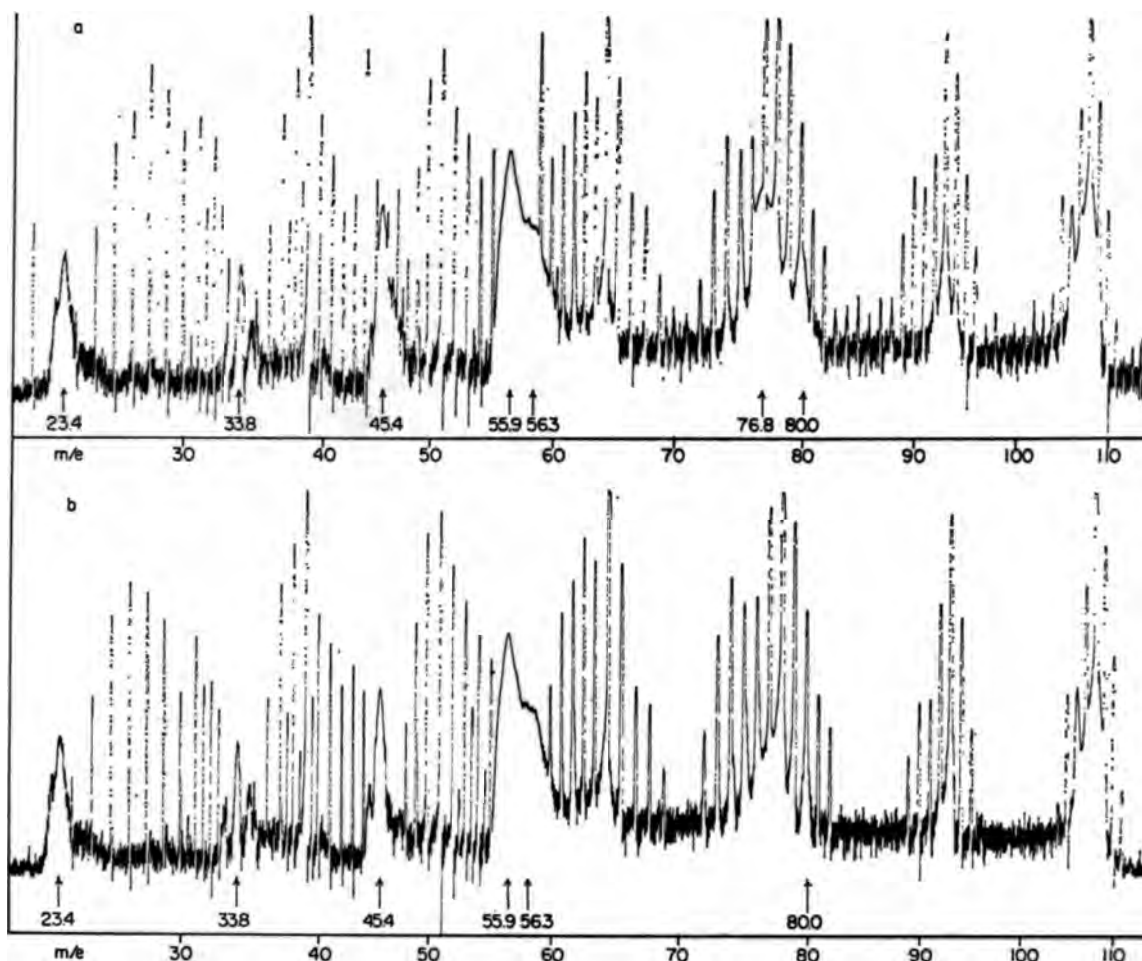


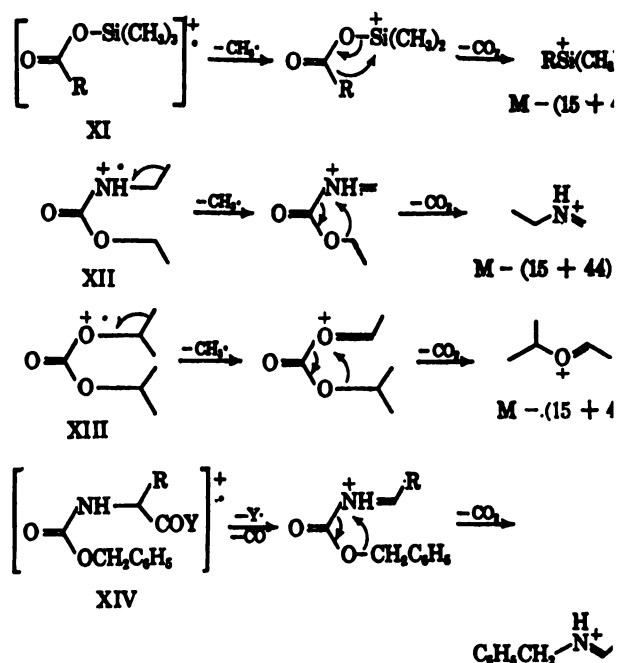
Figure 2. a. Logarithmic transfer recorder trace of the low-resolution mass spectrum of methyl phenyl carbonate. b. Logarithmic transfer recorder trace of the low-resolution mass spectrum of anisole.

trons to the most electrophilic site available. Thus in the transition state, the partial charge on the phenoxy oxygen will become less positive in character, and bond forming to the methyl group will be more advanced than bond breaking of the O-CO bond. Scheme I, on the other hand, would predict a negative ρ value if the rate-determining transition state lies between I and da, since its formation would be inhibited by electron-withdrawing substituents and facilitated by electron-releasing groups.

Other instances of electron impact induced group migrations accompanied by carbon dioxide expulsion have been documented.⁴ These reactions are most prevalent in gaseous ions where an especially electron-deficient center is developed adjacent to the carbonyl moiety, and can then be visualized as involving a nucleophilic 1,3-group shift to that positive site.

For example, alkyl group migration apparently occurs only after initial cleavage has generated a full positive charge in the vicinity of the migration receptor site in trimethylsilyl esters of some fatty acids²⁶ (XI), in ethyl N-ethylcarbamate¹⁷ (XII), in dialkyl carbonates such as XIII,⁸ and with benzyloxycarbonyl derivatives of certain amino acid esters²⁷ (XIV).

Other processes that can be rationalized similarly are the successive loss of a methyl group and hydrogen

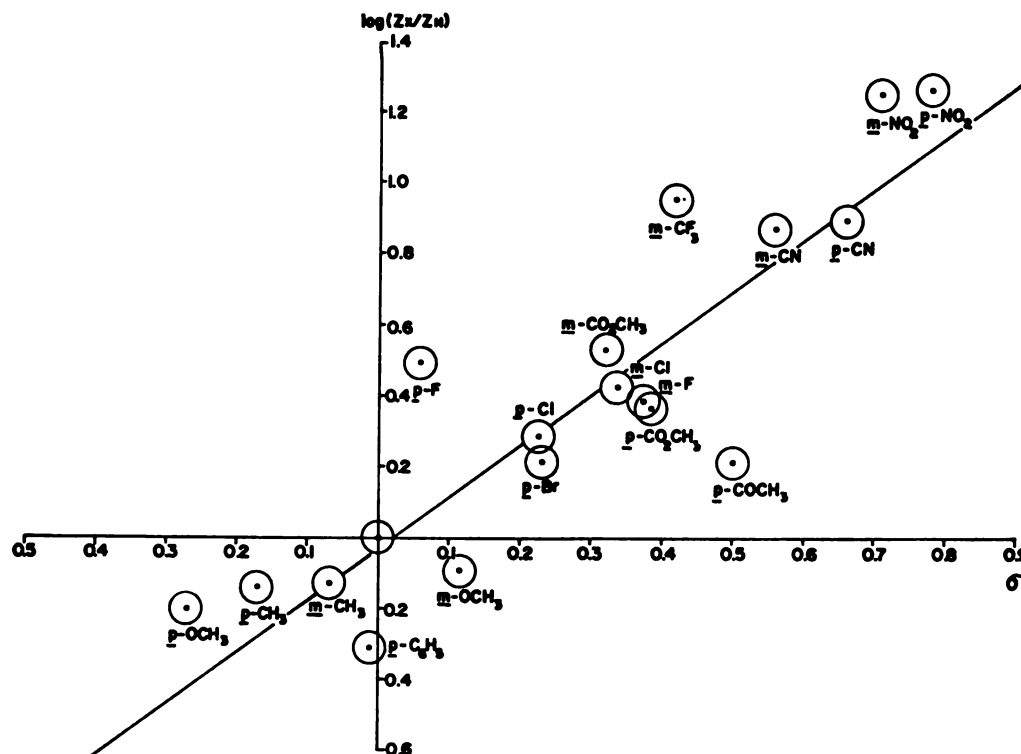


cyanide from amidines,²⁸ and of a methyl group a formaldehyde from formaldehyde acetals of second and tertiary alcohols²⁹ and also from the trimethylsilyl derivative of benzyl alcohol.³⁰

(26) R. M. Teeter, Abstracts of the Tenth Annual Conference on Mass Spectrometry, A.S.T.M. Committee E-14, New Orleans, La., 1962, p 51.

(27) R. T. Aplin, J. H. Jones, and B. Liberek, *Chem. Commun.*, 794 (1966).

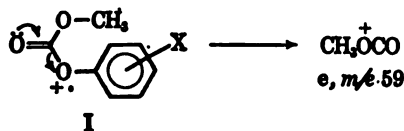
(28) A. K. Bose, I. Kugachevsky, P. T. Funke, and K. G. I. *Tetrahedron Letters*, 3065 (1965).



3. Correlation of the m/e 59 ion (e) intensity in the 70-ev mass spectra of substituted aryl methyl carbonates I with σ . Least-squares $\rho = +1.43$, standard deviation = 0.18.

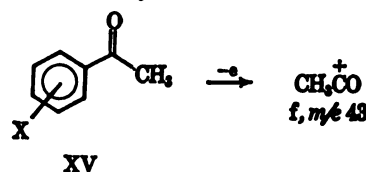
should be pointed out, however, that group migration with concomitant expulsion of carbon dioxide can operate in radical ions where initial α cleavage is inhibited, for example, in esters of α,β -unsaturated³¹ aryl methyl and aryl phenyl carbonates,⁸ and N-arylcarbamates.³²

A characteristic peak appears at m/e 59 in the 70-ev spectra of all aryl methyl carbonates I, consistently as an ion of composition $C_6H_5O_2^+$ (e). At 12 ev, the process is completely suppressed. The contribution of fragment e to the higher voltage total ionization is only dependent on the aryl substituent X, ranging from 1.8% Σ_{40} (I, X = p -OCH₃) to 18.0% Σ_{40} (I, X = p -C₆H₅). The relevant data (in which the abundance of e compared with that of the molecular ion I) are reduced as a Hammett^{33,34} plot in Figure 3.



In this case, σ constants^{15a} gave a correlation with a point scatter than that obtained using σ^+ values.^{15b} It is interesting to compare the slope of $\rho = +1.43$ for reaction I \rightarrow e with that of $\rho = +0.78$ for the formation of α cleavage ion f in substituted acetophenones,³⁵ and $\rho = +0.67$ for the production of e (59) from substituted methyl benzoates.⁷ This suggests that bond breaking has proceeded to a greater extent in the transition state for cleavage in the car-

bonates (I \rightarrow e) compared with the acetophenones (XV \rightarrow f) and the methyl benzoates.



It is pertinent at this point to comment briefly on the application of Hammett $\sigma\rho$ studies to electron impact induced rearrangements and fragmentations. In ground electronic state (thermal) reactions, those processes which develop relatively large fractional charges in the transition state (compared to the reactants) at the reaction site exhibit the largest numerical reaction constants³³ (ρ), whereas processes in which charge is merely redistributed in the transition state are characterized by small ρ values.³⁴

In conventional mass spectrometry, one is dealing with gaseous unimolecular endothermic reactions, where the transition state may be expected to resemble the products rather than the reactant,³⁵ and where both reactant and transition state bear a full positive charge. This description allows the possibility of relatively large reaction constants. On the other hand, it has been pointed out³⁶ that the transition state for a gas-

(33) For example, quoted in ref 15b, $\rho = -4.67$ for SN1 solvolysis of *t*-cumyl chlorides in ethanol at 25°, and -4.74 for ionization of substituted benzylidene alcohols. K. Wiberg and T. M. Shryne, *J. Am. Chem. Soc.*, **77**, 2774 (1955), report $\rho = -3.86$ and -3.56 for the thermal rearrangement of α -arylethyl chlorocarbonates in dioxane and toluene, respectively.

(34) For example, $\rho = +0.81$ for the SN2 reaction of iodide ion with substituted benzyl chlorides in acetone: G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935); and $\rho = +0.023$ for homolytic C-Br bond dissociation in substituted benzyl bromides in toluene: M. Swarc, C. H. Leigh, and A. H. Schon, *J. Chem. Phys.*, **19**, 657 (1951).

(35) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(36) H. M. R. Hoffmann and A. Maccoll, *ibid.*, **81**, 3774 (1959).

P. Brown, C. Djerassi, G. Schroll, H. J. Jakobsen, and S.-O. Ison, *J. Am. Chem. Soc.*, **87**, 4559 (1965).
J. B. Thomson, J. Diekmann, and C. Djerassi, to be published.
J. H. Bowie, D. H. Williams, P. Madsen, G. Schroll, and S.-O. Ison, *Tetrahedron*, **23**, 305 (1967).
C. P. Lewis, *Anal. Chem.*, **36**, 1582 (1964).

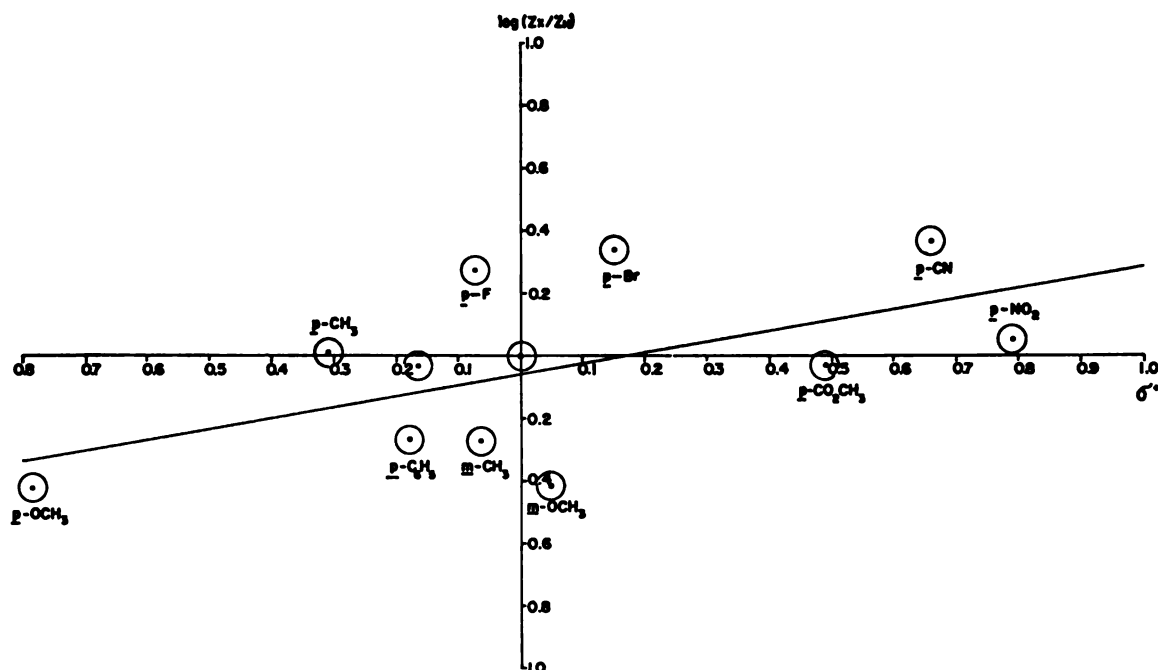


Figure 4. Correlation of the $M - 44$ ion IV intensity in the 12-ev mass spectra of substituted aryl phenyl carbonates II with σ^+ . Least-squares slope (ρ) = +0.34, standard deviation = 0.18.

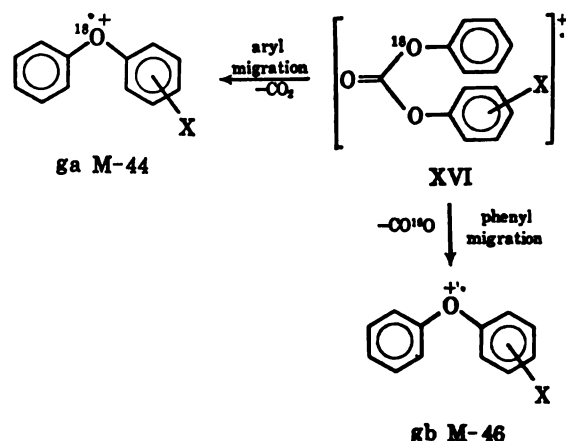
phase heterolysis will be considerably less ionic than the equivalent process in solution, due to the absence of external solvation. Applying this argument to gaseous ions under low pressure leads to the prediction of relatively small reaction constants. Insufficient data are available at present, but $\rho = +1.43$ for the reaction $I \rightarrow e$ represents the largest numerical reaction constant obtained so far.

Aryl Phenyl Carbonates. The high- and low-voltage mass spectra of diphenyl carbonate^{8,10} (II, $X = H$) and of its substituted analogs all display important peaks due to the expulsion of carbon dioxide ($II \rightarrow IV$).¹¹ As with the aryl methyl compounds (I), the $M - 44$ process persists at low voltage, at the expense of all other competing reactions. To avoid approaching the threshold of the appearance potential¹⁰ of the $M - 44$ species IV too closely, spectra for kinetic treatment were again recorded at 12 ev.

Group migration to oxygen as the receptor site is also envisaged in the aryl phenyl series, by analogy with methyl migration in the aryl methyl carbonates I. In support of this contention may be cited the fact that the mass spectrum of diphenyl carbonate (II, $X = H$) contains all the peaks characteristic of diphenyl ether (IV, $X = H$) itself, and especially all the metastable peaks¹⁷ displayed by diphenyl ether, with identical peak shapes and abundances,¹⁹ relative to the molecular ion. It should be noted, however, that although there is some positive evidence for representing the $M - 44$ radical ion from diphenyl carbonate and the molecular ion of diphenyl ether by the same structure (formalism IV, $X = H$), the rearrangement ion is apparently formed with some excess energy. The heats of formation of $C_{12}H_{10}O^+$ have been reported¹⁰ as 257 and 220 kcal/mole for diphenyl carbonate and diphenyl ether, respectively.

(37) These appear at m/e 140.0 (141³/142), m/e 118.6 (142³/170), m/e 93.8 (115³/141), m/e 50.9 (93³/170), m/e 33.8 (51³/77), and m/e 23.4 (39³/65), and were observed as before employing the logarithmic transfer recorder.

Since decarboxylation can occur with either aryl or phenyl group migration, ¹⁸O-labeling of the phenoxy moiety was effected (XVI). Thus aryl migration then



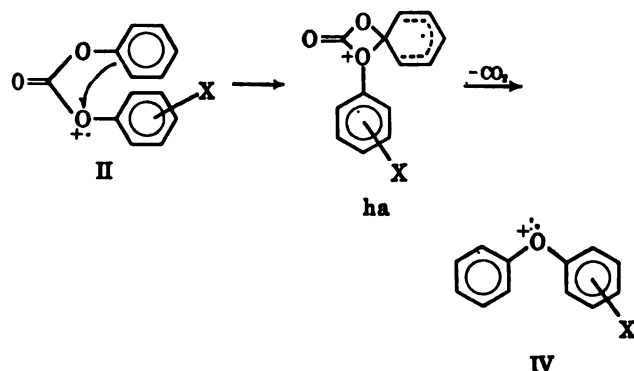
furnishes the $M - 44$ ion ga (with label retention), whereas phenyl migration affords the $M - 46$ species gb. In this way, the over-all rate of decarboxylation for each aryl phenyl carbonate can be divided into two partial rates, for aryl and phenyl group migration, respectively.

In Figure 4 the kinetic data for phenyl migration ($XVI \rightarrow gb$) are correlated with σ^+ values,^{15b} the use of which gave a plot with slightly less scatter than did σ constants.^{15a} The smaller slope of $\rho = +0.34$ for phenyl compared to $\rho = +0.67$ for methyl migration could be interpreted as a lesser dependence on substituent effects at the receptor site for shifting of the more electronically versatile phenyl group, but the uncertainty in the magnitude of the slope in Figure 4 is rather large.

Two possible mechanisms for decarboxylation by phenyl migration are described in Schemes III and IV. Scheme III is analogous to Scheme I for aryl methyl carbonates I, and is considered less probable on the same grounds. Making the reasonable assumption

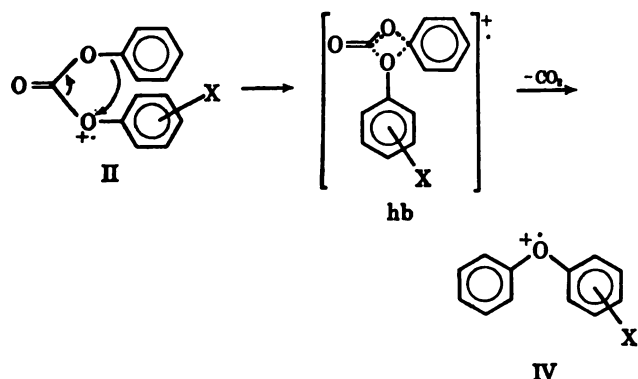
that the rate-controlling transition state would lie between II and ha, a negative ρ value for the Hammett correlation would be anticipated. In this system, therefore, the occurrence of phenyl bridging (as in a σ -bonded intermediate such as ha) appears unlikely.

Scheme III



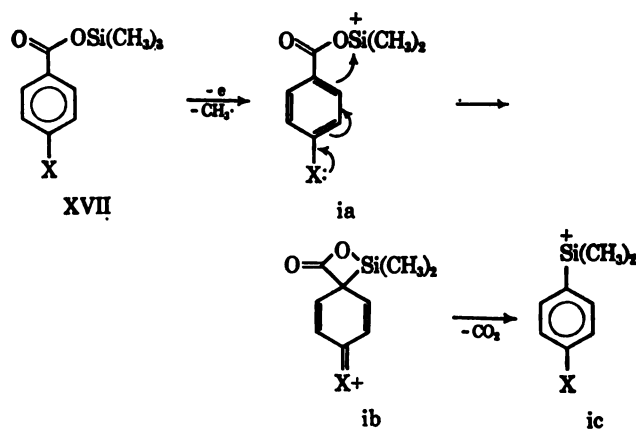
Scheme IV is the phenyl analog of Scheme II for the methyl compounds I, and as before, satisfactorily accounts for the positive ρ value obtained. In view of the small numerical value of ρ , and the as yet unknown range of reaction constant magnitudes for a representative cross section of electron impact induced processes, it is perhaps too early at present to assess finally the significance of ρ in this case, except to note that it has a positive sign.

Scheme IV

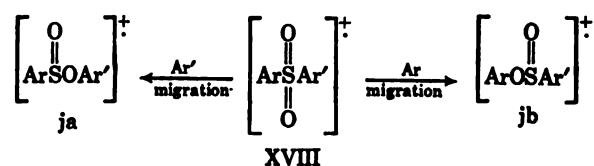


Relative Migratory Aptitudes of Aryl Groups. In addition to revealing the electronic requirements at the receptor site for migration, the model carbonate system also produced information pertaining to the nature of the itinerant group. Despite the wide-spread occurrence in mass spectrometry of rearrangement processes involving intramolecular transfer of atoms or groups other than hydrogen,⁴ the literature to date still contains only a few isolated references to the relative migratory propensities of the peripatetic groups.

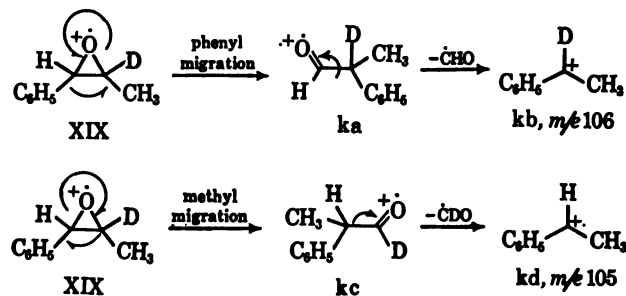
In the mass spectra of trimethylsilyl esters of substituted benzoic acids XVII, an approximate correlation between relative abundance of the rearrangement ion ic and the electronic character of the aromatic substituent X was noted.³⁸ In fact, electron-donating groups X increased the extent of rearrangement by aryl migration (ia \rightarrow ib \rightarrow ic), relative to electron-withdrawing substituents. However, the intensity of a mass spectral peak depends on the rates of decomposition of the ions contributing to it, as well as on their rates of formation, and unfortunately both sets of rates are very probably dependent on X in this instance.



In a study of the mass spectra of diaryl sulfones, evidence was adduced³⁹ for the operation of an aryl rearrangement process XVIII \rightarrow ja, jb. In a series of unsymmetrical diaryl sulfones, preferential migration of the more nucleophilic aryl group was consistently observed, although it was clearly recognized that different rates of decomposition of different rearrangement ions contributed to the lack of internal consistency in the formulation of a relative migratory aptitude scale.



It has been reported recently³⁹ that phenyl migration is more favored than a methyl shift in the fragmentation of 1-phenyl-2-d-epoxypropane (XIX). This estimate was made by comparing the relative intensities of the extremely small peaks at m/e 106 and 105, due to species kb and kd, respectively, and is uncomplicated by the absence of any necessity to allow for different rates of further decomposition of the rearrangement ions (kb, kd), apart from a H/D isotope effect.



In the aryl phenyl carbonate system, aryl migration (XVI \rightarrow ga) and phenyl migration (XVI \rightarrow gb) both furnish formally the same aryl phenyl ether radical ion, except for the isotope label in ga. Therefore, any further minor decomposition⁴⁰ suffered by the rearrangement ions at 12 eV is independent of which group has shifted. The extent of rearrangement occurring

(38) S. Meyerson, H. Drews, and E. K. Fields, *Anal. Chem.*, **36**, 1294 (1964).

(39) H. E. Audier, J. F. Dupin, M. Fétizon, and Y. Hoppilliard, *Tetrahedron Letters*, 2077 (1966).

(40) Most of the carbonates II contain in their mass spectra small M - (44 + 28) peaks, due to further loss of carbon monoxide from the aryl phenyl ether radical ion,⁴¹ for which no correction was made.

(41) J. H. Beynon, G. R. Lester, and A. E. Williams, *J. Phys. Chem.*, **63**, 1861 (1959).

Table II. Relative Migratory Aptitude Data for Aryl Groups in the Electron Impact Induced Decarboxylation of Aryl Phenyl Carbonates II

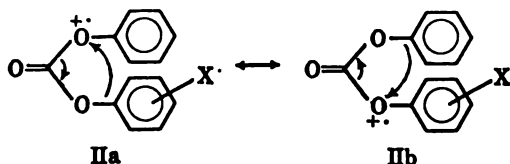
$$[C_6H_5OCOOC_6H_4X]^+ \longrightarrow [C_6H_5OC_6H_4X]^+ + CO_2$$

Substituent	Migrating group ^a		Total rate	σ^{+b}	Aryl migratory aptitudes	
	Phenyl	Aryl			Carbon-ates	Pina-cols ^{c,d}
<i>p</i> -OCH ₃	48	52	0.396	-0.778	1.1	500
<i>m</i> -OCH ₃	30	70	0.636	-0.047	2.3	1.6
<i>o</i> -OCH ₃	>98	<2	0.340	...	<0.02	0.3
α -Naphthyl (= C ₁₀ H ₇ X)	95	5	0.989	...	0.05	...
<i>p</i> -C ₆ H ₅	39	61	0.693	-0.179	1.6	11.5
2,6-Dimethyl	6	94	0.946	...	15.7	...
<i>p</i> -CH ₃	63	37	0.809	-0.311	0.6	15.7
<i>m</i> -CH ₃	23	77	1.16	-0.066	3.4	1.9
<i>o</i> -CH ₃	21	79	0.798	...	3.8	...
H	50	50	1.00	0	1.0	1.0
<i>p</i> -CO ₂ CH ₃	80	20	0.574	0.489	0.25	...
<i>p</i> -Br	>99	<1	1.09	0.150	<0.01	0.7
<i>p</i> -F	>99	<1	0.938	-0.073	<0.01	...
<i>p</i> -CN	>99	<1	1.16	0.659	<0.01	...
<i>p</i> -NO ₂	>99	<1	0.561	0.790	<0.01	...

^a This ratio was found to be the same at 70, 15, and 12 ev within experimental error. ^b See ref 15b. ^c Acid-catalyzed rearrangement. ^d See ref 43.

by aryl (XVI \rightarrow ga) and phenyl (XVI \rightarrow gb) migration as determined by ¹⁸O labeling is shown in Table II. In 12 out of 15 examples, the over-all rate of decarboxylation decreases upon introduction of either electron-withdrawing or electron-releasing substituents, and is at a maximum when X = H.

This observation can be rationalized on the basis of charge distribution¹⁶ in the molecular ion, and by taking account of the relative basicities⁴³ of the aryl groups concerned. In an unsymmetrical aryl phenyl carbonate molecular ion (e.g., that of II), the positive charge will be unsymmetrically partitioned on either side of the carbonyl group. The direction and magnitude of this charge asymmetry will depend on the electronic character of the substituent X. The relative contributions of resonance forms IIa (preferred for electron-attracting groups X) and IIb (preferred for electron-donating substituents) provide an approximate description of the situation.



Thus simply on charge localization grounds, aryl migration to the most electrophilic center might be predicted to preponderate (see arrows in IIa) for X = + σ groups, and phenyl migration (see arrows in IIb) for X = - σ substituents. In fact, the reverse situation obtains (Table II), indicating that the nucleophilicity of the migrating group is critical. The more nucleophilic entity is preferentially itinerant (arrows, IIb) when X = + σ substituents (e.g., *p*-NO₂, *p*-CN, *p*-F, *p*-Br, *p*-CO₂CH₃, *o*-OCH₃), although the rate of migration is lower than in diphenyl carbonate (II, X = H) itself, since IIb is a higher energy resonance form of the molecular ion. Conversely, when X = - σ groups

(42) As for example toward electrophilic substitution.^{4b}

(e.g., CH₃, *p*-C₆H₅, *m*- and *p*-OCH₃), migration of the more basic aryl moiety (arrows, IIa) is preferred, again at a lower rate than when X = H, since IIa is now a higher energy resonance contributor.

Charge localization and nucleophilicity, therefore, oppose each other in determining the over-all migratory propensities of aryl groups in this particular system. The more basic aryl groups, with electron-releasing substituents, excel at both charge localization and migration. Conversely, the less nucleophilic aryl groups, with electron-withdrawing substituents, are poorer at both charge localization and migration, and the relative migratory aptitudes tend to be leveled by internal compensation of these two effects.

The resulting aryl group migratory aptitudes (Table II, column 6) for the electron impact induced decarboxylation reaction (1,3 migration) are to be compared with those for acid-catalyzed rearrangement of substituted benzpinacols⁴³ (1,2 migration) (Table II, column 7). It can be seen that the electron impact process migration propensities follow only in an extremely qualitative sense those observed for the carbonium ion process in solution.⁴⁴ Further studies are in progress to determine the relative migratory aptitudes of both aryl and alkyl groups in other mass spectral rearrangement reactions.

Experimental Section

Mass Spectra. The low-resolution mass spectra of the aryl methyl carbonates I were obtained by Drs. A. M. Duffield and J. K. MacLeod, using an Atlas CH-4 instrument and operating under the following conditions: ionizing voltage 70, 15, and 12 ev, inlet temperature 70°, AN-4 ion source at 180°. Low-resolution spectra of the aryl phenyl carbonates II were recorded by Mr. N. S. Garcia, employing a CEC 21-103 machine equipped with an all-glass heated inlet system at 200° and ion source temperature 250°. All high-resolution mass measurements were secured by Mr. R. G. Ross, with an AEI MS-9 double-focusing mass spectrometer of apparent resolution 1 part in 15,000, and fitted with an all-glass heated inlet system at 200°, and ion source temperature 250°.

For quantitative relative abundance measurements, the spectra of each series of compounds I and II were run sequentially under identical operating conditions. At least duplicate determinations were made for each individual compounds, and it was found that peak heights were reproducible to within $\pm 1\%$.

The ALGOL computer program for least-squares treatment of the Hammett plot data was kindly supplied by Dr. J. I. Brauman.

Preparation of Carbonates. Unlabeled aryl methyl carbonates and aryl phenyl carbonates were prepared as before,⁸ from methyl and phenyl chloroformates, respectively. ¹⁸O-Labeled aryl methyl

Table III. Melting Points of Solid Carbonate Esters

CH ₃ OCOOC ₆ H ₄ X		C ₆ H ₅ OCOOC ₆ H ₄ X	
X	Mp, °C	X	Mp, °C
<i>p</i> -NO ₂	114-115	<i>p</i> -NO ₂	130-131
<i>m</i> -NO ₂	74-75	<i>p</i> -CN	88-90
<i>p</i> -CN	89-90	<i>p</i> -F	79-80
<i>m</i> -CN	62-63	<i>p</i> -Br	104-105
<i>p</i> -CO ₂ CH ₃	70-71	<i>p</i> -Cl	103-104
<i>m</i> -CO ₂ CH ₃	49-50	<i>p</i> -CO ₂ CH ₃	94-95
<i>p</i> -COCH ₃	88-89	<i>p</i> -C ₆ H ₅	195-197
<i>p</i> -C ₆ H ₅	83-84	<i>p</i> -OCH ₃	92-94

(43) W. E. Bachmann and J. W. Ferguson, *J. Am. Chem. Soc.*, **56**, 2081 (1934).

(44) In a study of aryl group migratory aptitudes in the Baeyer-Villiger rearrangement (1,2 migration to oxygen) of substituted acetophenones, M. F. Hawthorne and W. D. Emmons, *ibid.*, **80**, 6398 (1958), report the relative rate sequence *p*-CH₃ > H > *p*-Cl > *p*-Br > *m*-NO₂ > *p*-NO₂, with $\rho = -1.45$ (acetonitrile, 29.8°).

carbonates (VI, X = H, CN, OCH₃) were made by converting methanol-¹⁸O (55.5% enriched)^{4a} to the chloroformate, which was then treated with the appropriate phenol in pyridine.⁵ ¹⁸O-Labeled methyl phenyl carbonate (V) and all ¹⁸O-labeled aryl phenyl carbonates XII were prepared by transforming ¹⁸O-phenol^{4a} (diluted to 37.5% enrichment) to the chloroformate, and then add-

ing methanol or the appropriate substituted phenol, respectively.⁵ The carbonate esters were purified as before,⁵ using gas-liquid chromatography and several injection-collection cycles for liquids, and recrystallization to constant melting point for solids.

Identity and purity of all unlabeled carbonates were determined by elemental combustion analysis, gas-liquid or thin layer chromatography, and infrared and low-resolution mass spectra. The retention times or *R_f* values, infrared and mass spectra, and melting points (Table III) of the labeled carbonates were critically compared with those of the corresponding unlabeled materials.

(45) Supplied by Yeda Research and Development Co. Ltd., Rehovoth, Israel.

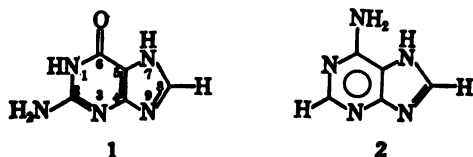
Mass Spectra of Nucleic Acid Derivatives. II. Guanine, Adenine, and Related Compounds^{1a}

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Contribution from the National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014, and the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. Received November 17, 1966

Abstract: The mass spectra of guanine, its 1-, 3-, and 7-methyl derivatives, and of isocytosine, hypoxanthine, adenine, and 6-methylaminopurine have been analyzed with the aid of high-resolution mass measurements, metastable peaks, and deuterium labeling. The major electron-impact fragmentation pattern exhibited by guanine and its mono-N-methyl derivatives consists of initial expulsion of a cyanamide fragment, which contains N-1, C-2, and the amino nitrogen atom, followed by decarbonylation. This sequence thus involves all the guanine atoms which take part in the Watson-Crick pattern of hydrogen bonding in polynucleotides. In contrast, the initial fragment expelled from the adenine molecular ion originates uniquely from a single site only when the amino group is methylated.

Guanine (2-amino-6-oxypurine; the prevailing 1H tautomer is shown as 1) and adenine (6-amino-purine, 2) comprise the major purine components of



both ribo- and deoxyribonucleic acids, and of a variety of coenzymes and biosynthetic intermediates as well.² Most of the minor purine constituents of both transfer RNA^{3,4} and of DNA⁵ consist of mono- and dimethyl derivatives of 1 and 2.

It has recently been demonstrated that adenine also is the principal component of a number of alkaloids, including the cytokinins, which under certain conditions are powerful stimulators of plant cell division. The naturally occurring compounds in this series include zeatin, 6-(4-hydroxy-3-methyl-2-butenyl)aminopurine, isolated as the free base⁶ and possibly as a nucleoside and nucleotide⁷ from maize, and its deoxy derivative,

6-(3-methyl-2-butenyl)aminopurine.^{8,9} The latter compound has been isolated both from a bacterium¹⁰ and, in the form of its ribonucleoside, as a minor component of transfer RNA in yeast^{8,11} and in calf liver.⁸ The isomeric 6-amino-3-(3-methyl-2-butenyl)purine, which is devoid of cytokinin activity, has been identified as the alkaloid triacanthine.¹²

Mass spectrometry played a significant but limited role in the elucidation of the structures of these substituted adenine derivatives, and has also been applied in studies of the mechanism of biological methylation of transfer RNA,¹³ but to date no systematic study of the mass spectra of the parent compounds has been published. The mass spectra of purine nucleosides, in which the fragmentation patterns of the purine moieties have received relatively little attention, have been used in studies both of nucleic acid components^{13,14} and of certain antibiotics.^{15,16} We present here the mass spectra of guanine, adenine, and some of

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(1) (a) Part I of this series: J. M. Rice, G. O. Dudek, and M. Barber, *J. Am. Chem. Soc.*, **87**, 4569 (1965). (b) National Cancer Institute. (c) To whom inquiries should be addressed at Harvard University.

(2) The 7(9) prototropic tautomerism of purines unsubstituted in the imidazole ring is ignored in these studies; the imidazole proton is generally represented arbitrarily as residing on N-7.

(3) Abbreviations and notation used in this paper: RNA, ribonucleic acid; DNA, deoxyribonucleic acid; M, molecular (parent) ion; M - *n*, the *m/e* value of a fragment ion formed by loss of *n* mass units from the molecular ion.

(4) L. R. Mandel and E. Borek, *Biochemistry*, **2**, 555 (1963).

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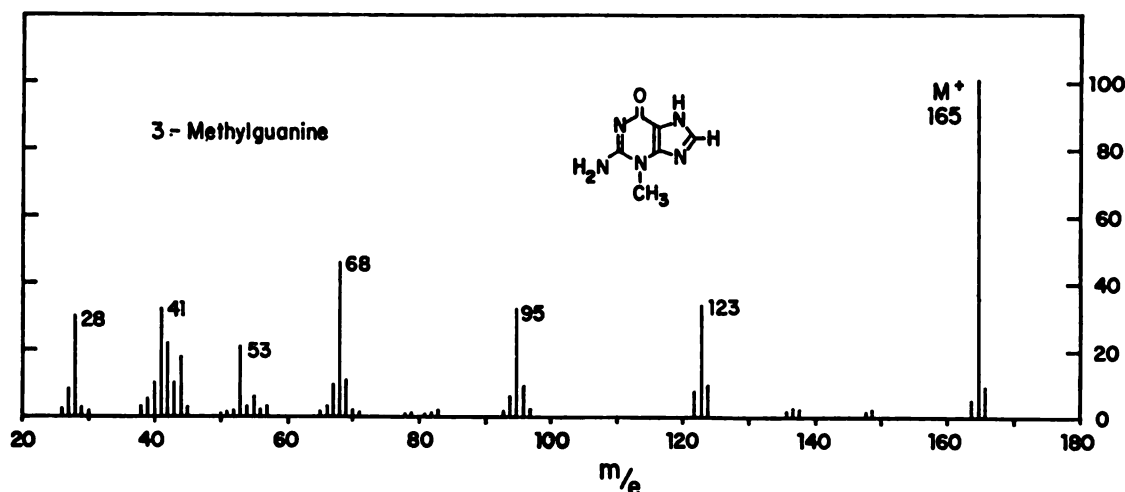


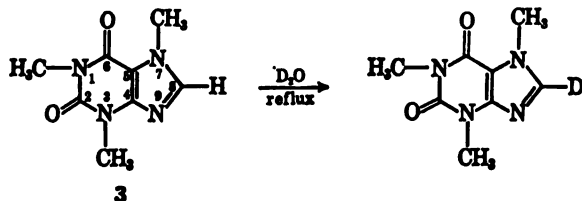
Figure 1. Mass spectrum of 3-methylguanine at 70 eV.

their derivatives, in which the fragmentation patterns have been characterized by metastable peaks and by high-resolution mass measurements of fragment ions. We have sought especially to identify fragments which originate characteristically and uniquely from specific atomic groupings within these molecules, and, where possible, to suggest reasonable structures and mechanisms for the formation of fragment ions.

Experimental Section

The compounds studied were commercial preparations of the highest purity available, and were obtained from the California Corporation for Biochemical Research, Schwarz Bioresearch Inc., Cyclo Chemical Corp., K and K Laboratories Inc., or Aldrich Chemical Co. All preparations were checked for chromatographic homogeneity on paper prior to use. 3-Methylguanine (Cyclo) contained a trace of yellow contaminant, apparently quite polar from its chromatographic behavior, which could be removed by recrystallization from water and which did not contribute significant "noise" to the spectrum of the much more volatile purine. A more polar, ultraviolet-absorbing impurity, identified by R_f values and by infrared spectroscopy as guanine, invariably contaminated samples of 1-methylguanine, and was found in amounts ranging from a trace to more than 90% of the mixture. Preparations containing only traces of guanine provided intense spectra of the more volatile 1-methyl derivative which displayed no significant peak at m/e 151, the molecular ion and base peak in the spectrum of guanine, and were used without purification.

Readily exchangeable protons (amino, imidazole, "hydroxy") were replaced with deuterium by warming briefly (*ca.* 15 min) in neutral or basic D_2O and then rotary evaporating the neutralized solution to dryness. If necessary, the procedure was repeated until the expected number of deuterium atoms had been incorporated. Prolonged refluxing (*ca.* 1 hr) in D_2O effects replacement of an additional proton by deuterium. This has been shown to occur at C-8 in purine,¹⁷ and is presumed to occur at this position in substituted purines as well. The reaction seems to be general for imidazole derivatives,^{18,19} and occurs readily in caffeine (3), where the reaction

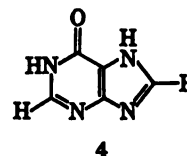


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(19) G. O. Dudek and J. M. Rice, unpublished observations.

can be followed unambiguously by pmr spectroscopy.¹⁸ In the cases of adenine and hypoxanthine (6-oxypurine; the 1H tautomer is illustrated as 4), where the magnetic resonance signals of the C-2 and C-8 protons are very close together and are both pH and concentration dependent, only one peak decreases steadily in intensity and finally disappears as deuteration proceeds. Thus hypoxanthine (mol wt 136) readily exchanges two protons for deuterium, forming 1,7(9)-dideuteriohypoxanthine (hypoxanthine- d_2 ,



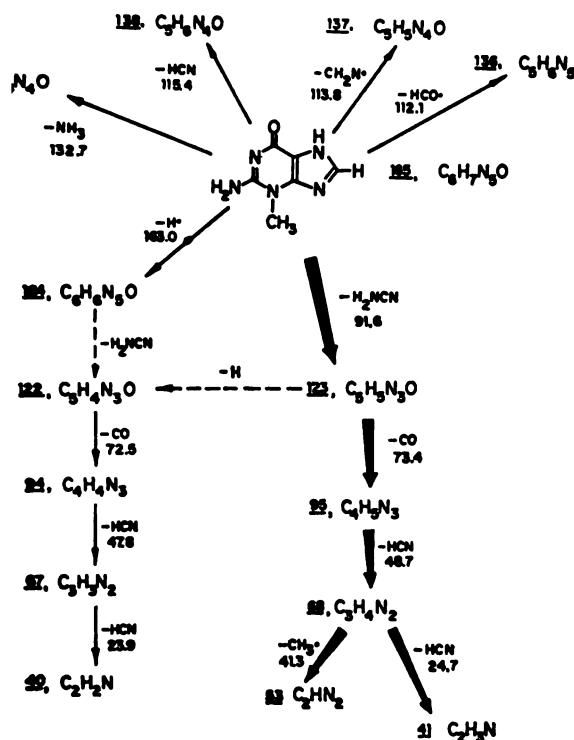
mol wt 138), which on prolonged refluxing slowly exchanges a third hydrogen atom to yield 1,7(9),8-trideuteriohypoxanthine (hypoxanthine- d_3 , mol wt 139). Adenine behaves similarly.

Mass spectra were obtained with an Associated Electrical Industries (Ltd.) MS-9 double-focussing mass spectrometer, using a direct-insertion probe. The voltage of the electron beam was occasionally lowered from the standard 70 eV to 30, 20, or 16 eV to suppress high-energy fragmentation paths and to increase the intensity of metastable peaks. Standards for high-resolution mass measurements included argon, nitrogen, and fragments of perfluorotri-*n*-butylamine.

Results and Discussion

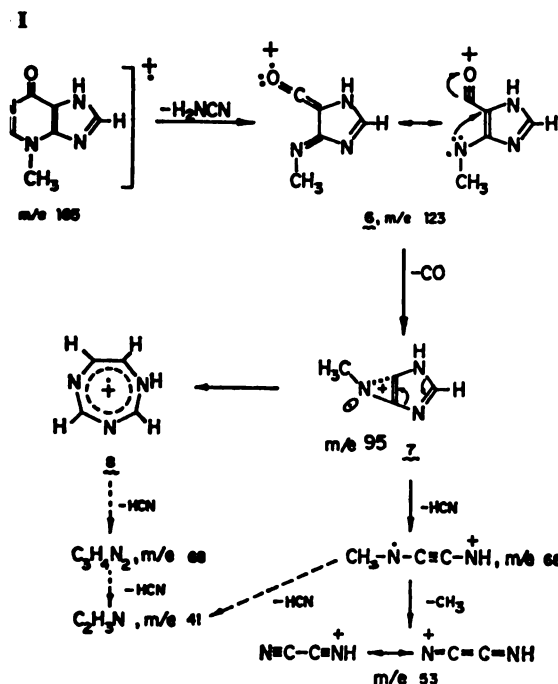
The most intense peak in the mass spectra of guanine and its 1-, 3-, and 7-methyl derivatives is that of the molecular ion, from which a variety of fragments are expelled to produce three groups of primary fragment peaks of weak (less than 10%) to moderate (less than 40%) relative intensity. These occur at $M - (16-17)$, due to loss of the amino group or ammonia; at $M - (41-42)$ or, in the case of 1-methylguanine, at $M - (55-56)$, resulting from expulsion of cyanamide fragments; and in some cases at $M - (27-30)$ due to ejection of carbonyl and methylamine fragments. The initial expulsion of a neutral cyanamide fragment is the predominant and most characteristic mode of decomposition of a guanine molecular ion, and is followed by a well-defined sequence of subsequent fragmentation steps which give rise to the major peaks in the mass spectra of these compounds. The cyanamide fragments originate uniquely from N-1, C-2, and the amino group in the pyrimidine ring of guanine, a conclusion which follows from comparison of the mass spectra of its N-methyl derivatives.

The mass spectrum of 3-methylguanine (Figure 1) is characterized by fragment ion peaks at m/e 123, 95,



2. Fragmentation paths of 3-methylguanine. The m/e values of observed metastable peaks are given to 0.1 mass unit, together with the transitions to which they have been assigned. Dashed lines designate transitions for which metastable peaks were not observed, but which reasonably account for the presence in the mass spectrum of the indicated peaks. Heavy arrows indicate the primary fragmentation processes. The elemental compositions of all ions are indicated in this and other fragmentation diagrams were established by high-resolution mass measurements.

and 41, whose sequential formation from the molecular ion at m/e 165 is well documented by the presence of metastable peaks (Figure 2). Mechanisms for some of these fragmentation processes are proposed in Scheme I.²⁰ Expulsion of cyanamide from the mo-



The conjugated π -electron systems of the molecular ion and the positive fragment ions can accommodate delocalization of the posi-

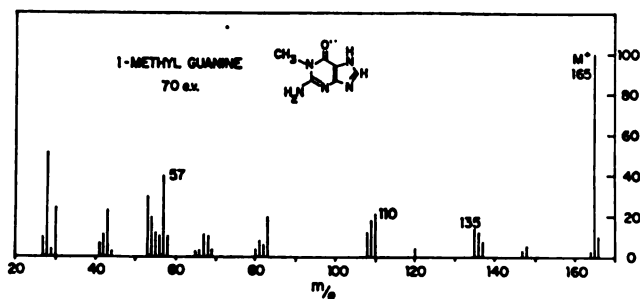


Figure 3. Mass spectrum of 1-methylguanine at 70 eV.

lecular ion, 5, is readily explained by a retro Diels-Alder mechanism which results in the formation of ion 6 at m/e 123. Decarbonylation is the only significant fragmentation reaction of ions having the elemental composition of 6; a metastable peak at m/e 75.0 ($123 \rightarrow 96$) for the loss of HCN is too weak to be considered unequivocal. The decarbonylation product at m/e 95, ion 7, loses HCN followed by either the methyl group or another molecule of HCN. While 7 is a likely candidate for rearrangement, and could give rise to highly stabilized heteroaromatic ions such as 8 by redistributing its methyl hydrogen atoms within an expanded ring, the methyl group remains intact in a substantial fraction of these ions. The fragmentation of 7, therefore, probably proceeds by several paths, among them the sequence indicated.

The ions at m/e 122 and 124 may derive partly from the molecular ion, but this interpretation is not supported by the presence of metastable peaks. The m/e 122 ion is probably formed primarily by expulsion of a hydrogen atom from 6, chiefly from the methyl group. Except for the ^{13}C -containing fragment at m/e 124, these are even-electron ions, and although they follow basically the fragmentation sequence outlined in Scheme I, their fragments at m/e 67 and 69 show no tendency to eject a methyl radical: the peak at m/e 54 is small and that at m/e 52 is negligible. The molecular ion can also lose HCN and, by processes involving hydrogen rearrangements, H_2CN (not CO !), HCO , or NH_3 . However, the resulting peaks at m/e 136–138 and at 148 are very small, as are the secondary fragmentation peaks which appear in clusters at intervals of approximately 27 mass units below the group at m/e 136–138.

The location of the methyl group in 1-methylguanine has several important consequences for the electron-impact fragmentation patterns of this molecule. First, the methyl group is always lost with the cyanamide fragments, as a result of which peaks are observed at m/e 110 and 109 (i.e., at $M - 55$ and $M - 56$ in Figure 3). Neutral methylcyanamide fragments expelled from the molecular ion retain three or four of the five hydrogen atoms originally associated with the amino and methyl groups. When all five are retained, i.e., when hydrogen rearrangement does not accompany frag-

ment, the positive charge (and the unpaired electron in ion radicals) over all the atoms of second-row elements present except (perhaps) methyl carbon atoms. It is often extremely difficult adequately to represent the structures of such ions, especially when they contain many heteroatoms whose "lone pair" electrons in fact contribute to the π -electron population. In attempting to understand fragmentation patterns it is frequently more instructive to consider a single valence-bond structure for a given ion, rather than the resonance hybrid to which it contributes. We have freely adopted this approach in Scheme I and elsewhere in this paper.

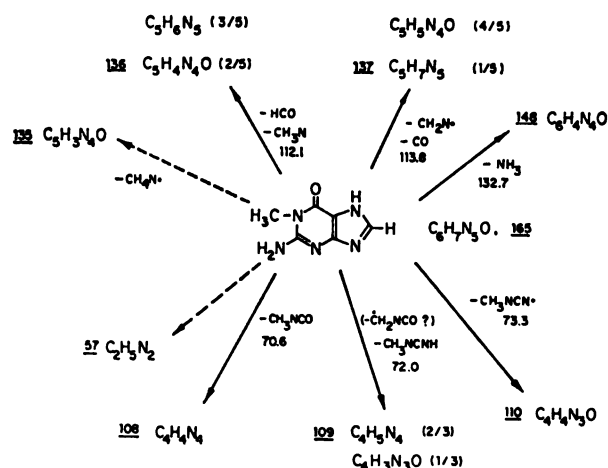


Figure 4. Electron-impact fragmentation reactions of the 1-methyl-guanine molecular ion.

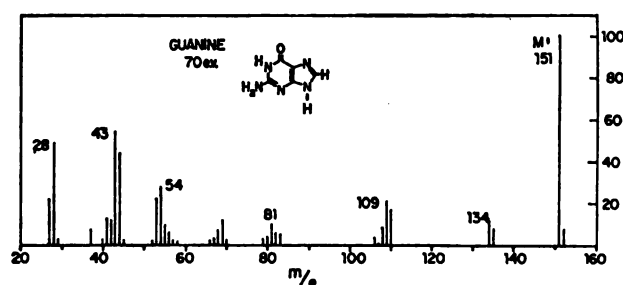


Figure 5. Mass spectrum of guanine at 70 eV.

mentation, the methylcyanamide fragment also retains the charge, and gives rise to the major component of the peak at m/e 57. As expected, loss of neutral cyanamide fragments is followed by decarbonylation and subsequent loss of HCN. There are no significant peaks at $M - 41$ and $M - 42$, which indicates that N-1 is always the sole nuclear nitrogen atom lost when cyanamide fragments are expelled from guanine derivatives. This generalization applies even when, as in the present case, the arrangement of double bonds in the pyrimidine ring interferes with the mechanism presented in Scheme I for this reaction. This interference is a second consequence of the location of the methyl group at N-1, and results in lower relative intensities for the ions produced in the series of reactions initiated by expulsion of a cyanamide fragment (compare peaks at m/e 123, 95, and 68 in Figure 1 with corresponding peaks at m/e 109–110, 81–82, and 54–55 in Figure 3). The presence of the methyl group at N-1 also tends to stabilize the positive charge in that region of the guanine molecule. The stabilization of charge, together with the decreased occurrence of competing processes, results in an increased tendency for cleavage of the "single" bonds in the molecular ion in the vicinity of N-1, as indicated by the increased intensity of peaks at m/e 135–137 (loss of carbonyl or methylamine fragments). Some of these fragments can also be lost simultaneously, producing the major component of the m/e 109 peak and all of the m/e 108 ions (Figure 4).

The mass spectrum of guanine (Figure 5) is essentially identical with that of 1-methylguanine below m/e 120, with the exception that peaks at m/e 43 and 44, due to CH_2N_2^+ and CH_4N_2^+ (cyanamide) ions originating at

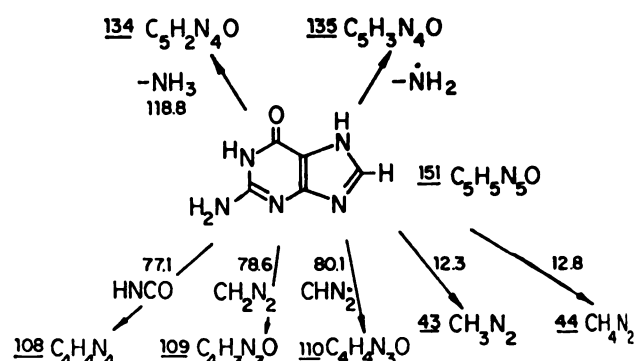


Figure 6. Major electron-impact fragmentation reactions of the guanine molecular ion.

least in part from the molecular ion, replace the corresponding m/e 57 peak in the spectrum of 1-methylguanine. Decarbonylation is not a significant decomposition reaction for the guanine molecular ion in the absence of a methyl group at N-1. Deamination (followed by decarbonylation) and expulsion of HNCO are the only major fragmentation processes which compete with loss of cyanamide (Figure 6). The ions at m/e 109–110 produced by the latter reaction eject CO and HCN, preferably but not exclusively in the order given, producing the peaks at m/e 81–83 and 54–55; these processes are not completely defined by metastable peaks. The ability of guanine to lose cyanamide fragments containing one or two hydrogen atoms, the loss of fragments other than cyanamide from the molecular ion, and the over-all low intensity of fragment ion peaks resemble the characteristics of 1-methylguanine, rather than those of 3-methylguanine. This suggests that the prevailing tautomer of guanine in the vapor phase is the linearly conjugated structure 1 in which the pyrimidine ring proton resides on N-1; this is, of course, the familiar tautomer encountered in aqueous solutions and in polynucleotides.

The mass spectrum of 7-methylguanine (Figure 7) is more plentifully endowed with metastable peaks than the spectrum of guanine. A more complete analysis of the fragmentation paths is therefore possible (Figure 8), but the major features of the spectra of the two compounds are quite similar. The 7-methylguanine molecular ion undergoes deamination and loss of cyanamide fragments, but reactions involving expulsion of CO, HCO, or methylamine fragments are extremely minor processes in sharp contrast to the behavior of the 1-methyl isomer. Ejection of an isocyanate fragment from the molecular ion also does not occur to any significant extent, although this reaction is undergone both by the 1-methyl isomer and by guanine itself. The major fragmentation path consists of ejection of cyanamide fragments, giving rise to the peaks at m/e 123 and 124, after which much of the fragmentation pattern is analogous to that of 3-methylguanine with respect to the m/e values, but not the relative intensities, of successive fragmentation peaks (compare Figures 2 and 8). It is noteworthy that ion 9 at m/e 95, the un-rearranged product of successive loss of cyanamide and CO from the 7-methylguanine molecular ion, differs from the corresponding daughter ion of 3-methylguanine (7) only in the position of the methyl group, which in 9 is poorly situated to participate in

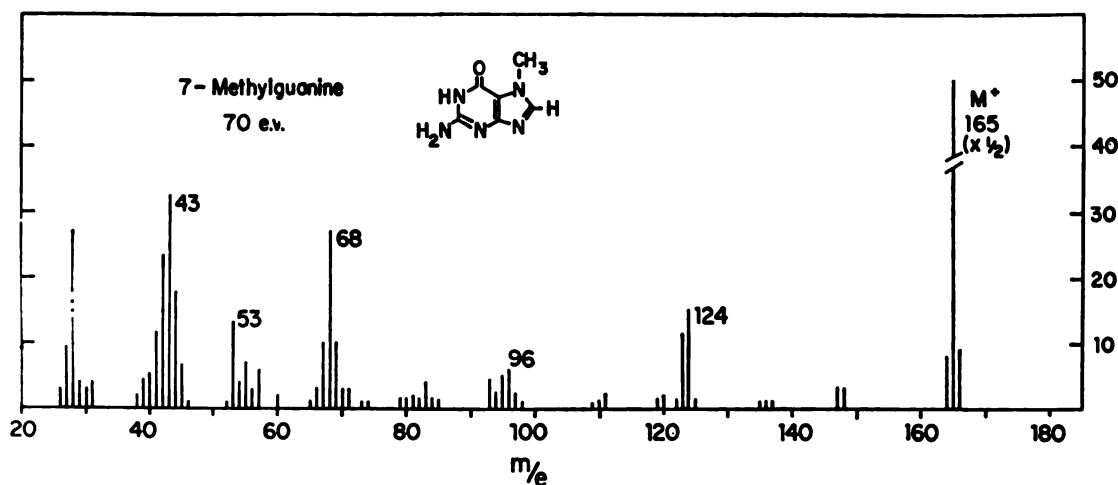


Figure 7. Mass spectrum of 7-methylguanine at 70 ev.

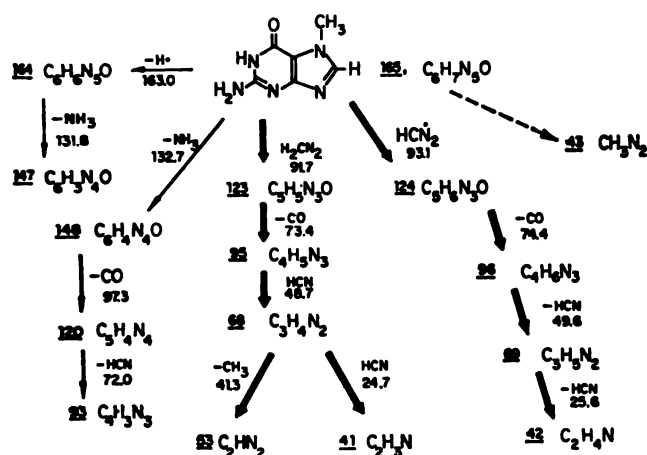
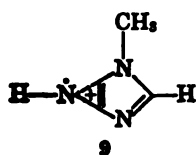


Figure 8. Fragmentation paths of 7-methylguanine.

ring expansion to structures such as 8. This may explain why the m/e 95 peak is prominent in Figure 1 but very weak in Figure 7, while the m/e 68 peak which results from loss of HCN from the m/e 95 ions is prominent in both.



The combined presence of the amino group at C-2 and the keto function at C-6 in guanine and its mono-methyl derivatives serves to limit the fragmentation reactions of the molecular ion to the pyrimidine ring. The mass spectrum (Figure 9) of 2-amino-4-oxypyrimidine (isocytosine), whose arrangement of functional groups corresponds to that of guanine, is qualitatively quite similar to the high-mass region of the spectrum of the latter. Analysis of metastable peaks, together with high-resolution mass measurement of fragment ions (Figure 10), confirms that the same neutral fragments and the CH_2NH_2^+ ion are expelled from the molecular ions of both compounds. However, it is apparent from Figure 9 that loss of CO from the molecular ion is a far more important process for isocytosine than it is for guanine or any of the mono-N-methyl-

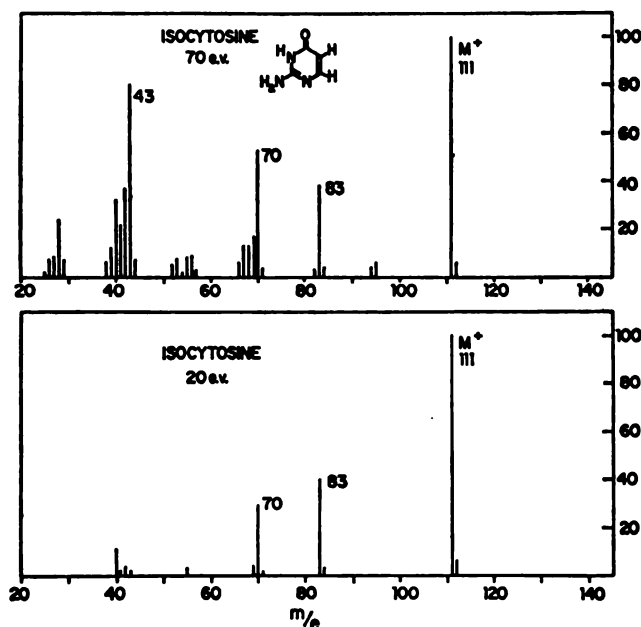


Figure 9. Mass spectra of isocytosine at 70 and 20 ev.

guanines, and that fragmentation in general is much more facile for the pyrimidine ion. It follows that the aromatic imidazole ring fused to the isocytosine molecule in guanine derivatives stabilizes the molecular ion by delocalizing the positive charge and thus depresses the tendency toward fragmentation, but does not otherwise alter the modes of decomposition of the molecular ion. This stabilization is least effective when the arrangement of bonds in the pyrimidine ring allows the molecular ion to undergo a facile retro Diels-Alder reaction, as in the case of 3-methylguanine, or of 2,6-dioxypurines (xanthines).²¹

Purines which contain only one functional group in the pyrimidine ring show a much less pronounced tendency for one fragmentation reaction of the molecular ion to predominate over all the others. Omission of the amino group from the guanine molecule yields hypoxanthine (4), whose mass spectrum (Figure 11) is notable for the extremely low intensities of its fragment

(21) G. Spiteller and M. Spiteller-Friedmann, *Monatsh. Chem.*, **93**, 632 (1962); J. M. Rice and G. O. Dudek, in preparation.

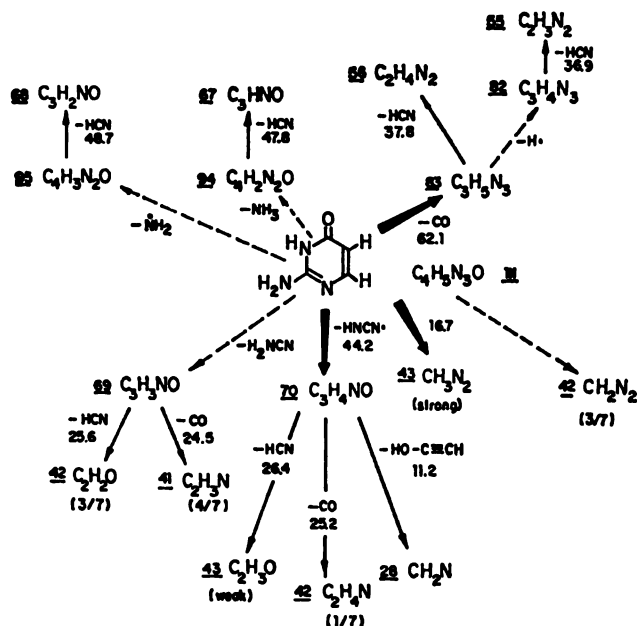


Figure 10. Major fragmentation paths of isocytosine. The distribution of fragment ions suggests that the 3H tautomer of isocytosine (shown) predominates in the vapor phase.

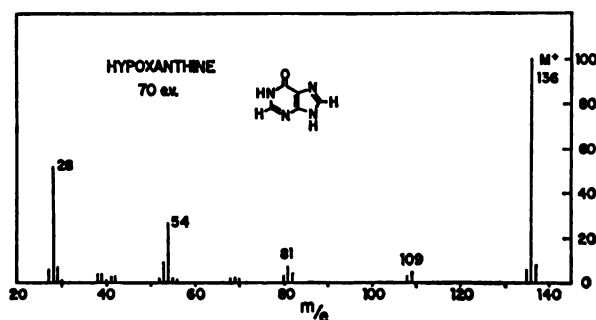


Figure 11. Mass spectrum of hypoxanthine at 70 eV.

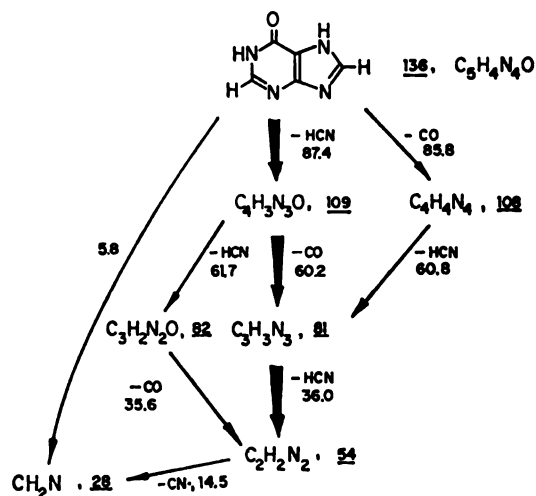


Figure 12. Fragmentation paths of hypoxanthine. The existence of multiple fragmentation reactions for the molecular ion suggests that the 1H tautomer predominates in the vapor phase.

ion peaks. This spectrum suggests, however, that the major determinant of the guanine fragmentation pattern is the carbonyl function and not the amino groups, for to a large extent hypoxanthine expels neutral fragments

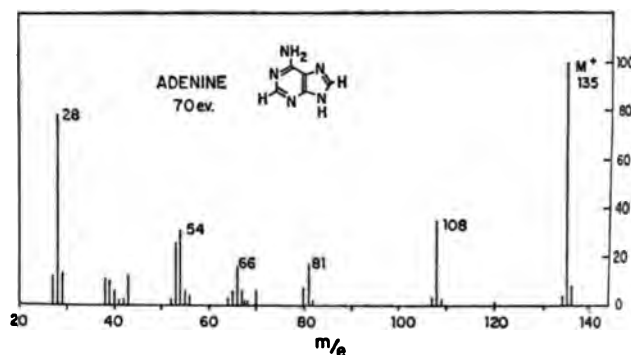


Figure 13. Mass spectrum of adenine at 70 eV.

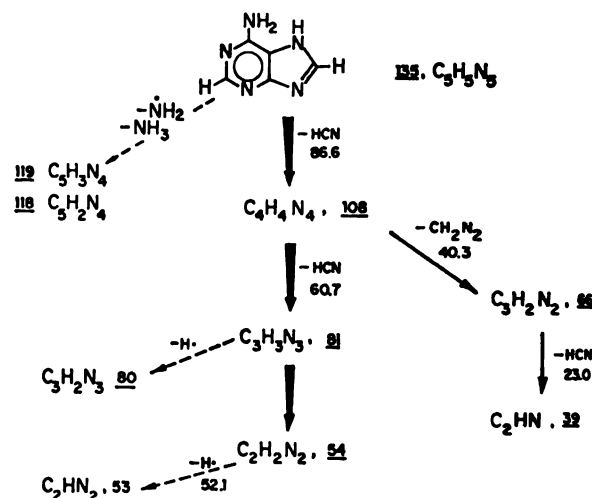
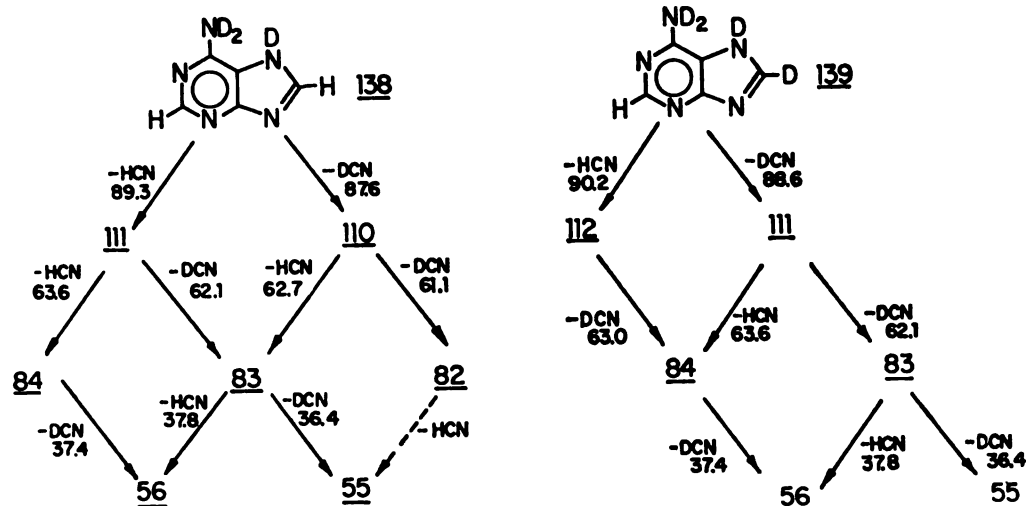


Figure 14. Principal fragmentation paths of adenine.

from the same sites and in the same order as guanine. The molecular ion can eject a hydrogen atom, CO, or HCN, but the preferred process is expulsion of HCN, followed by CO and another molecule of HCN (Figure 12). The $M - 27$ peak persists *with undiminished relative intensity* in the mass spectra of hypoxanthine- d_1 and hypoxanthine- d_3 , and loss of HCN from the latter *must* include C-2. The initial loss of HCN from the hypoxanthine molecular ion thus corresponds principally to the expulsion of cyanamide fragments by guanine, and is inferred to involve N-1 as well as C-2. The subsequent decarbonylation and loss of HCN represent a continuation of the guanine fragmentation pattern. Expulsion of a charged cyanamide fragment from guanine also finds an analogy in the formation of H_2CN^+ from hypoxanthine, but not all of the protonated HCN fragments which originate from the molecular ion do so from the same site as the neutral HCN discussed above. The m/e 28 peak due to H_2CN^+ shifts cleanly to m/e 29 ($HDCN^+$) in the spectrum of hypoxanthine- d_3 , but its total intensity is divided nearly equally between peaks at m/e 29 and 30 (D_2CN^+) in the spectrum of hypoxanthine- d_3 . A metastable peak in the latter spectrum at m/e 6.5 (139 \rightarrow 30) confirms the origin of some of the D_2CN^+ ions from the molecular ion, and therefore from the imidazole ring.

If the carbonyl group of hypoxanthine and its associated proton are replaced by an amino group, the neutral fragments expelled from the resulting adenine



The multiple origins of cyanide molecules produced at each stage of fragmentation in adenine- d_5 and adenine- d_4 .

ar ion no longer show any tendency to originate from a single site. The mass spectrum of (2; Figure 13) is characterized chiefly by fragmentation peaks at m/e 108, 81, and 54 due to successive loss of three molecules of HCN, although other fragments are occasionally lost along the way (Figure 15). CN and DCN can be lost in all possible sequences from the adenine- d_5 and adenine- d_4 molecular ions, as indicated in Figure 15, proving that many fragmentation paths contribute to the mass spectrum. Similar behavior of the unsubstituted purine molecule has recently been analyzed in detail.²²

Loss of the amino group from the molecular ion is an entirely minor process for adenine, but if the amino group is methyl substituted, the initial fragments lost from the molecular ion originate predominately from the methylamino group. 6-Methylaminopurine (Figure 16) preferentially expels 28 or 29 mass units (CH_2N or CH_3N) from the molecular ion. This process consists of the methylamino group with concomitant loss of one or two hydrogen atoms to the purine ring, followed in each case by successive loss of molecules of HCN. A high-energy variant, not at 16 eV, involves initial loss of a hydrogen atom from the methylamino group by the remaining 29 mass units of the methylamino group. When the entire methylamino group is lost as a single unit, it retains the positive charge, giving rise to the CH_4N^+ ion at m/e 30. Methylation of the amino group thus introduces a powerful and unifying influence into the chaotic array of fragmentation patterns which otherwise characterize the adenine molecule.

Conclusions

The characteristics of guanine appear to be much more favorable than those of adenine or hypoxanthine for the study of such reactions.

Tatematsu, T. Goto, and S. Matsuura, *Nippon Kagaku Zasshi*, 86, 1566 (1965).

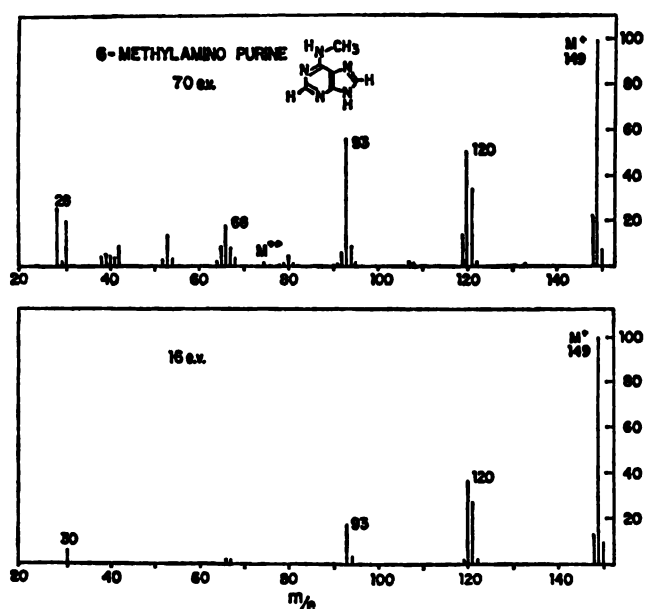


Figure 16. Mass spectra of 6-methylaminopurine at 70 and 16 eV.

for obtaining unambiguous structural information from the mass spectra of derivatives of these compounds. It is noteworthy that guanine in nucleic acids is much more reactive than adenine toward both mutagens of the mustard type²³ and certain carcinogenic compounds,²⁴ and the application of mass spectrometry to the study of such reactions should prove fruitful.

Acknowledgments. We wish to thank Dr. Hiroyasu Utiyama for his help with Japanese literature, and Dr. Burton Tropp for a sample of 6-methylaminopurine.

(23) P. Brooks and P. D. Lawley, *Biochem. J.*, 77, 478 (1960).

(24) E. Kriek, *Biochem. Biophys. Res. Commun.*, 20, 793 (1965); E. C. Miller, U. Juhl, and J. A. Miller, *Science*, 153, 1125 (1966).

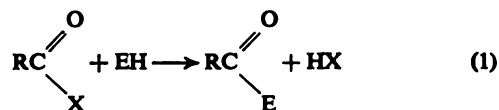
Optical Properties and the Chemical Nature of Acyl-Chymotrypsin Linkages

Elliot Charney and Sidney A. Bernhard

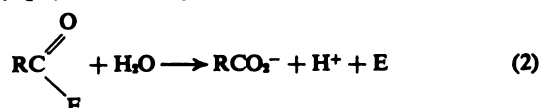
Contribution from the Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland, and the Department of Chemistry and Institute of Molecular Biology, Eugene, Oregon. Received November 19, 1966

Abstract: On the supposition that the specific spectral properties of mono- β -arylacryloyl enzymes are related to their special reactivity, the spectra and optical rotatory dispersions of α -chymotrypsin and some acyl derivatives have been examined and compared with the spectra and optical rotatory dispersions of a group of relevant small molecules. The reactivities of these acyl enzymes have previously been correlated with their catalytic functions in specific substrate reactions, and there are considerable presumptive arguments that the acyl-enzyme linkage is *via* a specific serine hydroxyl oxygen (an ester linkage). The spectral properties, especially the large red shifts on acylation, and chemical reactivities of these mono- β -arylacryloyl enzymes differ from those of small molecule model acylserine esters. On the basis of the comparisons of their optical properties, these differences are found to be due to an *endo*-energetic configurational change which takes place when the enzyme is acylated with the β -acryloyl substrates. It is found that the "native" β -acryloyl enzyme has a "*s-cis*" configuration in contrast to the small molecule model compounds which are predominantly in the "*s-trans*" configuration. The magnitude of the induced optical rotatory activity attributable to the transition associated with the absorption band of the β -acryloyl component of the acetylated enzyme, nmr measurements on model compounds, and other spectral information are shown to exclude other possible configurational changes such as out-of-plane skewing or *cis-trans* isomerization about the double bonds. Chemical perturbation (*via* enzyme substituents) of an otherwise conventional acyl-serine linkage is also considered and rejected as an unlikely origin of the observed spectral shifts.

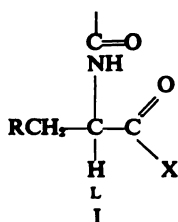
A number of detailed studies of the chemical and spectral properties of aroyl chymotrypsins have been reported.¹⁻³ These aroyl enzymes can be prepared, virtually stoichiometrically, by reactions of the type illustrated in eq 1. Under appropriate conditions



of pH, when the "leaving group" is strongly electron withdrawing, this specific monoacylation reaction may be sufficiently faster than the succeeding deacylation reaction (eq 2) for the acyl intermediate to be studied in

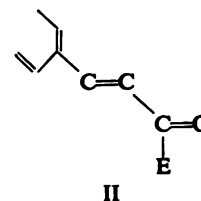


isolation. A variety of parallels can be drawn between the relatively slow pathways of acylation and deacylation exhibited with these aroyl acylating agents and the rapid turnover of specific substrates (I) of α -chymotrypsin. Although many of the monoaroyl-



chymotrypsin derivatives are sufficiently stable to be studied spectrophotometrically by conventional tech-

niques, they are all nevertheless strikingly more reactive than the corresponding aroylalkyl esters. This comparison is of significance since denaturation of the monoacyl enzyme leads to the formation of an identifiable monoacylserine O-ester peptide.³⁻⁵ The aromatic nature of the acyl-enzyme derivatives reported herein is of no particular chemical catalytic consequence; aliphatic acyl enzymes have similar chemical properties.^{6,7} Due to its intense ultraviolet absorption, the aroyl group provides an indicator of the electronic environment at the site of covalent attachment to the enzyme. The effectiveness of this system as an electronic indicator can be greatly enhanced by extension of the π -resonance systems as in derivatives of type II or III because the intense π - π^* transition occurs at longer wavelengths and so sufficiently outside the region of ultraviolet absorption of the enzyme to simplify the spectrophotometric measurements. In addition, equally energetic shifts result in larger shifts in wavelength because of the inverse nature of the relationship between energy and wavelength.

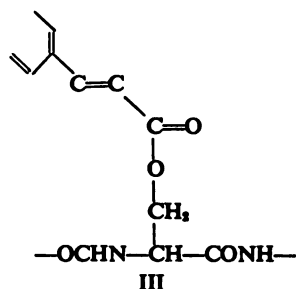


Denatured solutions of the mono- β -arylacryloyl-enzyme derivatives have similar chemical properties and identical ultraviolet and/or near-visible spectra when compared with model serine peptides containing

- (1) M. L. Bender, G. R. Schonbaum, and B. Zerner, *J. Am. Chem. Soc.*, **84**, 2540 (1962).
- (2) M. Caplow and W. P. Jencks, *Biochemistry*, **1**, 883 (1962).
- (3) S. A. Bernhard, S. J. Lau, and H. Noller, *ibid.*, **4**, 1108 (1965).

- (4) R. A. Oosterbaan, P. Kurst, J. Van Rotterdam, and J. A. Cohen, *Biochim. Biophys. Acta*, **27**, 557 (1958).
- (5) H. Noller and S. A. Bernhard, *Biochemistry*, **4**, 1118 (1965).
- (6) M. L. Bender, *J. Am. Chem. Soc.*, **84**, 2540 (1962).
- (7) A. K. Balls and H. N. Wood, *J. Biol. Chem.*, **219**, 245 (1956).

responding acyl ester linkage (III).^{3,4} On the hand, the native derivatives have strikingly dif-



chemical and spectral properties. The studies herein were undertaken as part of an attempt to investigate the relevance of these unusual spectral ties to the chemical catalytic process.

In order to clarify our objective in the present of experiments, it is well to restate a number of usually noted facts concerning the spectral properties of acyl enzymes of type II in the native and in the red (or degraded) state.

The strong long-wavelength electronic transition acyl chromophore is always "red shifted" in the acyl enzyme, relative to the denatured enzyme;⁵ red derivatives are *always* identical in spectrum with small model O-acylserine-peptide derivatives and chemically degraded O-acylserine-enzyme fragments.^{1,2}

The same strong long-wavelength electronic transition in the native acyl-enzyme derivative is always comparable in intensity to that of the denatured or compound derivatives.

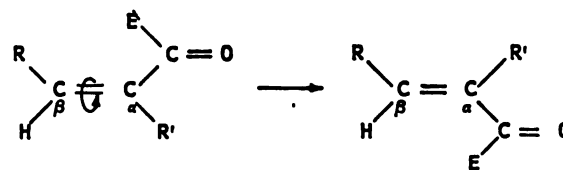
This spectral "red shift" which varies considerably from derivative to derivative ($\Delta\lambda$ can be as large as 100 m μ) is unexpected in view of the finding that this acyl enzyme binding site resembles an environment of low polarity (a "hydrophobic" binding site); acyl chromophores thus far considered are "blue" when transferred to solvents of low polarity. Attempts have been previously proposed to exclude the possibility that the red shift arises from a difference in "microenvironment polarity" surrounding the chromophore in the native vs. the denatured (unfolded) acyl enzyme.⁶

All experimental measurements of the kinetics of denaturation, enzyme inactivation, and disappearance of the red shift in the acyl chromophore have failed to indicate any "uncoupling" in the three processes (the kinetics of the three processes are identical). The implication is that this red shift is a relevant feature of the catalytic process.

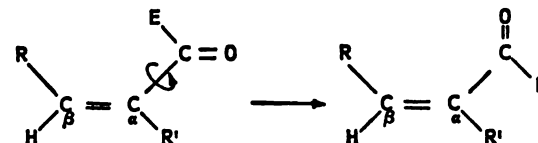
Various explanations for the red shift have been previously proposed,^{1,2} but no clear-cut choice is

from recent studies⁷ with somewhat conflicting results are most relevant in this respect. One by Kallos and Avatis would further emphasize the special requirement for explaining the red shift of the native derivatives since these authors have demonstrated from studies of model compounds that the solvent-dependent blue shift observed when an active site is bound to the active site of the enzyme is directly related to the polarity of the binding site. In the other, Westheimer, *et al.*, the photolysis products of diazoacetyl-chymotrypsin and control water is present at the active site. If the latter result requires that the active site has a polar environment, then no special requirement for a spectral shift large enough to overcome the solvent effect. Kallos and K. Avatis, *Biochemistry*, 5, 1979 (1966); J. Shafer, J. Lowsky, R. Laursen, F. Finn, and F. H. Westheimer, *J. Biol. Chem.*, 241, 421 (1966). We wish to thank the referee for calling the matter to our attention.

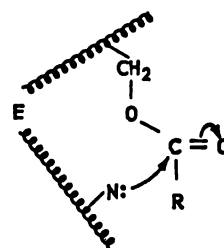
(a) cis — trans



(b) s-cis — s-trans



(c) nucleophilic:



electrophilic interaction:

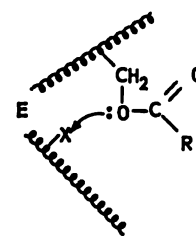


Figure 1. Potential mechanisms for the perturbation of the β -arylacryloyl-enzyme spectra: E = enzyme or peptide. The fact that the acryloyl group is shown linked to the enzyme or peptide before and after the isomerization is not intended to indicate necessarily that the isomerizations or out-of-plane rotations take place after acylation. The arrows are intended to indicate out-of-plane bending which for angles less than 180° results in skewed configurations.

evident from the existing experimental data. The alternatives previously proposed are as follows.

(1) The acyl enzyme is a "chemically perturbed" serine ester, the perturbation being of a type thus far not observed in model compound esters of this type.

(2) The native acyl-enzyme linkage is not *via* a serine O-ester linkage, but rather *via* an *active* acyl linkage which is transferred to the hydroxyl oxygen of serine upon denaturation of the acyl enzyme.

Extensive investigations of the denaturation process, under a variety of conditions of pH, have thus far demonstrated the invariant coupling of the red-shift disappearance to the denaturation process, and hence led us to reject as unlikely (although not impossible) the second of these alternatives. We chose, therefore, to consider the detailed electronic and stereochemical possibilities consistent with the former alternative. Three straightforward mechanisms for perturbing the spectra of esters of type III can be summarized as follows: (1) *cis-trans* isomerizations or "out-of-plane" rotations about the α,β double bond; (2) *s-trans-s-cis* isomerizations or rotation about the acryloyl carbon-carbon single bonds; (3) interactions with electrophiles at either carbonyl oxygen or interactions with nucleophiles at the carbonyl carbon *via* the constituent amino acid residues of the enzyme protein or *via* solvent. These mechanisms are summarized in Figure 1.

The present experiments are designed to explore the first two possibilities. Experimental data of two types

have been obtained from spectroscopic and optical rotatory dispersion studies of both model arylacryloyl compounds and of related acyl enzymes.

Experimental Section

Model Compounds and Reagents. Cinnamic acid, β -(2-furyl)acrylic acid, methyl cinnamate, and ethyl β -(2-furyl)acrylate were purified commercial samples previously described.³ β -(2-Furyl)acrolein and α -methyl- β -(2-furyl)acrolein were obtained from K & K Chemical Co. The former was recrystallized from water and the latter redistilled under reduced pressure. α -Methylcinnamic acid (Aldrich Chemical Co.) was recrystallized from water and dried under vacuum. N-[β -(2-Furyl)acryloyl]imidazole was prepared as previously described.

N-Carbobenzoyloxy-O-furylacryloyl-L-serinamide was prepared from a recrystallized sample of N-carbobenzoyloxy-L-serinamide, the optical purity of which has been established; 0.01 mole of the amide was dissolved in 20 ml of cold (5°) pyridine and 0.01 mole of β -(2-furyl)acryloyl chloride⁴ in 10 ml of tetrahydrofuran was slowly added. Solvent was removed after 5 min by flash evaporation at room temperature. The resultant gum was extracted exhaustively with aqueous phosphate buffer (0.5 M, pH 6.7). The ethyl acetate layer was then dried over Na_2SO_4 , filtered, and made slightly turbid by the addition of Skellysolve B. On standing at 5° crystals formed. These were filtered, air dried, dissolved in 95% ethanol, recrystallized from hot ethanol-H₂O (~50% v/v), and dried in a vacuum oven at 40°; mp 158–160°; equiv of serine/358 g of product, 0.98; ϵ_M 2.6×10^4 (OD/M cm) at 303 m μ .

β -(2-Furyl)acryloyl- α -chymotrypsin was prepared by the stoichiometric reaction of α -chymotrypsin with the acylimidazole as described previously.⁴ The method involved the addition of microliter quantities of the acylimidazole to milliliter quantities of enzyme solution. It was therefore possible to measure spectra and optical properties of the enzyme solution before and after acylation, without transfer of sample from one cell to another. Denatured enzyme and denatured acyl enzyme were prepared in soluble form by the addition of concentrated (0.1 M) solutions of sodium dodecyl sulfate (to a final concentration of about 0.02 M).

Spectrograde organic solvents (Matheson Coleman and Bell Chemical Co.) were utilized throughout.

Spectrophotometric and Optical Rotatory Dispersion Measurements. All spectrophotometric studies were carried out in a Cary Model 14 spectrophotometer. Maximal slit widths were approximately 0.2 mm. Optical rotatory dispersion measurements were performed with the aid of a Cary Model 60 spectropolarimeter at spectral band widths of 20 Å or less. Cylindrical quartz cells could be used interchangeably in the two instruments. Unless otherwise noted, optical densities in the polarimetric experiments did not exceed 1.0 OD. Depending on the stability of samples, the spectra of polarimetric samples were determined either concurrently (with aliquots of the same solutions) or by direct measurements in the polarimetric sample cells, after the polarimetric measurements were completed. The kinetics of deacylation of the acyl enzyme was measured spectrophotometrically as previously described.^{1,4} Changes in polarimetric properties associated with deacylation were measured both at fixed wavelengths as a function of time and by repeated scanning of the wavelength region at regular intervals in the spectropolarimeter. All spectrophotometric measurements were made at 25° except for the kinetic studies which were run at 27°. Spectropolarimetric studies were all at 27°.

Results and Discussion

The spectral absorption and optical rotatory dispersion measurements were designed to explore two suggested origins of the red shift of acyl derivatives of the native enzyme. The spectral characteristics of a variety of β -acryloyl derivatives are summarized in Table I. These compounds have been selected with regard to the relevance of their chemical and electronic structure to these spectral shifts. The choice of the furylacryloyl and cinnamoyl derivatives is dictated by the steric and spectral characteristics which make them not only suitable substrates for the enzyme but, as noted earlier, peculiarly sensitive indicators of the chemical and physical effects of their environment.

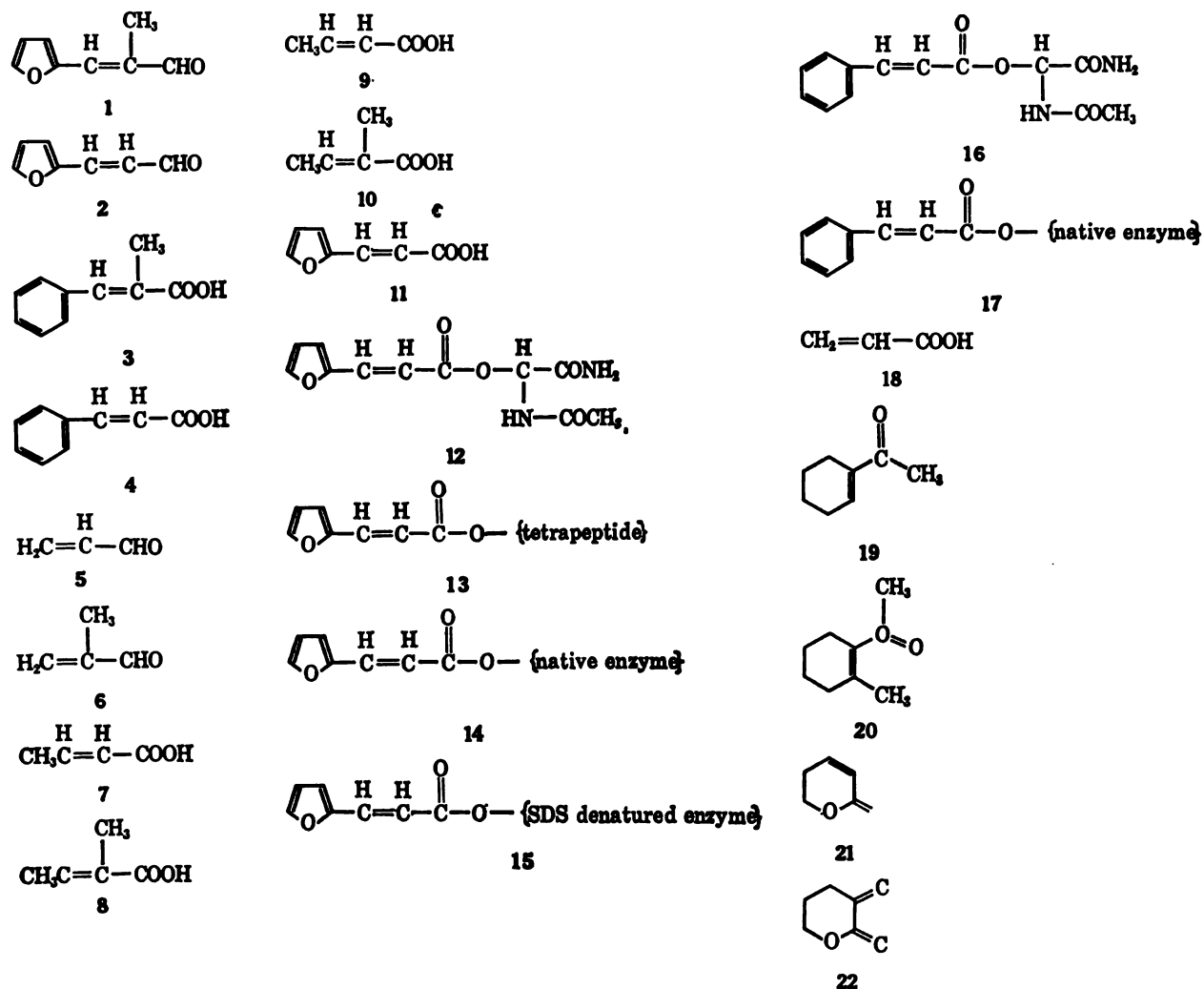
Table I

Compd	Solvent	λ_{max} , m μ	ϵ_{max}	Ref
α -Methyl- β -(2-furyl)acrolein (1)	CH_2Cl_2	316	2.80×10^4	a
β -(2-Furyl)acrolein (2)	CH_2Cl_2	315	2.86×10^4	a
α -Methylcinnamic acid (3)	CH_2Cl_2	271	1.45×10^4	a
Cinnamic acid (<i>trans</i>) (4)	CH_2Cl_2	279	2.17×10^4	a
Acrolein (5)	$\text{C}_2\text{H}_5\text{OH}$	207	1.12×10^4	b
α -Methylacrolein (6)	$\text{C}_2\text{H}_5\text{OH}$	216	1.10×10^4	b
<i>trans</i> -Methacrylic acid (7)	$\text{C}_2\text{H}_5\text{OH}$	205	1.40×10^4	c
α -Methyl- <i>trans</i> -methacrylic acid (8)	$\text{C}_2\text{H}_5\text{OH}$	213	1.25×10^4	c
<i>cis</i> -Methacrylic acid (9)	$\text{C}_2\text{H}_5\text{OH}$	205.5	1.35×10^4	c
α -Methyl- <i>cis</i> -methacrylic acid (10)	$\text{C}_2\text{H}_5\text{OH}$	216	0.90×10^4	c
β -(2-Furyl)acrylic acid (11)		308	2.5×10^4	a
N-Acetyl-O-furylacryloyl-serinamide (12)	H_2O	309		d
N-Carbobenzoyloxythreonyl-(O-furylacryloyl)seryl-methionylalanylmethylate (13)	H_2O	308		d
Furylacryloyl derivative on native enzyme (24)	H_2O (pH 4.2)	320	1.92×10^4	d
Furylacryloyl derivative on SDS-denatured enzyme (15)	H_2O	309		d
N-Acetyl-O-cinnamoyl-serinamide (16)	H_2O	281	2.4×10^4	d
Cinnamoyl derivative on native enzyme (17)	H_2O (pH 4.2)	292	1.7×10^4	d
Acrylic acid (18)	$\text{C}_2\text{H}_5\text{OH}$	200	1.0×10^4	c
1-Acetylcyclohex-1-ene (<i>s-trans</i>) (19)		232	1.25×10^4	e
1-Acetyl-2-methylcyclohex-1-ene (20)		245	0.05×10^4	e
Hex-2-eno-S-lactone (21)	$\text{C}_2\text{H}_5\text{OH}$	205	1.07×10^4	f
5-Hydroxypent-1-ene-2-carboxylic acid lactone (22)	$\text{C}_2\text{H}_5\text{OH}$	220	0.57×10^4	g

* Our measurements. ^b W. F. Forbes and R. Shilton, *J. Am. Chem. Soc.*, **81**, 786 (1959). ^c A. T. Nielsen, *J. Org. Chem.*, **22**, 1539 (1957). ^d Ref 3. ^e H. H. Jaffé and M. Orchin, ref 18, p 421. ^f U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1372 (1953). ^g E. R. H. Jones, T. Y. Shen, and N. E. Whiting, *ibid.*, 230 (1950).

We will consider first the possibility that the red shift results from "out-of-plane" bending about the α,β double bond or from *cis-trans* isomerization with respect to this bond and show from ultraviolet spectral data, nmr measurements, and measurements of induced optical activity that these mechanisms cannot be the origin of the red shift.

A. "Out-of-Plane" Bending about the α,β Double Bond. To demonstrate the effect of out-of-plane bending as a factor in the observed spectral shifts, we chose to examine the substituted derivatives α -methylfurylacrolein (1) and α -methylcinnamic acid (3) relative to their unsubstituted homologs furylacrolein (2) and cinnamic acid (4). The former two compounds would be expected to be skewed into a nonplanar (with respect to the conjugated system) configuration because of the effect of α -methyl substitution on the van der Waal's contacts (Figure 2). Note that in both cases the α -methyl carbon-*ortho* carbon (or oxygen) contact distance is about 2.5 Å in the planar conformation. Nonbonded C-C contacts this short have never to our knowledge been observed in crystals. The ultraviolet spectra of these compounds (Figure 3) must be examined for perturbing effects other than the known red shift that occurs on α -methyl substitution (see, for example,



the spectral effect of α -methyl substitution in acrolein (5, 6) and methacrylic acid (7, 8 and 9, 10—Table I). Note that, instead of the red shift, there is a large blue shift of λ_{\max} in α -methylcinnamic acid derivatives and a lack of a red shift in the furoyl derivative. The effect is more pronounced in α -methylcinnamic acid, presumably due to the more unfavorable contacts with two α -carbons in the phenyl derivative relative to one carbon and one oxygen in the furoyl case. It is clear that a large twist out of planarity about the double bond, as must occur in the two α -methyl derivatives,¹⁰ is inconsistent with the observed spectra of the acyl enzymes. The enzyme derivatives of type II show no large decrease in extinction. More important, the shift in λ_{\max} for the native acyl enzyme is in the wrong direction. In fact, the blue shift in λ_{\max} due to out-

of-plane distortion is undoubtedly even greater than that observed since, as we have seen, the α -methyl group contributes electronically (*ca.* 10 m μ) to an increase in λ_{\max} over the homologous α -hydrogen derivative

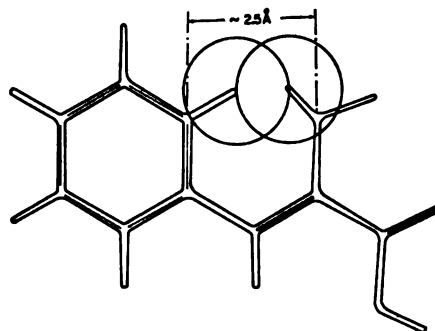


Figure 2. α -Methyl-*trans*-cinnamic acid drawn to scale in the planar conformation from Dreiding models, showing the van der Waals overlap of hydrogen atoms on the aromatic ring with those on the methyl group. Two of the three methyl hydrogens are eclipsed with respect to the plane of the ring. van der Waals radius of hydrogen = 1.00 Å.

(see Table I). The effects of out-of-plane twisting in skewed dienes have been very extensively investigated in regard to the effect of skew on both the ultraviolet spectra^{12,13} and the optical rotatory dispersion.¹⁴

(12) H. Suzuki, *Bull. Chem. Soc. Japan*, **35**, 1715 (1962).

(13) N. L. Allinger and N. A. Muller, *J. Am. Chem. Soc.*, **86**, 2811 (1964).

(14) E. Charney, *Tetrahedron*, **21**, 3127 (1965).

(10) As noted above, examination of space-filling models¹¹ of α -methylcinnamic acid indicated that the acrylic group would not maintain a planar configuration. This is in accord with the observed blue shift relative to cinnamic acid. To check this, we examined the nmr chemical shift of α -methylcinnamic acid relative to α -methylacrylic acid. On the basis of the coordinates taken from the models and the theory of the effect of aromatic ring currents on nmr chemical shifts (C. E. Johnson and F. E. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958)), the α -methyl protons in the cinnamic acid derivative are expected to be 31 cps downfield with respect to those of the acrylic acid derivatives if the entire conjugated system is planar and *upfield* by about 5 cps if the system is skewed about 90° out of plane. The experimentally observed shift is 11 cps *upfield*, in excellent confirmation of the ultraviolet interpretation of nonplanarity. We wish to thank Mr. Robert Bradley of the National Institutes of Health for making these measurements.

(11) Pauling, Corey, and Koltun models developed by the Atomic Models Subcommittee of the Biophysics and Biophysical Chemistry Study Section of the National Institutes of Health.

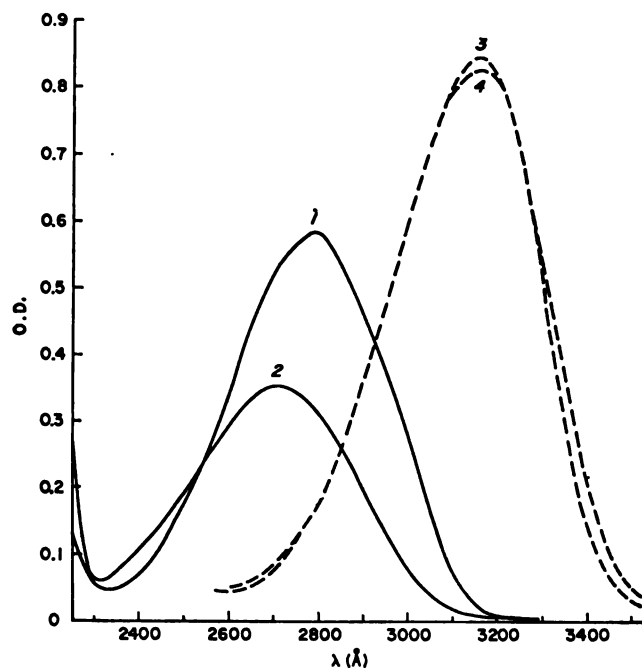


Figure 3. Ultraviolet spectra of acryloyl derivatives: (1) *trans*-cinnamic acid, $0.253 \times 10^{-3} M$; (2) α -methylcinnamic acid, $0.253 \times 10^{-3} M$; (3) furalacrolein, $0.296 \times 10^{-3} M$; (4) α -methylfurylacrolein, $0.296 \times 10^{-3} M$. All spectra were taken in 1-cm cells; solvent CH_2Cl_2 .

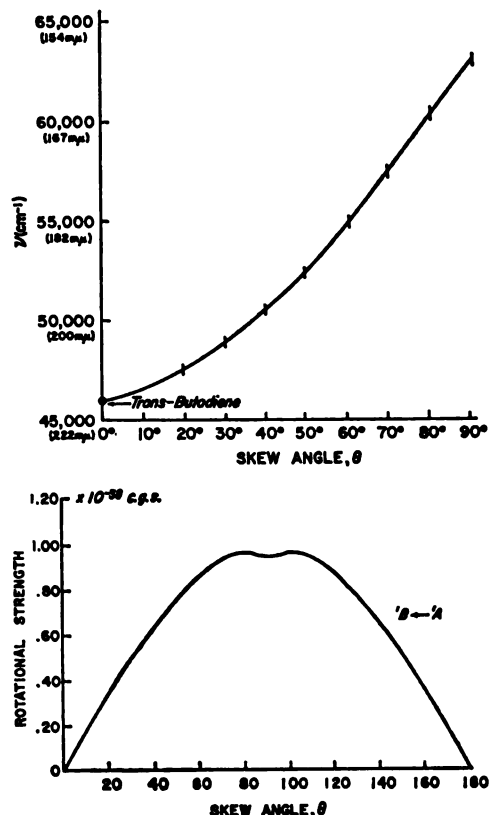


Figure 4. Optical absorption and rotatory activity of nonplanar conjugated dienes calculated from Hückel molecular orbitals. (a) Dependence on skew angle of the long-wavelength $\pi \rightarrow \pi^*$ transition of a conjugated diene. (b) Dependence on the skew angle of the rotational strength of the long-wavelength $\pi \rightarrow \pi^*$ transition of a conjugated diene (positive rotational strength corresponding to right-handed helical configuration, only, is shown).

Although a large out-of-plane skew can be ruled out solely on the basis of the foregoing considerations

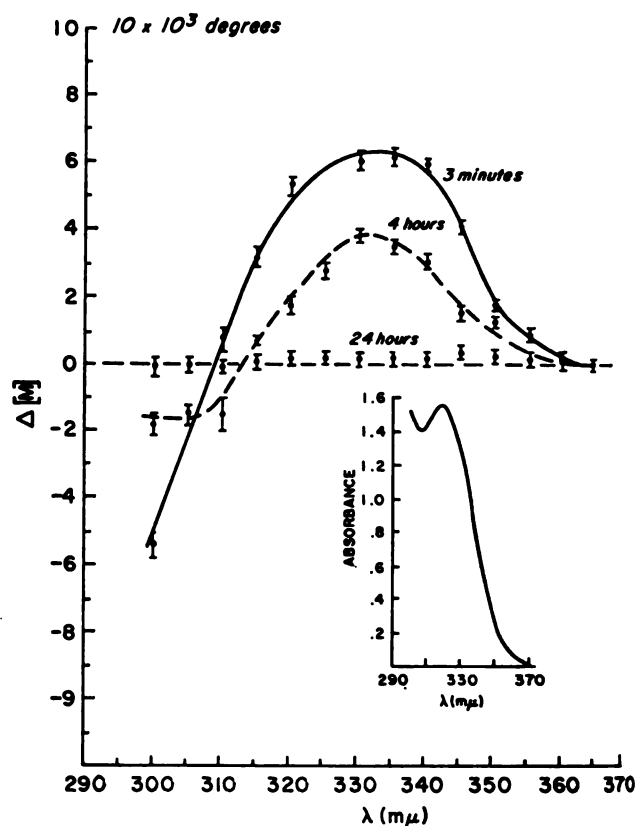


Figure 5. Induced molar rotation $[\Delta M] = [M](FAI + \alpha$ -chymotrypsin) $- [M](\alpha$ -chymotrypsin) of acetylated enzyme complex on native enzyme at pH 4.30, 27°; (FAI) 0.0142 mg/ml; (α -chymotrypsin) 2.61 mg/ml. Insert: absorption spectrum 3 min after addition of FAI.

and of the observed spectra of native acyl enzymes, smaller skew angles cannot be summarily dismissed on this basis. In the case of small angles, however, the recent interpretation of the ultraviolet spectra^{12,13} and the optical rotatory dispersion¹⁴ of skewed conjugated systems offers some help. The effect of skew angle on λ_{max} is shown schematically in Figure 4a. For small skew angles a blue shift is predicted, but the shift is small enough so that structural environmental effects may have stronger influences on the position of maximum absorption. The possibility of out-of-plane skew of the chromophoric group in the native acyl enzyme can, however, be tested more quantitatively by comparing the observed optical activity with that predicted from theoretical considerations. Rotational strength is expected to be very similar to that calculated for skew dienes (Figure 4b). It is easy to see that, although only small spectral shifts are expected, the rotational strength undergoes a large change even for small angles. The optical rotatory dispersion of α -chymotrypsin and β -(2-furyl)acryloyl- α -chymotrypsin in native and denatured (sodium dodecyl sulfate) states was therefore measured. A notable difference was observed between the native enzyme and the native acyl enzyme (Figure 5). Note that this difference in rotatory dispersion disappears when the enzymes are denatured (Table II). The "Cotton effect" induced by furylacryloylation corresponds approximately in wavelength to that predicted on the basis of the measured absorption band due to the furylacryloyl chromophore of the native enzyme (Figure 5, insert). The induced rotatory

Optical Activity of Acyl Complexes

Complex	Rotation ^a (1-cm path length), deg
α -Chymotrypsin (2.61 mg/ml)	-0.0740 ± 0.0004
α -Chymotrypsin (2.61 mg/ml) plus N- β -(2-furyl)acryloyl- imidazole (0.0167 mg/ml)	-0.0690 ± 0.0004
α -Chymotrypsin (2.70 mg/ml) denatured with SDS	-0.0650 ± 0.0004
α -Chymotrypsin (2.70 mg/ml) plus N- β -(2-furyl)acryloyl- imidazole (0.0133 mg/ml) denatured with SDS	-0.0650 ± 0.0004
N-CBZ- α -furylacryloyl-L- serinamide ($5.6 \times 10^{-4} M$)	0.000 ± 0.0004

ations measured at 3350 Å, the peak of induced activity in II, the native acyl-enzyme complex. The activity of solution was measured 3 min after the addition of the acryloyl compound. In a separate experiment at pH 6.24 the maximum induced was found to be from 20 to 25% higher than that obtained in I. I and II were measured at pH 4.30, III and IV at pH 6.24. Measured on the Cary 60 spectropolarimeter at the University of Oregon, for which we wish to thank Professor John Schell. Measured on the Cary 60 spectropolarimeter at the National Institutes of Health.

tion is related to the catalytic site configuration indicated by the fact that this induced rotatory activity disappears with time (Figure 5), presumably a process related to the deacylation of the acyl enzyme (and regeneration of the native enzyme).¹⁵ Additional evidence for this comes from the measurement of the optical activity of the same chromophore bound to a model serine peptide, N-carbobenzyloxycarboxamide. As indicated in Table II, no induced activity within the noise limited detectability of the instrument (approximately $\pm 0.0004^\circ$ under the conditions of measurement) is observed. Induced effects of the type observed with the native acyl enzyme can have two origins. (a) The chromophoric group itself remains planar, i.e., the nuclear positions are essentially planar configuration but the charge distribution is distorted by the asymmetric environment of the enzyme to give rise to induced optical activity in the positions of the chromophore. This effect will likely be very much smaller than the second type. (b) The chromophoric group itself skews into a non-planar configuration. It is this type which gives rise to optical activity observed in the ultraviolet transition, for example, the steroid dienes.¹⁶ Although there is apparent qualitative consistency between the

it should be noted that vicinal dissymmetry is sufficient for optical activity, a condition which is fulfilled when the molecule is bound to a site in fairly rigid orientation (see, for example, D. D. Ulmer, T.-K. Li, and B. L. Vallee, *Proc. Natl. Acad. Sci.* 47, 1155 (1961), and the results of a recent investigation of induced optical activity by K. Yamaoka and R. Resnik, *J. Phys. Chem.* 70, 4051 (1966)). Thus it is not a necessity that the optical activity disappears even if the helical or otherwise rigidly oriented structure of the protein is destroyed. Nevertheless, it does appear likely that destruction of the secondary or tertiary structure is likely to wash out most of the optical activity by increasing the symmetry of the system or destroy it completely by releasing the bound substrate from its rigid orientation. In fact the disappearance of the induced activity, as is the case here, with SDS denaturation of the α -chymotrypsin, may be used to draw the tentative conclusion that the substrate has been released from its rigid configuration with the protein.

J. Moscovitz, E. Charney, U. Weiss, and H. Ziffer, *J. Am. Chem. Soc.* 83, 4661 (1961); E. Charney, H. Ziffer, and U. Weiss, *Tetrahedron*, (1965); R. Deen and H. Y. C. Jacobs, *Koninkl. Nedl. Akad. Wet. Proc. Ser. C*, 64, 313 (1961).

observed rotatory dispersion properties and the "skewed double bond hypothesis," the quantitative measure of the "trough" of the "Cotton effect" (Table II) is inconsistent with this hypothesis. Small out-of-plane twists are associated with very much larger troughs in the rotatory dispersion. The magnitude of the expected optical activity may be calculated using the simple approximation that the order of the activity will be that expected from a skew diene (or larger since the conjugated groupings are more extended in the cinnamoyl and furylacryloyl compounds). On this basis it is calculated¹⁴ that the observed optical activity (molar amplitude = 12×10^3 degrees/M dm (Table II)) cannot come from configurations skewed more than 3 or 4°, hardly enough to account for significant perturbations in the absorption spectra. We conclude therefore that there is no significant out-of-plane twisting about the α,β double bond in the native acyl enzyme.

B. Planar *cis-trans* Isomerization about the α,β Double Bond. This possibility can be eliminated from a consideration of the spectra of model compounds (Table I). For example, the wavelength of maximum absorption of *cis*- and *trans*-methacrylic acids (7, 9) differ by only 0.5 m μ , and while this is at 205 m μ , it is still energetically much smaller than the 11-m μ shifts observed in the cinnamoyl-native enzyme complex (17) (about 120 cm⁻¹ compared to about 1400 cm⁻¹ for the latter). The shift to α -methyl-*cis*-methacrylic acid (10) from the *trans* configuration (8) is accompanied by a small shift of 3 m μ to the red (somewhat more energetic than the unsubstituted acrylic acid), but, more generally, where the unsaturated system extends over more than two bonds shifts to the blue are encountered. For example, the long-wavelength band of *cis*-stilbene is about 280 m μ compared to about 295 m μ for the *trans* compound, and in 1,4-diphenylbutadiene, the conversion from the *trans,trans* configuration to the *cis,trans* is accompanied by a blue shift of about 17 m μ .¹⁷ The experimental evidence is in full qualitative accord with either simple molecular orbital or free-electron theory,¹⁸ which predicts increasing red shifts with increasing *trans* extension of conjugated systems.

C. *s-trans-s-cis* Isomerization about the Acryloyl Carbon-Carbon Single Bond. Spectral data relating to *cis-trans* isomerization of esters of this type are limited. Nevertheless, a number of pertinent studies have been reported.

Referring first to spectral investigations, we note that the methyl ketones 19 and 20, which are known from infrared studies¹⁹ to be respectively in the planar *s-trans* and *s-cis* configuration, have their long-wavelength strong absorption (presumably the $\pi \rightarrow \pi^*$) at 232 and 245 m μ , respectively, a shift of about 2280 cm⁻¹ to the red. In the case of the lactones 21 and 22 in which the nominal double bonds are respectively *s-trans* and *s-cis*, the peaks of the same strong absorption band are at 205 and 220 m μ , a 3230-cm⁻¹ shift to longer wavelengths,²⁰ and while a small part of this

(17) J. H. Pinckard, B. Willie, and H. Zechmeister, *J. Am. Chem. Soc.* 70, 1938 (1948).

(18) See, e.g., the discussion in H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962.

(19) R. L. Erskin and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(20) This spectral shift is frequently referred to for configurations of the type of compounds 21 and 22 as due to differences between endocyclic and exocyclic configurations. Without taking up the general

very large change may be due to the hyperconjugative effect of an extra carbon substituent, certainly the major part arises from the relative ground and electronically excited state stabilities of the *s-trans* and *s-cis* configurations.¹⁸

Studies of the conjugated dienes, both experimentally and theoretically,^{21,22} have also shown the *s-trans* → *s-cis* configurational change is accompanied by large red shifts.

One of the most interesting related studies is that of deGroot and Lamb²³ who studied rotational isomers of a number of acrylic molecules by ultrasonic relaxation. Table III summarizes these data on cinnamaldehyde and furoylacrolein. Compare the difference in ground-state energy of these compounds with the data of Bernhard, *et al.*,² on the spectral shifts of cinnamoyl and furoyl derivatives upon formation of the acyl enzymes, respectively 1400 and 1140 cm⁻¹ (309 → 320 mμ and 281 → 292 mμ). The relative energy differences ($\Delta E_{\text{cinnamoyl}}/\Delta E_{\text{furoylacryloyl}}$) are 1.23, determined from the spectral shifts, and 1.25, determined from the ultrasonic relaxation studies. The observed red shift is hence consistent with the postulate of *cis-trans* isomerization about the ester single bonds. Moreover, the observed thermodynamic stability of the acyl enzyme²⁴ is consistent with that expected from a *trans-cis* isomerization between absorbed (*s-trans*) ester substrate and covalent (*s-cis*) acyl enzyme ester.

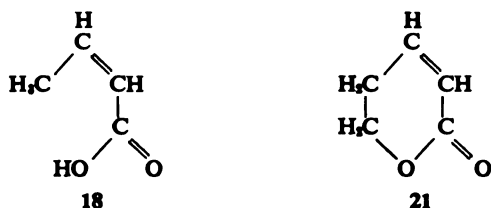
Table III^a

	transition state	
	ΔH_1^\ddagger	ΔH_2^\ddagger
	<i>s-trans</i>	<i>s-cis</i>
	ΔH_0	ΔH_0
	ΔH_0 , kcal/mole	ΔH_0 , kcal/mole
Cinnamoylaldehyde	5.62	1.5
Furoylacrolein	5.10	1.2

^a Data from ultrasonic relaxation studies, ref 16.

The hypothesis of *s-trans* → *s-cis* isomerization is supported by two other facts about native acyl enzymes.

questions of this attribution, it should be sufficient to point out that, for this case, the strong perturbation which might be expected from lactone formation is observed to give a much smaller effect than the *s-trans* → *s-cis* (endo → exocyclic) transformation. Thus *s-trans*-β-methacrylic



acid (18) has λ_{max} 205.5 mμ (ϵ 1.35 × 10⁴) while the *s-trans* lactone 21 has λ_{max} 205 mμ (ϵ 1.07 × 10⁴).

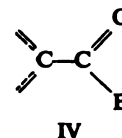
(21) R. S. Mulliken and C. A. Rieke, *Rept. Progr. Phys.*, **8**, 231 (1941).

(22) N. Allinger and C. Tai, *J. Am. Chem. Soc.*, **87**, 2081 (1965).

(23) M. S. deGroot and J. Lamb, *Proc. Roy. Soc. (London)*, **A242**, 36 (1957).

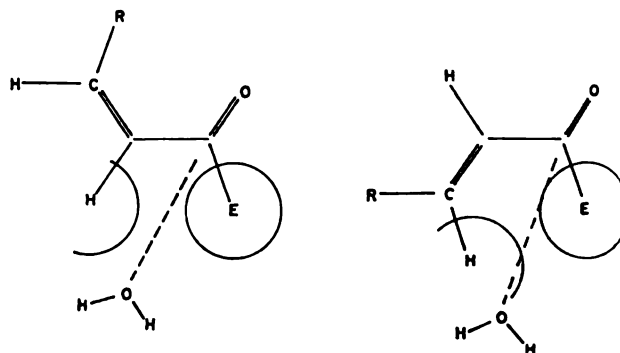
(24) M. L. Bender, G. R. Schonbaum, and B. Zerner, *J. Am. Chem. Soc.*, **84**, 2562 (1962).

(1) Although native acyl enzymes of type II are all significantly red shifted relative to the corresponding alkyl esters (III), acyl enzymes of type IV (in which λ_{max} and ϵ_{max} are comparable, e.g., benzoyl-, *meta*- and *para*-substituted benzoyl-, and 2-furoylchymotrypsins) are only slightly, or not at all, red shifted.² In the latter



acyl enzymes there is either no distinction (benzoyl and *para*-substituted benzoyl) or little distinction (2-furoyl and *meta*-substituted benzoyl) between the *s-cis* and *s-trans* configurations; hence there should be no spectral shift.

(2) Acyl enzymes of type IV are kinetically far more stable toward hydrolysis than are acyl enzymes of type II.^{2,24,25} This kinetic stability is not a consequence of electronic contributions ("substituent effects") from the acyl moiety.²⁶ Acetyl- and cinnamoylchymotrypsins are hydrolyzed at comparable rates. Benzoylchymotrypsin is hydrolyzed nearly two orders of magnitude more slowly. If the native acyl enzyme is always in the *s-cis* configuration so as to allow for attack by water (*i.e.*, if the *s-cis* configuration is of importance in the catalytic pathway), the branched planar β,β',α configuration in IV may block the nucleophilic attack



by water. In this regard it is interesting to note the nonplanar (L) configuration at the α-carbon atom of specific substrates (I) (a requirement for very rapid catalysis), indicative, if the "cis-ester" hypothesis is correct, of a highly critical stereospecificity for nucleophilic attack.

Conclusions

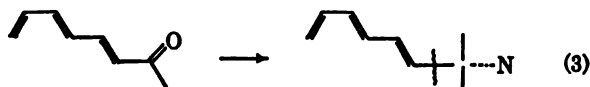
The spectral investigations reported here support the hypothesis that the acylation of α-chymotrypsin with acryloyl substrates is accompanied by a *s-trans* to *s-cis* configurational change about the acryloyl single bond. The possibility of chemical perturbation other than structural has not been experimentally examined, but some of the spectral data have a bearing on this ques-

(25) In connection with the mechanism of chymotrypsin activity, T. C. Bruice [*J. Polymer Sci.*, **49**, 101 (1961)] has previously suggested the possible requirement of a *trans-cis* change in the O-ester configuration, similar, and possibly related mechanistically, if not spectroscopically, to the conformational change described here.

(26) S. A. Bernhard, E. Hershberger, and J. Keizer, *Biochemistry*, **5**, 4120 (1966).

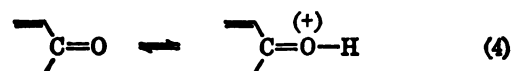
tion.²⁷ If, as seems likely from these results, the endoenergetic configurational change does occur, then any

(27) External chemical modification of the ester linkage: none of the above-mentioned data excludes the possibility of chemical interaction somewhere in the proximity of the ester linkage. From the known properties of esters, aqueous solvent, and amino acid residues of the protein, the plausible loci of chemical interaction are at either of the two ester oxygens or at the carbonyl carbon. Nucleophilic interaction at the (electrophilic) carbonyl carbon can be rejected as a significant contribution, since such attack would effectively decrease the intensity and blue shifts. To a rough approximation, this type of interaction would transform the spectrum of a cinnamoyl derivative to that of a styrene derivative (eq 3). Such an acyl-enzyme derivative would be virtually



unobservable spectroscopically. Electrophilic interaction at oxygen is, however, a distinct possibility. The most obvious electrophilic agent is, of course, a proton (eq 4). Indeed, the spectra of the N-methylamides of cinnamic and furylacrylic acids in strongly acid solutions (approximately 1 M HCl)²⁸ are red shifted to precisely the same wavelengths as

model of the active site of α -chymotrypsin must accommodate this requirement.



the corresponding acryloyl enzymes. This result is not unexpected, since protonation of N-methylamides is known to occur at the carbonyl oxygen,²⁹ a process which would lead to electron delocalization at the C-N bond and hence to a spectrum essentially the same as that observed in the corresponding aldehydes and ketones. The spectra of the protonated furoyl and benzoyl-N-methylamides are similarly red shifted. No such large red shift is observed, however, with the corresponding furoyl and benzoyl enzymes.¹ Moreover, protonation of this type (eq 4) is seemingly unlikely at or near neutrality, where the spectra of the acyl enzymes have been measured. The possibility that hydrogen bonding at carbonyl oxygen, rather than complete proton transfer, is the origin of the red shift cannot be ruled out. No significant red shifts have been noted, however, in the spectra of cinnamoyl and furylacryloyl esters in the presence of very strong hydrogen-bond donors (relative to the corresponding spectra in pure H₂O).³

(28) S. A. Bernhard and S. J. Lau, unpublished results.

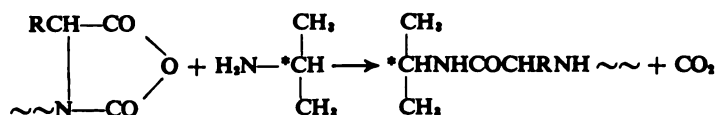
(29) A. Berger, A. Loewenstein, and S. Meiboom, *J. Am. Chem. Soc.*, **81**, 62 (1959).

The Mechanism of Polymerization of N-Carboxyanhydrides in Dimethylformamide. Evidence of the Presence of Cyclic Terminals in Polymers Obtained by Strong Base Initiation

M. Terbojevich, G. Pizzolo, E. Peggion, A. Cosani, and E. Scoffone

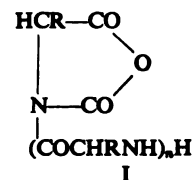
Contribution from the Institute of Organic Chemistry, University of Padua, Padua, Italy, and VIII Sez. Centro Nazionale di Chimica Macromolecolare, Padua, Italy. Received December 28, 1966

Abstract: γ -Benzyl-L-glutamate N-carboxyanhydride was polymerized in DMF using C¹⁴-labeled amines as initiators. All the radioactivity was incorporated in the polymers obtained by C¹⁴-isopropylamine initiation, indicating that normal primary amine polymerization is operative in this case. No radioactivity was found in the polymers when C¹⁴-methyl-diisopropylamine was used as the initiator. The Bamford mechanism is operative in this case. Using C¹⁴-diisopropylamine both mechanisms are simultaneously operative. Polymers prepared by initiation with unlabeled diisopropyl- and methyl-diisopropylamine and treated with an excess of C¹⁴-labeled isopropylamine exhibit considerable radioactivity. This radioactivity must be due only to reaction between the labeled amine and cyclic terminal present in the polymers.



On the basis of extent of the radioactivity incorporated in polymers "killed" with C¹⁴-labeled isopropylamine, the number of polymer molecules containing cyclic terminals, *i.e.*, formed *via* Bamford mechanism, was estimated. It was found that cyclic terminals deactivate *after* the end of the polymerization.

In previous papers^{1,2} we presented evidence of the existence of bifunctional intermediates in the polymerization of N-carboxyanhydride (NCA) in dimethylformamide (DMF) initiated by strong bases. We found that when the polymerization mixture at 95% conversion is concentrated, a marked increase in molecular weight of the polymer is observed. We interpreted this fact assuming that coupling between bifunctional species occurs during concentration. These species are



formed if initiation and propagation occur *via* "active monomer" mechanisms, as suggested by Bamford³ and Szwarc.⁴

(1) A. Cosani, G. D'Este, E. Peggion, and E. Scoffone, *Biopolymers*, **4**, 395 (1966).

(2) E. Peggion, E. Scoffone, A. Cosani, and A. Portolan, *ibid.*, **4**, 405 (1966).

(3) C. H. Bamford and H. Block, in "Polyamino Acids, Polypeptides, and Proteins," M. A. Stahmann Ed., University of Wisconsin Press, Madison, Wis., 1962, p 65.

(4) M. Szwarc, *Advan. Polymer Sci.*, **4**, 1 (1965).

This paper presents definitive evidence for the Bamford-Szwarc mechanism in the case of NCA polymerization initiated by strong base type initiators in DMF.

Moreover, further support for the "normal primary amine" addition mechanism is presented when primary amines are used as the initiators. The work has been carried out using radioactive amines.

Experimental Section

Materials. Dimethylformamide (DMF) reagent grade was distilled under vacuum, over phosphorus pentoxide, immediately before use. DMF not freshly distilled was able to induce the polymerization of γ -benzyl-L-glutamate N-carboxyanhydride without addition of the initiator. Ethyl ether was refluxed over sodium metal and then distilled. Isopropylamine (IPA), diisopropylamine (DIPA), and methyl-diisopropylamine (MDIPA) were of reagent grade. They were dried over potassium metal and then fractionally distilled. Monomer γ -benzyl-L-glutamate N-carboxyanhydride (NCA) was prepared according to the literature.⁵

Labeled Amines. C^{14} IPA, DIPA, and MDIPA hydrochlorides were prepared as previously described.⁶ The free C^{14} amines were obtained by exchange between the labeled hydrochlorides and the corresponding unlabeled pure amines. Radioactive standardization was carried out as previously described.⁷

Radioactivity Measurements. Weighed samples of polymer were dissolved in a known volume of freshly distilled, anhydrous DMF. These solutions were mixed with the phosphor solution (5 g of 2,5-diphenyloxazole and 0.5 g of 1,4-bis[2-(5-phenyloxazolyl)benzene] in 1 l. of toluene). The radioactivity measurements were performed at -20° using a SELO scintillation counter with super-scaler at 1020 v and bias at 5 v.

Initiation with Labeled Amines. i. **Physical Adsorption Checks.** Some preliminary checks were carried out in order to determine the physical adsorption of the labeled initiators on the polymers.

A typical experiment was as follows. To a solution of preformed polymer (500 mg) in DMF (25 ml) C^{14} -labeled IPA was added in an amount corresponding to that used to initiate polymerization. The mixture was stirred vigorously, and after 1 hr the solvent and the radioactive amine were evaporated under vacuum. The polymer was then dissolved in methylene chloride and precipitated by pouring the solution into ethyl ether. The polymer was isolated by filtration, redissolved in methylene chloride, and treated with a large excess of unlabeled IPA. The polymer was finally precipitated by pouring the solution into ethyl ether. Dissolution in methylene chloride, treatment with unlabeled IPA, and precipitation were repeated four times. The final polymer had only 0.5% (or less) of adsorbed radioactive amine. Analogous experiments were carried out with C^{14} -labeled DIPA and MDIPA with identical results.

ii. **Polymerization.** Poly- γ -benzyl-L-glutamate (PBLG) samples were prepared by NCA polymerization in DMF using proper A/I ratios (see Table II). The radioactive initiators were introduced by direct distillation into the reaction mixture cooled at -190° . The exact amounts of initiators used were determined by counting the total radioactivity of the polymerization mixtures. When the conversion reached at least 98% (checked by infrared) each polymerization mixture was divided in two parts. The first was treated according to procedure A and the second treated according to procedure B.

Procedure A. One-half of the reaction mixture was treated with a large excess of unlabeled IPA. Then the amine and solvent were distilled out, and the polymer was redissolved in methylene chloride and precipitated by pouring the solution into ethyl ether. Redissolution in methylene chloride, treatment with an excess of unlabeled initiating amine, and reprecipitation were repeated four times in the same way as described in Adsorption Checks.

Procedure B. One-half of the reaction mixture was concentrated to an oil in a rotating evaporator, diluted with methylene chloride, and precipitated by pouring into ethyl ether. The polymer was then redissolved, treated with an excess of unlabeled initiating

amine, and reprecipitated; this procedure was repeated four times.

Killing Experiments with C^{14} -Labeled Isopropylamine. i. **Absorption Test.** Polymer (230 mg) and 275 mg of monomer γ -benzyl-L-glutamate NCA were dissolved in 21 ml of DMF and treated with 2.5 ml of C^{14} -labeled IPA. After 1 hr the radioactive amine was distilled out and 2.5 ml of unlabeled IPA was added to the solution. After 1 hr the amine was again distilled out. The treatment with unlabeled IPA was repeated four times. Finally, all solvent was evaporated. The polymer was then redissolved in methylene chloride, treated with unlabeled IPA, and precipitated by pouring the solution into ethyl ether. Solution in CH_2Cl_2 , treatment with unlabeled IPA, and precipitation into ethyl ether were repeated four times. The final polymer exhibits no trace of radioactivity. This means that the above procedure completely eliminates contamination of the polymer due to radioactive amine or to the product (ether soluble)



formed by reaction of the radioactive amine with the monomer.

ii. **Killing.** Two polymerization experiments were carried out in DMF using unlabeled DIPA and MDIPA as the initiators. In both cases the following polymerization conditions were used: monomer, 0.500 g; DMF, 25 ml; molar ratio of monomer to initiator, A/I , 20.

At various times of reaction, portions of the polymerization mixtures were taken away. Each portion was divided in two parts. The first was treated with 3 ml of C^{14} -labeled IPA. The polymer was then recovered according to the laborious procedure described in Absorption Test.

The second was concentrated to an oil in a rotating evaporator; the polymer was redissolved in methylene chloride and precipitated by pouring the solution into ethyl ether.

Molecular Weight Determinations. Molecular weights (\bar{M}_w) of the polymers were determined by viscometry in dichloroacetic acid solution (a Ubbelohde viscometer was used) using Doty's relation⁸ $[\eta] = 2.78 \times 10^{-4} \bar{M}^{0.57}$.

Results and Discussion

Initiation. Table I shows the results of polymerization experiments carried out in DMF using C^{14} -labeled initiators. These results are qualitatively similar to those obtained with the same monomer and initiators in dioxane.^{7,9}

From these data it is evident that IPA mainly behaves like a "normal primary amine" initiator while MDIPA behaves like a strong base type initiator.

Both mechanisms appear to be operating simultaneously using C^{14} -DIPA. In this case we can roughly estimate the fraction of labeled molecules in the polymeric mixture. In fact, assuming $\overline{DP}_n = 0.5\overline{DP}_w$ (this assumption is justified by our previous work),¹ the number of polymer molecules per 100 mg of polymer can be calculated. The experimental radioactivity measured on the polymer is directly proportional to the number of polymer molecules containing labeled initiator at their ends. It is easy to verify that the ratio between the per cent of initial radioactivity present in the polymers and the quantity $T = (A/I)(100/\overline{DP}_n)$ gives directly the number fraction of labeled polymer molecules in the polymeric mixture. From Table II it can be seen that, by DIPA initiation, 5–10% of polymer molecules contain labeled initiator at their end, i.e., have been formed *via* the "primary amine" mechanism. Of course these values must be considered as roughly approximate.

(5) E. R. Blout and R. H. Karlson, *J. Am. Chem. Soc.*, **78**, 941 (1956).

(6) C. Colombini, M. Terbojevich, and E. Peggion, *J. Labelled Compds.*, **1**, 195 (1965).

(7) E. Peggion, M. Terbojevich, A. Cosani, and C. Colombini, *J. Am. Chem. Soc.*, **88**, 3631 (1966).

(8) P. Doty, J. H. Bradbury, and A. M. Holtzer, *ibid.*, **78**, 947 (1956).

(9) M. Goodman and J. H. Hutchison, *ibid.*, **88**, 3627 (1966).

Table I. Polymerization of γ -Benzyl-L-glutamate NCA in DMF; Initiation by C^{14} -Labeled IPA, DIPA, and MDIPA

Run code	Initiator	A/I	\bar{M}_w^a	—Polymers obtained via procedure A ^b —		—Polymers obtained via procedure B ^b —	
				Initial radioactivity in the polymers, %		Initial radioactivity in the polymers, %	
Z1C14	IPA	20	11,000	100		11,000	100
AA1C14	DIPA	17	16,500	4.3		51,500	4.4
AA2C14	DIPA	20	15,000	2.8		39,500	2.4
AG1C14	DIPA	18	14,500	2.9		36,500	2.7
AA3C14	MDIPA	26	22,500	0.3		180,000	0
AG2C14	MDIPA	19	15,000	0.8		77,000	0.3

\bar{M}_w = weight-average molecular weight. ^b See Experimental Section.

Table II. Polymerization of γ -Benzyl-L-glutamate NCA in DMF; Initiation by C^{14} -DIPA in DMF; Polymers Have Been Obtained Procedure A

Run code	A/I	\bar{M}_w	\bar{M}_n^a	Labeled polymer molecules, % ^b
AA1C14	17	16,500	8250	10
AA2C14	20	15,000	7500	5
AG1C14	18	14,500	7250	5

Number-average molecular weight. ^b Calculated by the ratio between the experimental radioactivities found on the polymers and the quantity $T = (A/I)(100/\bar{DP}_n)$ (\bar{DP}_n being the number-average degree of polymerization, which is assumed to be equal to \bar{DP}_w).

Presence of Cyclic Terminals in Polymers Obtained with Strong Bases Type Initiators. The most serious objection to the Bamford-Szwarc mechanism was the lack of experimental evidence of the ring compound at the end of the polymer.⁴

The occurrence of coupling phenomena in polymers obtained in DMF using DIPA as the initiator was the first experimental evidence that bifunctional intermediates, I, do exist.^{1,2} Also, from the data of Table I large differences appear between \bar{M}_w of polymers obtained by "killing" with IPA and polymers obtained by concentration of the reaction mixture before precipitation. We explained the higher \bar{M}_w of the "concentrated" polymers by the extensive occurrence of coupling reactions between bifunctional intermediates. *Coupling does not occur for polymers initiated by IPA, indicating that, in this case, no cyclic terminals are generated.* Further evidence of the presence of cyclic terminals on polymers obtained by DIPA or MDIPA initiation arises from the following experiments. We ran two polymerization experiments in DMF under standard conditions as indicated in Tables III and IV. Portions of the reaction mixture were removed at different reaction times. All portions were divided in two parts.

The first was treated with a large excess of C^{14} -labeled IPA. Then amine and solvent were evaporated. The polymer was then recovered as described in the Experimental Section.

The second was concentrated in a rotating evaporator, treated with methylene chloride, and then poured into diethyl ether.

In Tables III and IV it is shown that all polymers "killed" with C^{14} -labeled IPA exhibit marked radioactivity. As described in the Experimental Section, the procedure we used in these experiments excludes the

Table III. Polymerization of γ -Benzyl-L-glutamate NCA in DMF; Initiation by Unlabeled DIPA; Killing Experiment with C^{14} -Labeled IPA

Reaction time, hr	Conversion, %	\bar{M}_w		Radioactivity in killed samples, (mmole of labeled amine/100 mg of polymer) $\times 10^3$	Estimated fraction of polymer molecules containing cyclic terminals ^a
		Killed sample	Concd sample		
0.2	70	7,000	80,000	1.74	0.61
1	98	9,000	42,000	0.93	0.42
3	100	10,000	33,000	0.66	0.33
24	100	11,700	13,500	0.11	0.07

^a Calculated by the extent of radioactivity incorporated in the killed samples and assuming $\bar{DP}_n = 0.5\bar{DP}_w$.

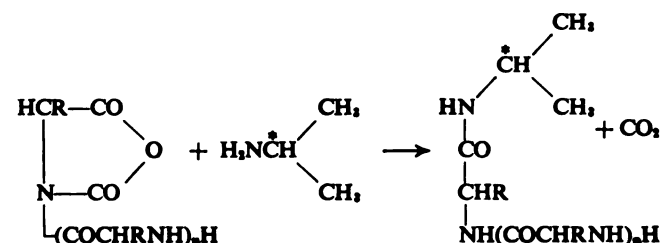
Table IV. Polymerization of γ -Benzyl-L-glutamate NCA in DMF; Initiation by Unlabeled MDIPA; Killing Experiment with C^{14} -Labeled IPA

Reaction time, hr	Conversion, %	\bar{M}_w		Radioactivity in killed polymers, (mmole of labeled amine/100 mg of polymer) $\times 10^3$	Estimated fraction of polymer molecules containing cyclic terminal ^a
		Killed sample	Concd sample		
0.5	60	10,000	108,000	1.42	0.71
24	100	28,000	43,000	0.24	0.34

^a Calculated as in Table III.

presence of radioactivity due to adsorption and to the presence of by-products of reaction between the residual unreacted monomer and radioactive amine or between the side chain of the polymer and radioactive amine.

Our results can be explained only by admitting the presence of cyclic terminals on the polymer chains



which react with the excess of radioactive amine leading to radioactive polymer.

An important fact emerges from the data of Tables III and IV. The extent of radioactivity incorporated in the "killed" polymers depends on the time at which the excess of radioactive amine has been added to the solution. For example, the first sample of Table III, killed at 70% conversion, contains 1.74×10^{-3} mmole of labeled amine per 100 mg of polymer. In the sample killed 24 hr after the beginning of the reaction, the amount of incorporated amine is 0.11×10^{-3} mmole per 100 mg of polymer. From the amounts of incorporated amine it is possible to calculate the percentage of polymer molecules containing cyclic ends. These calculations are reported in the last columns of Tables III and IV. From these data it appears clearly that the percentage of molecules with cyclic terminals decreases also after the practical end of the polymerization. Moreover, we must point out that the progressive deactivation of the cyclic terminals is not due to the coupling reaction between bifunctional intermediates. In fact, after the practical end of the polymerization, the molecular weight is substantially the same in all the samples killed at different times. The coupling reaction occurs only in the portions of reaction mixture concentrated in the rotating evaporator.

On the bases of all the above observations we can now explain the \bar{M}_w data of killed and concentrated samples of Tables III and IV. In fact immediately after the end of the reaction, there is a large number of polymer molecules with cyclic terminals. Therefore, the concentration of the reaction mixture at this point induces a large increase in the \bar{M}_w of the polymer due to the coupling reaction. About 24 hr after the beginning of the polymerization, a large fraction of cyclic terminals was deactivated. As a consequence, no important coupling reaction occurs by concentrating the polymerization mixture, and there are no substantial differences between \bar{M}_w of "killed" and "concentrated" samples.

It is significant that if we treat with C^{14} -IPA the "concentrated" polymers, in which a large number of cyclic terminals disappeared because of coupling reactions, very little radioactivity goes into the polymers. The results of such an experiment are shown in Table V. These data clearly indicate that a very small number of cyclic terminals is still present in the "concentrated" polymers.

Table V. Polymerization of γ -Benzyl-L-glutamate in DMF Initiation by DIPA; Treatment of Concentrated Samples with C^{14} -Labeled IPA

Reaction time, hr	Conversion, %	\bar{M}_w of the concd sample	Radioactivity incorporated in the sample treated with labeled IPA, (% of IPA/mg of mer)
0.5	80	60,000	4.

Conclusions

The data presented in this work allow us to conclude that γ -benzyl-L-glutamate NCA polymerizes in accordance with the Bamford mechanism when tertiary amines are used as initiators. In fact, we prove bifunctional intermediates do exist and that cyclic terminals are present in polymer molecules. However, the normal primary amine mechanism is operative with IPA as the initiator. Finally, both mechanisms are simultaneously operating with DIPA as initiator.

We pointed out that in the case of strong base-catalyzed polymerization, cyclic terminals deactivate after the end of the reaction. Since DMF not freshly distilled to induce NCA polymerization without addition of initiator, we suggest that deactivation occurs by reaction of cyclic terminals with impurities originating from solvent decomposition.

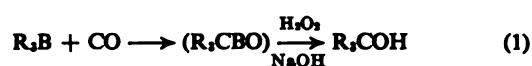
It is remarkable to observe that by MDIPA initiation we found only 70% of polymer molecules having cyclic terminals at 60% conversion. These findings are explained by the fact that cyclic terminals also appear during the polymerization by reaction with impurities. This termination reaction could be responsible for the presence of unlabeled polymer molecules in the killed polymers.

Also in the case of DIPA initiation, the percentage of polymer molecules with cyclic terminals is quite low. In this case, chain termination and the partial contribution of the "primary amine" mechanism can account for the low extent of polymer chains with cyclic terminals.

Communications to the Editor

Reaction of Carbon Monoxide at Atmospheric Pressure with Trialkylboranes. A Convenient Method for the Synthesis of Trialkylcarbinols via Hydroboration

Carbon monoxide at atmospheric pressure readily reacts at 100–125° with trialkylboranes, synthesized in diglyme solution, to provide a convenient, mild synthetic route to the corresponding trialkylcarbinols (1). In this way olefins, such as 2-butene,



cyclohexene, and norbornene, may be readily converted to highly hindered tertiary alcohols, tri-*sec*-butylcarbinol, tricyclohexylcarbinol, and tri-2-norbornylcarbinol, products available only in very low yield by the classical Grignard synthesis.

It was recently reported by Hillman that trialkylboranes react with carbon monoxide at high pressures in the range of 500 atm to give products oxidizable to trialkylcarbinols.¹ When the reaction was attempted at atmospheric pressure, only low yields of alcohols were obtained, less than 40% after 24-hr reaction.

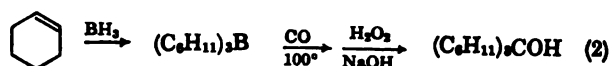
Trialkylboranes are now readily available via the hydroboration of olefins.² It was therefore apparent that the carbonylation of trialkylboranes thus prepared would offer a versatile route to the corresponding trialkylcarbinols. However, the apparent necessity of carrying out the carbonylation at high pressures represented a severe inconvenience for laboratory synthesis. Accordingly, we undertook to explore the possibility of accomplishing the carbonylation stage at atmospheric pressure in the same flask utilized for the hydroboration, by the automatic hydrogenator previously described³ as adapted for carbonylations.⁴

When tri-*n*-octylborane in diglyme solution (0.5 M) was used as standard substrate, we observed that at 25° approximately 1 mole of carbon monoxide was absorbed per mole of trialkylborane. The reaction was indeed complete absorption of the gas requiring some 5 hr. However, the rate of absorption increased with increasing temperature, so that at 125° complete carbonylation could be achieved in 3 hr. These results are summarized in Figure 1. The reaction mixture obtained in the carbonylation at 125° was oxidized with alkaline hydrogen peroxide, producing tri-*n*-octylcarbinol in 90% yield.

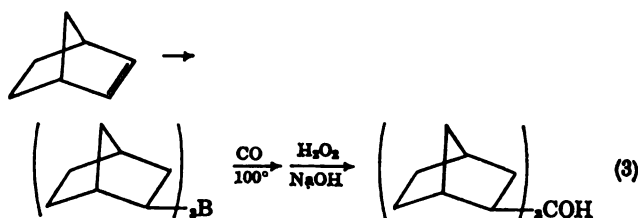
To explore the scope of this convenient synthesis, a series of representative olefins were hydroborated and the resulting organoboranes were carbonylated *in situ* in the presence of ethylene glycol.⁵ The reac-

tion mixtures were then oxidized with alkaline hydrogen peroxide and the trialkylcarbinols isolated.

It is noteworthy that this procedure yields trialkylcarbinols with highly branched alkyl groups, products which cannot be obtained in satisfactory yield by the methods presently available. Thus, 2-butene and isobutene were converted into tri-*sec*-butylcarbinol and triisobutylcarbinol in yields of 87 and 90%, respectively. Similarly, cyclopentene was converted into tricyclopentylcarbinol in 90% yield, and cyclohexene was converted into tricyclohexylcarbinol in 80% yield (2).



For comparison, tricyclohexylcarbinol is obtained in 7% yield from cyclohexyl chloride via the Grignard synthesis,⁶ and the yield is increased to 19% by the use of a special procedure involving sodium.⁷ Finally, 2-norbornylmagnesium halides rapidly equilibrate to a mixture of *exo* and *endo* derivatives.⁸ The hydroboration product of norbornene is known to provide the essentially pure tri-*exo*-norbornylborane.⁹ This was rapidly converted into a crystalline tri-2-norbornylcarbinol, melting sharply at 137–137.5°. Although we did not establish the stereochemistry, it is highly probable from previous experience with organoboranes³ that the reaction proceeds with retention to yield tri-



exo-norbornylcarbinol (3). The experimental results are summarized in Table I.

The following procedure describing the conversion of norbornene into tri-2-norbornylcarbinol is representative. A dry 500-ml flask equipped with a septum inlet, thermometer well, and magnetic stirrer was attached to the carbonylation apparatus,⁹ set up as previously described.⁴ The system was flushed with nitrogen. A solution of 2.84 g (75 mmoles) of sodium borohydride in 150 ml of diglyme was introduced, followed by 28.3 g (300 mmoles) of norbornene. The flask was immersed in an ice-water bath and the hydroboration achieved by the dropwise addition of 27.4 ml (100 mmoles) of boron trifluoride diglymate.¹⁰ The

(5) In most cases the reaction proceeded satisfactorily in the absence of added ethylene glycol. In some cases, however, we noted the formation of a less reactive, possibly polymeric, intermediate. The presence of the ethylene glycol circumvented this difficulty.

(6) O. Nuenhoeffer, *Ann.*, 509, 115 (1934).

(7) P. D. Bartlett and A. Schneider, *J. Am. Chem. Soc.*, 67, 141 (1945).

(8) F. R. Jensen and K. L. Nakamaya, *ibid.*, 88, 3437 (1966).

(9) We used a commercial model of the hydrogenator from Delmar Scientific Laboratories, Maywood, Ill. 60154.

(10) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 88, 1433 (1966).

E. D. Hillman, *J. Am. Chem. Soc.*, 84, 4715 (1962); 85, 982 (1963).

C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, 1962.

H. C. Brown and H. C. Brown, *J. Org. Chem.*, 31, 3989 (1966).

W. Rathke and H. C. Brown, *J. Am. Chem. Soc.*, 88, 2606 (1966).

Table I. Conversion of Olefins into Trialkylcarbinols by the Hydroboration-Carbonylation Reaction

Olefin	Product	$T_{1/2}$, ^a min	T_{100} , ^a min	Isolated yield, %	n_D^{20} (mp, °C) ^b Obsd	Lit.
1-Butene	Tri- <i>n</i> -butylcarbinol	50	500	90	1.4446	1.444
2-Butene	Tri- <i>sec</i> -butylcarbinol	12	60	87	1.4558	
Isobutene	Triisobutylcarbinol ^c	28 hr ^c	95 hr ^c	90	1.4392	1.439
1-Octene	Tri- <i>n</i> -octylcarbinol	45	300	90	1.4550	1.450
Cyclopentene	Tricyclopentylcarbinol	15	50	90	1.5128	
Cyclohexene	Tricyclohexylcarbinol ^d	9	30	80	(94.5–95°)	(93°)
Norbornene	Tri-2-norbornylcarbinol	10	45	80	(137–137.5°)	

^a Time for half and complete uptake of CO at 100°. ^b Analytical data within the usual accepted limits were obtained for all compounds. ^c Carbonylation at 125°. ^d Bromide derivative: mp 136° dec; lit. 136°.

solution was stirred at room temperature for 1 hr. Ethylene glycol, 10 ml, was added and the solution was heated and maintained at 100°. The system was flushed with carbon monoxide and the reaction initiated by vigorously stirring the contents of the flask magnetically. After 1 hr, absorption was complete. The system was flushed with nitrogen and then heated to 150° for 1 hr to ensure the migration of the alkyl groups. The flask

cohols were obtained analytically pure merely by piping off the solvent.

(11) National Science Foundation Fellow, 1964–1966.

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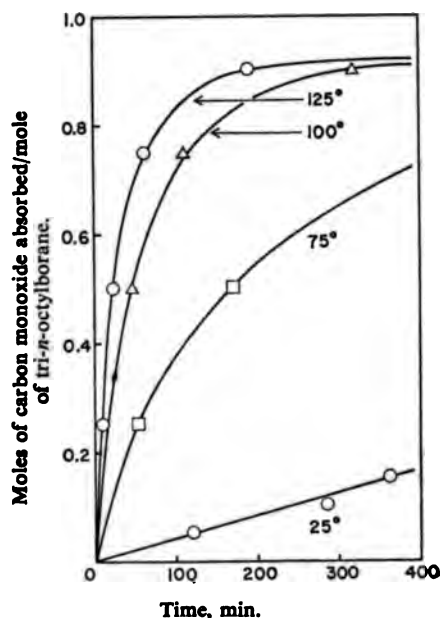


Figure 1. Reaction of carbon monoxide at atmospheric pressure with tri-*n*-octylborane in diglyme (0.5 M) at various temperatures.

was then immersed in an ice-water bath and 33 ml of 6 N sodium hydroxide was added, followed by dropwise addition of 33 ml of 30% hydrogen peroxide, maintaining a temperature just under 50°. The solution was then heated to 50° for 3 hr to complete the oxidation. Addition of water, 300 ml, to the cooled solution caused the precipitation of tri-2-norbornylcarbinol. The material was crystallized from pentane. There was obtained 25 g (80% yield) of pure tri-2-norbornylcarbinol, mp 137–137.5°.

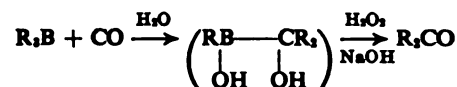
Liquid trialkylcarbinols were isolated by extracting the diluted oxidized mixtures with pentane. The al-

Reaction of Carbon Monoxide at Atmospheric Pressure with Trialkylboranes in the Presence of Water. A Convenient Synthesis of Dialkylketones via Hydroboration

Sir:

In the preceding communication we reported trialkylboranes in diglyme solution react readily with carbon monoxide at atmospheric pressure. Oxidation of the organoboron intermediate with alkaline hydrogen peroxide provides the trialkylcarbinols in excellent yields.¹

We now wish to report that the addition of quantities of water to the reaction mixture inhibits migration of the third alkyl group from boron to carbon.² Consequently, oxidation of the organoboron intermediate obtained in the presence of water produces the corresponding dialkyl ketone, instead of the trialkylcarbinol realized in the reaction in the absence of (1).

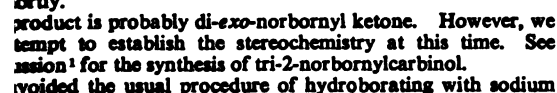
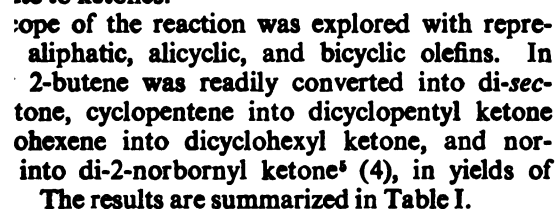


The following results illustrate the marked effect of the presence of relatively small quantities of water. Carbonylation of 100 mmoles of tri-*n*-butylborane in diglyme solution at 100° in the absence of any water produces 60 mmoles of tri-*n*-butylcarbinol and 40 mmoles of di-*n*-butylketone. In the presence of 1 g of water (150 mmoles) under otherwise identical conditions oxidation of the reaction mixture with alkaline hydrogen peroxide produces 90 mmoles of *n*-butyl ketone, 100 mmoles of *n*-butyl alcohol, and 10 mmoles of tri-*n*-butylcarbinol (2).

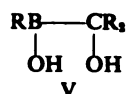
(1) H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 1567 (1967).

(2) M. E. D. Hillman, *ibid.*, **84**, 4715 (1962), utilized excess water as a reaction medium for the carbonylation of primary trialkylboranes and was able to control the migration of alkyl groups during carbonylation at high pressures by operating between 75 (transfer of two groups) and 150° (transfer of three groups).

story derivatives were prepared of all ketones. Satisfactory analyses were obtained for all new ketones. ^b Time for half and uptake of carbon monoxide. ^c The yield is based on the formation of 1 mole of ketone and 1 mole of alcohol from each mole of ketone. ^d 2,4-Dinitrophenylhydrazones, mp 93-94°. ^e 2,4-Dinitrophenylhydrazones, mp 142-145°.



borohydride and boron trifluoride diglymate since we had some indication that the presence of sodium fluoroborate facilitated the migration of the third alkyl group.



According to this mechanism, the successful trapping of intermediate II would provide a valuable means of converting olefins into their methylol derivatives. This is described in the following communication.⁸

(7) Hillman realized only dialkylcarbinols in his oxidations, with only traces of dialkyl ketones. We are unable to account for the difference between his results and our own, unless the presence of the diglyme protects the intermediate V from the hydrolysis by the base prior to the addition of the hydrogen peroxide. We have been able to obtain dialkylcarbinols by subjecting the reaction product to hydrolysis with aqueous alkali at elevated temperatures prior to oxidation with alkaline hydrogen peroxide.

(8) M. W. Rathke and H. C. Brown, *J. Am. Chem. Soc.*, **89**, 2740 (1967).

(9) National Science Foundation Fellow, 1964-1966.

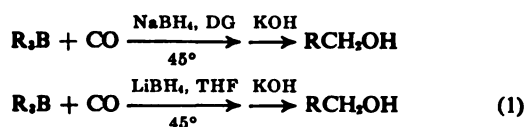
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Reaction of Carbon Monoxide at Atmospheric Pressure with Trialkylboranes in the Presence of Sodium or Lithium Borohydride. A Convenient Procedure for the Oxymethylation of Olefins via Hydroboration

Sir:

We wish to report that both sodium and lithium borohydrides markedly catalyze the rate of absorption of carbon monoxide at atmospheric pressure by trialkylboranes in ether solvents. The reaction can be controlled to achieve the transfer of but one alkyl group from boron to carbon. Consequently, hydrolysis of the reaction intermediate with ethanolic potassium hydroxide produces the homologated alcohol (1).



Consequently, carbonylation of organoboranes can now be controlled to achieve migration of all three groups from boron to carbon, providing the trialkylcarbinol;¹ two groups, providing the ketone or dialkylcarbinol;² or one group, providing the corresponding methylol derivative of the olefin.

By means of this latter reaction, described in this communication, we have been able to achieve the conversion of 1-octene into 1-nonanol, cyclopentene into cyclopentylmethanol, cyclohexene into cyclohexylmethanol, and norbornene into 2-*exo*-norbornylmethanol, in yields of 70-85%.

In previous experiments^{1,2} we found it necessary to operate at 100-125° in order to achieve absorption of carbon monoxide by trialkylboranes at a convenient rate. However, the rate of absorption is markedly enhanced by the presence of alkali metal borohydrides. Thus, the presence of 200 mmoles of sodium borohydride in a solution of 100 mmoles of triethylborane in 100 ml of diglyme caused the uptake of carbon monoxide to be complete in 1 hr at 45°. Hydrolysis with

(1) H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 2737 (1967).

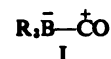
(2) H. C. Brown and M. W. Rathke, *ibid.*, **89**, 2738 (1967).

Table I. The Reaction of Carbon Monoxide at Atmospheric Pressure with Solutions of Triethylborane (1.00 M) at 45° Presence of Varying Amounts of Sodium Borohydride

Sodium borohydride, mmoles	Triethylborane, mmoles	Carbon monoxide absorbed, mmoles	Products, mmol
			Ethanol P
200	100	142	180
100	100	142	195
50	100	140	202
25	100	81	240

ethanolic potassium hydroxide, followed by oxymethylation with hydrogen peroxide, produced 180 mmoles of 1-propanol, 80 mmoles of 1-propanol, and 12 mmoles of ethylcarbinol. No trace of 1-butanol, corresponding to the doubly homologated alcohol, was found in the analysis.³

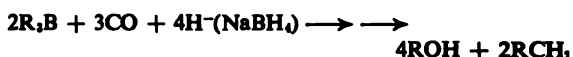
It is possible that the borohydride function reduces the initially formed carbonyl (I) of the



proposed mechanism.² This would be followed by transfer of one alkyl group from boron to carbon. However, at this stage we were more concerned with exploring the scope of this new synthesis than in clarifying the mechanism.

The data summarized in Table I indicate the stoichiometry for sodium borohydride to be 0.5NaBH₄/R₃B.

Analysis of the solutions for residual hydride indicated the following over-all stoichiometry (2).



The amount of carbon monoxide consumed in these reactions is not yet understood. We observed approximately 1.5 moles of carbon monoxide to be absorbed per mole of trialkylborane in all cases investigated, although the homologated alcohols isolated were the major product, plus the much smaller by-product, dialkylcarbinol, accounted for only 1 mole of gas. Possibly the excess consumption of carbon monoxide is the result of a direct reduction by an intermediate.

The observation that the reaction proceeds rapidly at 45° suggested the desirability of utilizing the most convenient solvent, tetrahydrofuran, for both the hydroboration and carbonylation stages. Lithium borohydride was therefore selected for its solubility in this solvent. Results obtained with this system are summarized in Table II.

The following procedure for the synthesis of 2-norbornylmethanol is representative. A dry flask, equipped with thermometer well, septum and magnetic stirrer, was attached to the carbonylation apparatus, set up as previously described.¹ The flask was flushed with nitrogen. Then, a solution of (150 mmoles) of norbornene in tetrahydrofuran (100 ml) was introduced into the flask and the flask was immersed in an ice-water bath. Hydroboration was achieved by adding dropwise 23.4 ml of a solu-

(3) The convenient synthesis of homologated alcohols by oxymethylation of dimethyloxosulfonium methylide with trialkylboranes has recently been reported: J. J. Tufariello and T. L. C. Lee, *ibid.*, **88**, 2738 (1966). However, this procedure produces appreciable amounts of the higher homologated alcohols.

Conversion of Olefins into the Corresponding Methyloles by the Hydroboration-Carbonylation Reaction

in	Product	$T_{10\%}$, min	$T_{100\%}$, min	Yield, ^a %
1-Propanol		15	87	80
1-Pentanol		55	216	72
1-Nonanol		130	400	70
Cyclopentylmethanol		56	230	69
Cyclohexylmethanol		35	125	80
2- <i>exo</i> -Norbornylmethanol ^b		100	350	85

glpc comparison with authentic samples. The yield is a theoretical production of 1 mole of alcohol from 1 mole 1). ^b The absence of the *endo* isomer was indicated by %).

(25 mmoles) in tetrahydrofuran, followed by at room temperature for 0.5 hr. Then 1.09 mmoles) of lithium borohydride was added and the mixture was heated to 45°. The system was purged with carbon monoxide and reaction initiated by stirring the contents of the flask magnetically. After 1 hr, absorption of carbon monoxide ceased and addition of 7 g of potassium hydroxide in 25 ml of ethanol was added. The reaction mixture was heated to 70° for 1 hr to hydrolyze the intermediate. The flask was cooled in an ice-water bath and 22.0% hydrogen peroxide was added dropwise to the borinic acid, keeping the temperature at 40°.

(It is purely a convenience to convert the boron intermediate to alcohols and boric acid.) The mixture was stirred for 1 hr and then saturated potassium carbonate. The supernatant liquid was analyzed by glpc, and a yield of 42.5 mmoles of norbornylmethanol, 85%, was established.

In the present three communications^{1,2} we have described the use of hydroboration-carbonylation for the synthesis of trialkylcarbinols, dialkyl ketones, and alkylmethanols from the corresponding olefins. We also found it possible to utilize this synthetic method for the synthesis of cyclic and polycyclic ketones and mixed ketones, as well as aldehydes and carboxylic acids. Finally, both hydroboration and carbonylation can tolerate a wide selection of functional groups. Consequently, it is now possible to synthesize many types of compounds, previously available through Grignard syntheses, while utilizing starting materials containing reactive functional groups. We are actively exploring this new exciting development and will communicate additional developments shortly.

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Received March 28, 1967

Photochemistry. II. The Photosensitized Addition of Butadiene to Acrylonitrile¹

Although the photosensitized cross-addition of dienophiles to olefins is well-known,² the corresponding

1: W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966).

photosensitized addition of dienophiles to dienes is much less common. Examples of the latter reaction have been confined to the addition of dienes to α,β -unsaturated carbonyl compounds,³ other dienes,⁴ the haloethylenes,⁵ and a simple olefin.⁶ The photosensitized dimerization of the dienes themselves^{4a,7} (the predominant reaction even in the presence of dienophiles^{5,6}) may be regarded as a special case, but other examples are lacking, and the reaction has not yet been demonstrated to be general.⁶

The major products from these photosensitized diene-dienophile cross-additions are solely^{3a,b,d} or predominantly^{3c,4,5} cyclobutanes with the exception of the photosensitized addition of 1,3-cyclohexadiene to cyclopentene⁶ (a poor dienophile⁸). When cyclohexenes are formed, they appear to be different (e.g., *exo* rather than *endo* in the case of cyclic dienes^{3c}) from the expected Diels-Alder (thermal) adducts. This fact, plus the observation of entirely different product ratios when the expected Diels-Alder adducts are formed, has led to the postulate that the photo- and thermal adducts result from quite different reaction paths.^{3c,5,7b,8}

We now wish to report what appears to be the first photosensitized cycloaddition of an α,β -unsaturated nitrile to a simple diene to yield products identical with those formed in the thermal (Diels-Alder) reaction, albeit in different ratios.

Irradiation of an equimolar mixture of butadiene (1) and α -acetoxyacrylonitrile (2) in the presence of 0.2 mole of a sensitizer through 7740 Pyrex glass ($\lambda > 280 \text{ m}\mu$)⁹ with a 450-w medium-pressure Hanovia mercury arc lamp at ca. 30° gave the three cross-adducts 3-5 (in yields of 30-50% of the total dimeric products, depending on the sensitizer¹⁰), previously observed from the thermal reaction,¹¹ along with the three butadiene dimers 6-8.^{7,12} The products were identified

(2) (a) G. S. Hammond and N. J. Turro, *Science*, **142**, 1541 (1963); (b) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 194; (c) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, p 536.

(3) (a) G. O. Schenck, W. Hartmann, S.-P. Mannsfeld, W. Metzner, and C. H. Krauch, *Chem. Ber.*, **95**, 1642 (1962); (b) G. O. Schenck, W. Hartmann, and R. Steinmetz, *ibid.*, **96**, 498 (1963); (c) G. O. Schenck, J. Kuhls, and C. H. Krauch, *Z. Naturforsch.*, **20b**, 635 (1965); *Ann.*, **693**, 20 (1966); (d) H.-D. Scharf and F. Korte, *Chem. Ber.*, **99**, 1299 (1966).

(4) (a) R. S.-H. Liu, Ph.D. Thesis, California Institute of Technology, 1965; (b) G. Sartori, V. Turba, A. Valvassori, and M. Riva, *Tetrahedron Letters*, **211**, 4777 (1966).

(5) N. J. Turro and P. D. Bartlett, *J. Org. Chem.*, **30**, 1849 (1965).

(6) R. S. H. Liu and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 1892 (1964).

(7) (a) G. S. Hammond, N. J. Turro, and A. Fischer, *ibid.*, **83**, 4674 (1961); (b) N. J. Turro and G. S. Hammond, *ibid.*, **84**, 2841 (1962); (c) G. O. Schenck and R. Steinmetz, *Bull. Soc. Chim. Belges*, **71**, 781 (1962); (d) D. J. Trecker, R. L. Brandon, and J. P. Henry, *Chem. Ind. (London)*, 652 (1963); (e) G. S. Hammond and R. S. H. Liu, *J. Am. Chem. Soc.*, **85**, 477 (1963); (f) G. S. Hammond, N. J. Turro, and R. S. H. Liu, *J. Org. Chem.*, **28**, 3297 (1963); (g) D. Valentine, N. J. Turro, Jr., and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 5202 (1964); (h) G. O. Schenck, S.-P. Mannsfeld, G. Schomburg, and C. H. Krauch, *Z. Naturforsch.*, **19b**, 18 (1964); (i) R. S. H. Liu, N. J. Turro, Jr., and G. S. Hammond, *J. Am. Chem. Soc.*, **87**, 3406 (1965); (j) R. B. Cundall and P. A. Griffiths, *Trans. Faraday Soc.*, **61**, 1968 (1965); (k) J. E. Baldwin and J. P. Nelson, *J. Org. Chem.*, **31**, 336 (1966).

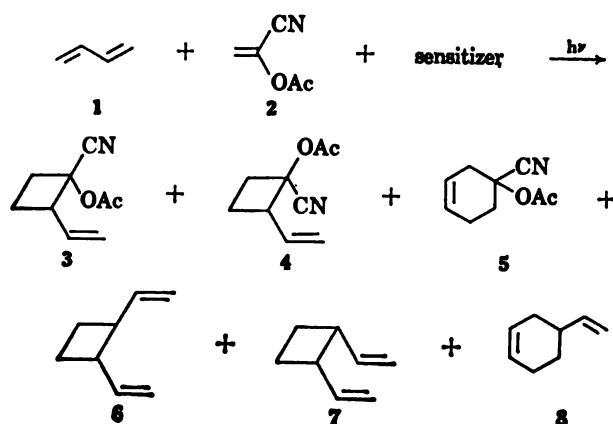
(8) (a) A. S. Onishchenko, "Diene Synthesis," L. Mandel, Translator, Daniel Davey & Co., Inc., New York, N. Y., 1964, p 278; (b) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **67**, 723 (1945).

(9) Reference 2c, p 742.

(10) W. L. Dilling, *J. Am. Chem. Soc.*, **89**, 2742 (1967).

(11) J. C. Little, *ibid.*, **87**, 4020 (1965).

(12) At butadiene conversions greater than ca. 20%, depending on the sensitizer, a copolymer of 1 and 2 was also formed. The products of the reaction, 3-8, were relatively stable under the reaction conditions.



by comparison of their gas chromatographic retention times with those of authentic materials.^{7f,11} Also the nmr and infrared spectra of samples isolated by preparative gas chromatography were compared with the spectra of authentic materials.¹³

The product distributions for various sensitizers are reported in the accompanying communication.¹⁰ For the present discussion, let it suffice to say that the cyclohexene 5 constituted 2–31% of the total cross-adducts 3–5, while the thermal reaction of 1 and 2 at 125–190° gave 77–91% 5. We interpret the fact that the cyclohexene 5 is formed at all in the sensitized cross-addition to indicate that the cyclohexene can arise *via* a two-step reaction.^{11,14}

Experiments on the unsensitized (direct irradiation through quartz¹⁵) photoreaction of 1 and 2 indicated that of the cross-addition processes only 1,2 addition occurred, probably *via* the excited singlet state of the diene 1.¹⁶

Acknowledgment. The authors wish to thank Mr. K. C. Whitman and Mr. F. L. Beman and co-workers for experimental assistance.

employed in this study. The conversions were kept low to avoid complications due to possible further reactions of the products. Another side reaction was observed when camphorquinone was used as the sensitizer. This sensitizer undergoes a photoreaction with butadiene to give a product which we have tentatively identified as a vinyloxetane (possibly several isomers) arising from the addition of one carbonyl group of triplet camphorquinone to one butadiene double bond. We have measured the (3 + 4):5 ratio at different stages of conversion and find no significant change.¹⁹

(13) The *cis*-divinylcyclobutane (7) was isolated as the thermal rearrangement product, 1,5-cyclooctadiene.^{7f}

(14) See R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 2046 (1965).

(15) Reference 2c, p 748.

(16) For the results of the unsensitized irradiation of butadiene alone see (a) R. Srinivasan and F. I. Sonntag, *J. Am. Chem. Soc.*, **87**, 3778 (1965); (b) I. Haller and R. Srinivasan, *J. Chem. Phys.*, **40**, 1992 (1964); (c) P. A. Leermakers and G. F. Vesley, *J. Chem. Educ.*, **41**, 535 (1964); (d) ref 2b, p 216.

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Received January 7, 1967

Organic Photochemistry. III. 1,2 *vs.* 1,4 Addition as a Function of Sensitizer Triplet Energy in a Cross-Addition Reaction¹

Sir:

In the preceding communication¹ we described the photosensitized cycloaddition of the diene 1 to the

(1) Part II: W. L. Dilling and J. C. Little, *J. Am. Chem. Soc.*, **89**, 2741 (1967).

olefin 2.² In this communication we report the of the sensitizer triplet energy on the product distribution.

The product distribution between the 1,2-dicyclobutanes and the 4-vinylcyclohexenes in the sensitized dimerization of butadiene or isoprene has been shown to be dependent on the triplet energy of sensitizer.³ This dependence was attributed to difference in the energy levels of the *cis*- and *trans*- triplets,⁴ the *trans* forms giving mostly cyclobutane and the *cis* forms giving relatively large amounts of cyclohexenes.

The product distributions for the cross-addition of 1 and 2 with various sensitizers are given in Table I. The relative amount of cyclobutanes 3 and 4 in the cross-adducts 3–5 as a function of the sensitizer triplet energy is shown in Figure 1 along with the curve obtained by Hammond and co-workers^{3c} for the dimerization of butadiene (1).

In general, our results on the cross-addition parallel quite closely those for the dimerization except for the depth of the minimum in the amount of cyclobutane in the 50-kcal/mole region. The breaking point at 50 kcal/mole can be explained, as in the case of dimerization,^{3c} by the *s-trans*- and *s-cis*-butadienes having lowest triplet energy levels at 59.6 kcal/mole^{3c} and ca. 53 kcal/mole,^{5b,c} respectively.⁶ The increase in the relative amount of cyclobutanes with sensitizers having triplet energies lower than 50 kcal/mole could be due to "nonvertical" excitation, as has been proposed for butadiene and isoprene dimerizations.^{3c}

We attribute the difference in the relative amount of cyclobutanes formed in the cross-addition and dimerization in the 50-kcal/mole region of Figure 1 to the difference in selectivity of ring closure of the *s-cis* triplet adduct, a, and the *s-cis*-1–1 adduct, b (Scheme 1). If the reasonable assumptions are made that the relative amounts of *cis* and *trans* triplets are proportional for any one sensitizer whether the olefin 2 is present or not, and that the reactivity of the two isomeric triplets with 2 (and with 1) are the same, then the difference in product distribution must reflect the difference in selectivity of ring closure of intermediates a and b. In the cross-intermediate, a, closed to a four-membered ring, 3 or 4, to a greater extent than did the intermediate, b. It has been shown from experiments on the termination reaction of free radical copolymerizations that cross-termination between unlike radicals is favored over termination between like radicals, to a rather large extent.⁷ Thus the coupling of unlike radicals such as the ring closure of a (with electron paired) is probably faster and therefore less selective than the coupling of like radicals as in b (with electron paired). Since the intermediates a and b can exist

(2) The numbering system in ref 1 is retained in this paper.

(3) (a) G. S. Hammond, N. J. Turro, and A. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961); (b) G. S. Hammond and R. S. H. Liu, *ibid.*, **85**, 477 (1963); (c) R. S. H. Liu, N. J. Turro, Jr., and G. S. Hammond, *ibid.*, **87**, 3406 (1965).

(4) For a theoretical explanation for this energy difference see (a) R. Hoffmann and R. A. Olofson, *ibid.*, **88**, 943 (1966); (b) ref 3c; (5) (a) R. E. Kellogg and W. T. Simpson, *J. Am. Chem. Soc.*, **87**, 4230 (1965); (b) D. F. Evans, *J. Chem. Soc.*, 1735 (1960).

(6) These explanations are based on the assumption that the reaction proceeded *via* the butadiene triplets rather than the α -acetoxy nitrile triplet.

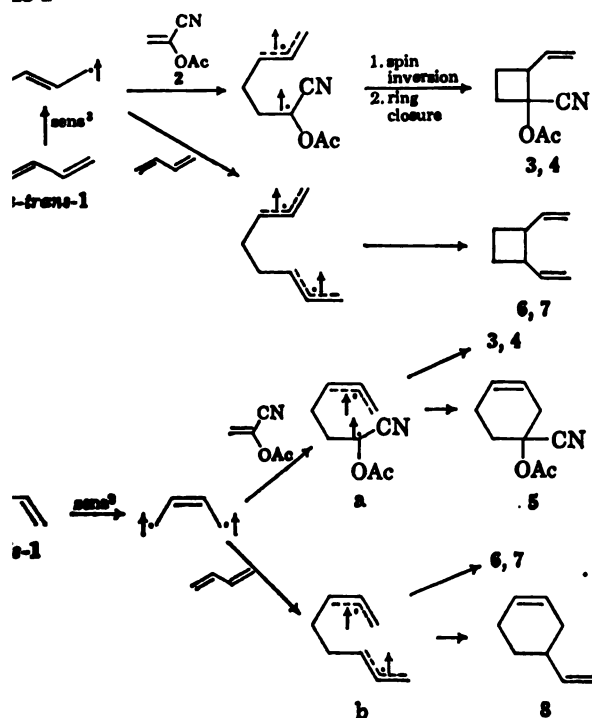
(7) C. Walling, "Free Radicals in Solution," John Wiley and Sons, New York, N. Y., 1957, p 146.

I. Composition of Products from Photosensitized Cross-Addition of Butadiene and α -Acetoxyacrylonitrile

Expt	Sensitizer ^a	E_T^b	Distribution of cross-adducts and dimers, % ^c				
			3 + 4 ^d	5	6	7	8
1	Acetophenone	73.6	34	0.7	56	7	2
2	Benzophenone	68.5	33	0.9	54	10	3
3	Triphenylene ^e	66.6	30	0.9	69
4	Anthraquinone ^e	62.4	60	3	31	6	...
5	Flavone	62.0	32	1.6	52	12	3
6	β -Naphthyl phenyl ketone	59.6	41	7	47	4	2
7	Biacetyl	54.9	38	12	28	7	14
8	Benzil	53.7	34	12	30	5	18
9	Camphorquinone	50	28	12	23	7	29
10	Pyrene ^e	48.7	38	17	34	11	...
11	Anthracene ^e	42.5	41	6	45	8	...
12	9,10-Dibromoanthracene ^e	40.2	45	1	44	10	...

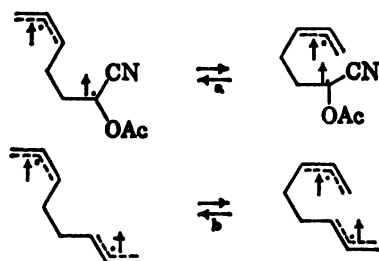
sensitizer (1.0 mmole) in 5.0 mmoles of 1 and 5.0 mmoles of 2. ^b Lowest triplet energy level in kilocalories per mole: W. G. Herkner, A. A. Lamola, and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 4537 (1964). See also ref 3c. ^c Determined by gas chromatography each component corrected for thermal conductivity variation in detector. ^d The *cis* and *trans* isomers were not separated. The nmr sum of the product isolated from the benzophenone-sensitized reaction showed two acetyl methyl groups at -2.05 and -2.07 ppm internal TMS of approximately equal intensity. ^e Saturated solution of sensitizer in equimolar mixture of 1 and 2. ^f Not determined due to low over-all conversion. ^g Not determined due to interference by a large excess of 2 and the presence of a small amount in the starting diene 1.

Scheme I



c number of conformations ranging from cyclic to extended (Scheme II), at the moment of spin inversion

Scheme II



diradicals may be at least partially in the extended conformation. If the ring closure of a is more rapid than b, then a larger proportion of the cyclobutanes 3 and 4 would be expected. By virtue of its selectivity, a has a greater chance to reach a conformation which

will lead to the more stable product, namely the cyclohexene 8.⁸

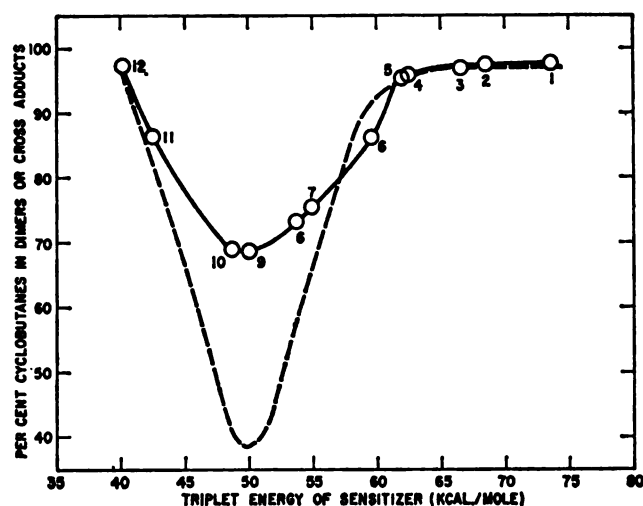


Figure 1. Butadiene- α -acetoxyacrylonitrile cross-adduct composition vs. triplet energy of sensitizer (solid line); butadiene dimer composition (dashed line, data of Hammond, *et al.*³⁰).

Acknowledgment. The author wishes to thank Dr. J. C. Little, Dr. T. Alfrey, Jr., and Dr. V. R. Sandel for many helpful discussions during this work, and Mr. K. C. Whitman for experimental assistance.

(8) "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956: (a) W. G. Dauben and K. S. Pitzer, p 38; (b) F. H. Westheimer, p 533.

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A New Peptide Coupling Reagent

Sir:

In recent years the potential utility of activated esters as coupling agents in peptide synthesis has been extended, first by the development of the isoxazolium salts and their derivatives¹ which generate enolic or

(1) (a) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem.*

Table I

	$\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}, \mu$	$\lambda_{\text{max}}^{\text{H}_2\text{O}}$ phenol, m μ (e)	λ_{max} anion, m μ (e)	p <i>K</i> _a (H ₂ O)
3-Hydroxy-2-methoxy- N-ethylbenzamide	1.460 (0.63), H-bonded NH	282 (1610)	306 (2000)	9.0
3-Methoxy-2-hydroxy- N-ethylbenzamide	1.502 (0.33), H-bonded OH	306 (2600)	331 (4850)	8.3
3-Acetoxy-2-hydroxy- N-ethylbenzamide (IIa)	1.485 (0.62), NH stretch	246 (6280) 299 (3800) 238 (8120)	326 (6530)	6.7

phenolic esters of peptide acids under convenient and mild conditions, and second by the discovery of peptide activated esters which discriminate effectively between aminolysis and racemization, even in polar solvents and under strongly basic conditions.³ We wish to report the preparation of 2-ethyl-7-hydroxybenzisoxazolium cation (I), a substance which combines both features in one system.

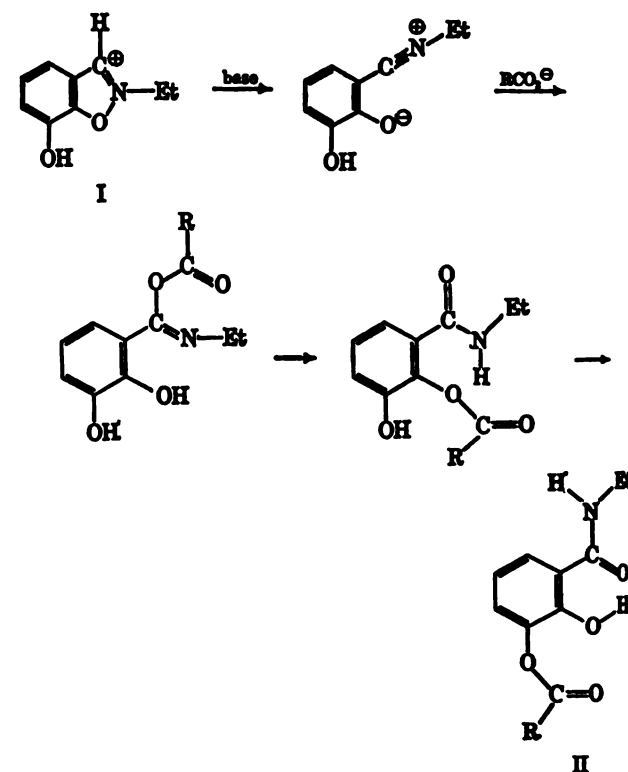
By means of procedures described previously,^{1b} 2,3-dihydroxybenzaldehyde³ can be converted in 75% yield to the fluoroborate salt of I, mp 136–137°.⁴ Addition of this salt as a powder to a vigorously stirred, chilled aqueous solution of sodium salts of carboxylic acids, overlaid with ethyl acetate and maintained at pH 4.5 with a pyridine buffer, results in the formation of 3-acyloxy-2-hydroxy-N-ethylbenzamides, II.⁵ Reactions are complete within 5 min under these conditions (*t*_{1/2} < 1 min, 25°, H₂O, pH 5) and the products can be isolated from the organic phase after acid and bicarbonate extractions. By analogy with the behavior of the 2-ethylbenzisoxazolium cation (III),⁶ the mechanism shown in Scheme I is assigned to this conversion. Under conditions which with III result in predominant azlactone formation,^{1b,c} I combines with ZGly-L-PheOH to yield IIc with no detectable formation (<0.5%) of the corresponding azlactone; I thus provides a method of converting peptide acids to activated esters without concomitant racemization.

That structure II corresponds to the products of these reactions follows from a study of the acetic acid product. This substance, infrared 1645 and 1760 cm⁻¹, whose spectra are compared in Table I with models, is also formed in 73% yield by aqueous acetylation of 2,3-dihydroxy-N-ethylbenzamide; its reaction with ethereal diazomethane-fluoroboric acid followed by hydrolysis yields 3-hydroxy-2-methoxy-N-ethylbenzamide.

Although otherwise similar to simple phenolic esters of peptide acids, peptide esters of structure II are remarkably resistant to racemization by tertiary amines. After 12 hr in dry DMF 0.4 M in triethylamine IIc is racemized to the extent of less than 1%.⁷ Under

identical conditions O(-ZGly-L-Phe)-N-ethylsalicylamide is racemized over 4000 times faster.

Scheme I



The remarkable base stability of these esters suggested their use in coupling reactions with salts of amino acids. When IIb and the tetramethylammonium salt of L-phenylalanine were combined in dry DMF, a quantitative precipitation of L-phenylalanine occurred and the soluble tetramethylammonium salt of IIb was formed. Addition of excess L-phenylalanine salt resulted in a rapid reaction (*t*_{1/2} ~ 1.5 min at 0.2 M amine), and isolation of the product after 15 min by addition of aqueous bicarbonate, extraction with ethyl acetate, and acidification yielded, after crystallization, 91% carbobenzoxyglycyl-L-phenylalanine, mp 129–130°, [α]_D²⁵ +39.9° (c 2.0, EtOH). Similarly, the tripeptide acid carbobenzoxyglycyl-L-phenylalanylglycine was obtained in 89% yield, mp 162–163°, [α]_D²⁵ -14.8° (c 1.3, EtOH), by condensation of IIc with glycine tetramethylammonium salt in DMSO. As a test of optical purity,⁸ the tripeptide acid was dissolved in aqueous base and converted with triethyloxonium ion to its ethyl ester in 60% yield; less than 0.5% of racemic ester was observed.

The favorable properties of these activated species appear to result from an interaction of several inde-

Soc., 83, 1007 (1961); (b) D. S. Kemp and R. B. Woodward, *Tetrahedron*, 21, 3019 (1965); (c) D. S. Kemp, Ph.D. Thesis, Harvard University, 1964.

(2) S. M. Beaumont, B. D. Hanford, J. H. Jones, and G. T. Young, *Chem. Commun.*, 4, 54 (1965); H. D. Jakubke and A. Voigt, *Chem. Ber.*, 99, 2419 (1966).

(3) K. W. Mertz and J. Fink, *Arch. Pharm.*, 289, 353 (1956).

(4) Satisfactory elemental analyses were obtained for all new substances.

(5) E.g., IIa, RCO = CH₃CO, 77% yield, mp 136–137°; IIb, RCO = ZGly, 85% yield, mp 121–122°; IIc, RCO = ZGly-L-Phe, 93% yield, mp 115–116°, [α]_D²⁵ -29.2° (c 2.0, CH₂Cl₂).

(6) D. S. Kemp, *Tetrahedron*, in press.

(7) Determined by its conversion by reaction with glycine ethyl ester to ZGly-L-Phe-GlyOEt in 80% yield; 0.5% DL isolated.⁸

(8) G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, 80, 2902 (1958).

tly favorable factors, among which the high of the esters II (IIb is ~20% dissociated in DMF in Et_3N), the inhibitory effect of acids on the zation of peptide esters,⁹ the reluctance of salts to assume a second negative charge, and their minolytic reactivity¹⁰ all figure prominently. Other investigations into the mechanism of these ses and their general applicability to peptide ng reactions are in progress and will be reported uently.

nowledgment. The support of the U. S. Public Service through Grants GM 13453-01 and -02 efully acknowledged.

f. D. S. Kemp and S. W. Chien, *J. Am. Chem. Soc.*, **89**, 2745

for a discussion of propinquity catalysis, see T. C. Bruice and nkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, 66, pp 150-169.

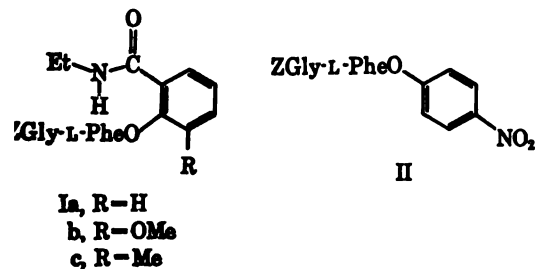
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Received December 30, 1966

ic Base Catalysis of Azlactone Formation

ent work^{1,2} has established azlactones as essential ediates in the racemization of many peptide ted species. While this and earlier work has clear a dependence of azlactone formation on the ice of base, the precise nature of the dependence ot been explored. By analogy with Winstein's on the cyclization of 2-benzamidoethyl tosylates,³ ould anticipate for a primary or secondary amide l nucleophilicity, dependent on the relative onditions of neutral amide and amide anion present ection medium. We wish to present evidence supports the presence of equilibrated amide s as the reactive intermediates leading to azlactone tion from four peptide activated esters.



le I presents first-order rate constants observed he triethylamine-catalyzed racemization of O-benzoxycyglycyl-L-phenylalanyl)-N-ethylsalicyl- (Ia)⁴ in dimethylformamide containing tri-

I. Goodman and K. C. Steuben, *J. Org. Chem.*, **27**, 3409 (1962); odman and L. Levine, *J. Am. Chem. Soc.*, **86**, 2918 (1964); odman and W. J. McGahren, *Ibid.*, **87**, 3028 (1965).
I. W. Williams and G. T. Young, *J. Chem. Soc.*, 3701 (1964); novics and G. T. Young, *Chem. Commun.*, 398 (1965).
L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183

I, mp 140-141°, $[\alpha]_D^{25} -21.7^\circ$ (c 2.2, CH_2CN); Ib, mp 149-150°, $[\alpha]_D^{25} -25.2^\circ$ (c 2.0, DMF); Ic, mp 125-126°, $[\alpha]_D^{25} -47.8^\circ$ (DMF); these esters were prepared in optically pure form by of the sodium salt of ZGly-L-PheOH in an aqueous pyridine with the appropriate 7-substituted N-ethylbenzisoxazolium

atisfactory elemental analyses were obtained for all new com-

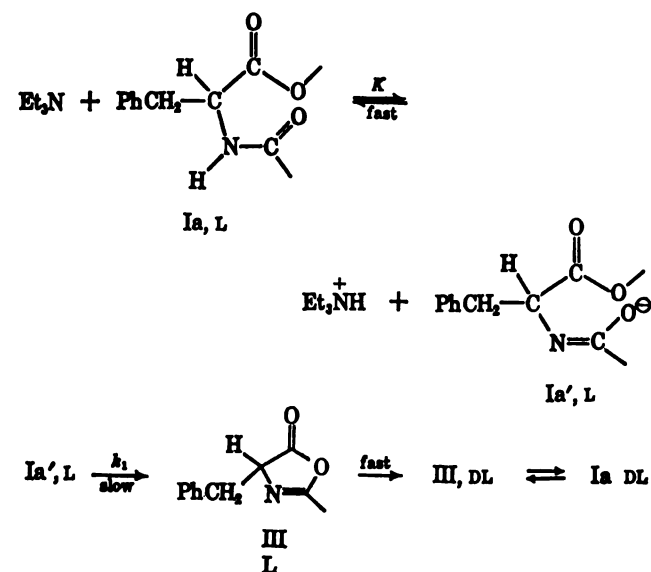
I. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).

Table I^a

[Et ₃ N]	[Et ₃ N ⁺ H] ^b	[Et ₃ N]/[Et ₃ N ⁺ H]	First-order ^c rate constant, min ⁻¹	Calcd rate ^d
0.2	No salt	...	12 × 10 ⁻³	
0.2	0.000	...	20 × 10 ⁻³	
0.2	0.01	20	3.0 × 10 ⁻³	3.0 × 10 ⁻³
0.2	0.015	13.3	2.4 × 10 ⁻³	2.1 × 10 ⁻³
0.2	0.02	10	1.7 × 10 ⁻³	1.7 × 10 ⁻³
0.2	0.05	4	0.86 × 10 ⁻³	0.83 × 10 ⁻³
0.2	0.2	1	0.38 × 10 ⁻³	0.37 × 10 ⁻³
0.4	0.04	10	1.9 × 10 ⁻³	
0.1	0.01	10	1.7 × 10 ⁻³	
0.05	0.005	10	1.5 × 10 ⁻³	
0.02	0.002	10	1.1 × 10 ⁻³	

^a Temperature 25°, DMF solvent. ^b Unless otherwise specified, sufficient $\text{Et}_3\text{N}^+\text{BF}_4^-$ was added to bring the total salt concentration to 0.2 M. ^c Ester concentration 10-20 mg/ml; rates followed polarimetrically, first-order rate law followed for at least three half-lives. ^d For rates at 0.2 M Et_3N , a plot of the observed first-order rate constant vs. $[\text{Et}_3\text{N}]/[\text{Et}_3\text{N}^+\text{H}]$ was linear with a slope, k_a , of $1.4 \times 10^{-3} \text{ min}^{-1}$ and a zero intercept, k_b , of 2.3×10^{-3} . Calculated rate = $k_a[\text{Et}_3\text{N}]/[\text{Et}_3\text{N}^+\text{H}] + k_b$.

ethylammonium fluoroborate. The observed linear dependence of rate on the amine:amine salt ratio, together with the striking insensitivity of rate to the absolute amine concentration at constant amine:amine salt ratio, are most easily interpreted as requiring the intermediacy of a conjugate base of Ia. A scheme consistent with this result is shown below.⁷



$$d[\text{DL-Ia}]/dt = k_1[\text{L-Ia}'] = k_1K[\text{L-Ia}][\text{Et}_3\text{N}]/[\text{Et}_3\text{NH}^+] \quad (1)$$

Similar behavior is observed for the esters Ib, Ic, and II (Table II). It is of interest that the intercepts, k_b , which are the limiting rates expected at constant amine concentration as the amine salt concentration is raised, most include all general base catalyzed terms; their magnitudes therefore bound the rates of simple base-catalyzed enolization for these esters. Although these results must be generalized with caution since they stand in contrast to other well-known salt effects on peptide racemization,² it would appear that in DMF tertiary amine catalyzed racemization of peptide phe-

(7) Although the formation of azlactones need not result in racemization, the reaction conditions of this study (polar solvent, excess of non-nucleophilic base) ensure that II racemizes faster than it reacts with phenolate anion, and therefore that k_1 is rate-determining.¹

Table II*

Ester	$k_{\text{rso}} = k_a[\text{Et}_3\text{N}]/[\text{Et}_3\text{N}^+\text{H}] + k_b$			
	k_a , min^{-1}	k_b , min^{-1}	k_{coupling}^b , $M^{-1} \text{min}^{-1}$	k_{coupling}/k_a
Ia	1.4×10^{-3}	2.3×10^{-3}	8.7×10^{-1}	600
Ib	2.3×10^{-4}	2.3×10^{-3}	2.1×10^{-1}	930
Ic	2.9×10^{-3}	2.3×10^{-3}	4.8×10^{-3}	1600
II	3.8×10^{-3}	1.4×10^{-3}	19.3	5100

* Rates followed polarimetrically; $\text{Et}_3\text{N} = 0.2 M$, $\text{Et}_3\text{N}^+\text{H} + \text{Et}_3\text{N}^+ = 0.2 M$, temperature 25° , DMF, anion = BF_4^- , $0.01 \leq [\text{Et}_3\text{N}^+\text{H}] \leq 0.2 M$; k_a and k_b obtained as described in Table I, footnote d. ^b Rates of the reaction, ester + GlyOEt \rightarrow ZGly-Phe-GlyOEt + phenol; rates followed by ultraviolet photometry in DMF, 30° ; ester, $1-2 \times 10^{-4} M$; GlyOEt, $0.01-0.5 M$; reactions were first order in ester to at least three-half-lives, first order in amine over at least a 3-fold concentration range.

nolic esters can be slowed by as much as 50-fold by the addition of the corresponding ammonium fluoroborate salt.

Included in Table II are rates of combination of the esters Ia-c and II with ethyl glycinate in DMF. Since the value of K in (1) should not vary significantly for these esters, the values of k_a may be taken as measures of the relative reactivities of the esters Ia-c and II toward an internal oxygen nucleophile. Comparing these values with the rates of reaction with an external amine, one finds a surprisingly good correlation, despite considerable variation of reactivity and structure.

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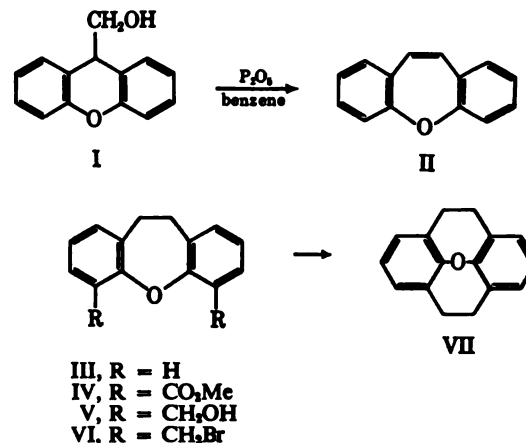
A Valence Tautomer of Pyrene *cis*-15,16-Epoxyde

Sir:

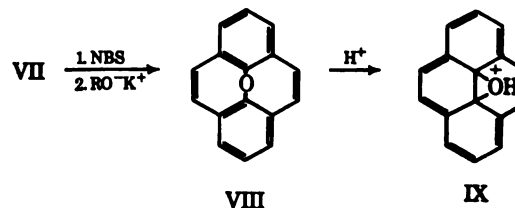
Recently we reported the synthesis of *trans*-15,16-dimethyldihydropyrene¹ and its photoisomerization to the corresponding metacyclophane valence tautomer.² Since then, syntheses of other examples of *trans*-15,16-dihydropyrenes have been described,^{3,4} but as yet no example has been reported of a *cis*-15,16-dihydropyrene derivative. We now wish to record the synthesis of 8,16-oxido[2.2]metacyclophane-1,9-diene (VIII), a valence tautomer of *cis*-pyrene 15,16-epoxide.

The starting material for this synthesis was xanthene-9-carbinol (I), which undergoes an acid-catalyzed rearrangement in essentially quantitative yield to give dibenz[b,f]oxepine (II).⁵ Reduction of II gave the corresponding dihydro derivative III as a colorless oil, bp $100-103^\circ$ (0.2 mm).⁶ Treatment of III with *n*-butyllithium followed by carbonation, according to the procedure used by Gilman for carbonating diphenyl

ether,⁷ gave the corresponding dicarboxylic acid by reaction with diazomethane, led to the dimethyl IV as white crystals, mp $94.5-95.0^\circ$, in 39% overall yield. Reduction of IV with lithium aluminum hydride provided the diol V as white crystals, mp $123-124^\circ$ in 98% yield. Conversion of V to the corresponding dibromide VI, white crystals, mp $124-125^\circ$, was accomplished in 90% yield using phosphorus tribromide. Cyclization of VI with phenyllithium to the corresponding metacyclophane VII, mp $94.0-95.5^\circ$, occurred smoothly in 75% yield.



Although VII is a metacyclophane derivative, the oxygen bridge forces the two benzene rings into a relationship in contrast to the normal *trans* geometry of [2.2]metacyclophanes.⁸ Further, it could be expected that the *cis* geometry of VII would allow no benzylic substitution. This was found to be the case. Treatment of VII with 2 equiv of *N*-bromosuccinimide gave the corresponding dibromide as a mixture of stereoisomers. Without separation, this mixture was then subjected to reaction with potassium *t*-butoxide in *t*-butyl alcohol to yield the desired unsaturated derivative, VIII, as white crystals, mp $119-120^\circ$. In support of its structural assignment, VIII shows an A_2B multiplet (6 H) at τ 2.66-3.30 and a singlet (at τ 2.92). Also, the ultraviolet absorption spectrum of VIII showed absorption maxima in cyclohexane at ϵ 15,700 and 302 m μ (ϵ 16,300), indicating conjugation between the aromatic rings and the unsaturated chains.⁹



Although the spectral data clearly establish that this is the correct structure of our product and that no valence tautomerization to the corresponding pyrene 15,16-epoxide structure does not occur, it was of interest to see whether conditions might be found for accomplishing this valence tautomerization. Initial attempts employing light and heat have

(1) V. Boekelheide and J. B. Phillips, *Proc. Natl. Acad. Sci. U. S. A.*, **51**, 550 (1964).

(2) H. Blattmann, D. Meuche, E. Heilbronner, R. J. Molyneux, and V. Boekelheide, *J. Am. Chem. Soc.*, **87**, 130 (1965).

(3) V. Boekelheide and T. Miyasaka, *ibid.*, **89**, 1709 (1967).

(4) H. B. Renfro, L. A. R. Hall, and J. A. Gurney, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Paper O-184.

(5) F. Anet, *Can. J. Chem.*, **35**, 1084 (1957).

(6) Satisfactory elemental analyses have been obtained for all of the compounds reported in this communication.

(7) K. Oita and H. Gilman, *J. Am. Chem. Soc.*, **79**, 339 (1957).

(8) W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *ibid.*, **83**, 943 (1961).

(9) The mass spectrum of VIII shows the expected parent molecular ion at m/e 218, with an even more intense signal at 202 corresponding to loss of oxygen.

success. However, when VIII is dissolved in acid, trifluoroacetic or sulfuric, the solution becomes deep green, the typical color of the *trans*-15,16-pyrene system. Furthermore, the absorption of such solutions in trifluoroacetic acid show peaks at 470, 560, and 647 $m\mu$, in good agreement with the spectra of *trans*-15,16-dimethyldihydropyrene derivatives.¹⁰

In view of the spectral correlations it is our belief that solutions of VIII in strong acid contain pyrene dioxide, the valence tautomer of VIII, presumably its protonated form as shown by IX. The intensity of the green color increases to a maximum approximately 30 min after dissolving VIII in trifluoroacetic acid (temperature 30°); the intensity then decreases slowly with the rate showing first-order kinetics suggesting IX is formed fairly rapidly and then undergoes slow decomposition. From this solution 1,6-pyrenequinone, and 1,8-pyrenequinone have been isolated and identified chromatographically and spectroscopically.¹¹ We have found that a solution of VIII in trifluoroacetic acid is stable, but the hydrocarbon is oxidized at room temperature by pertrifluoroacetic acid to yield a mixture containing the two quinones.

These observations indicate that the cation IX is formed by loss of OH^+ to form pertrifluoroacetic acid which would be difficult to explain the formation of the pyrenequinones from VIII.

Since the absorption maxima of VIII are still present in the acid, it is not possible to give exact values for extinction coefficients. However, the relative intensities of the absorption maxima are in reasonable accord with those of the dihydro-pyrene band at 560 $m\mu$ being extremely weak. No assignment of overtone bands could be made due to the presence of VIII initially.

Formation of pyrene as the reaction progressed (see below).
J. Fatiadi, *J. Chromatog.*, 20, 319 (1965).
National Institutes of Health Postdoctoral Fellow, 1966-1967.
Visiting Professor, on sabbatical leave from Oxford University.
Funded in part by a grant from the National Science Foundation.

B. Andes Hess, Jr.,¹² A. S. Bailey,¹³ V. Boekelheide¹⁴

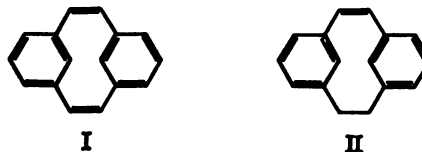
Department of Chemistry, University of Oregon
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Received April 4, 1967

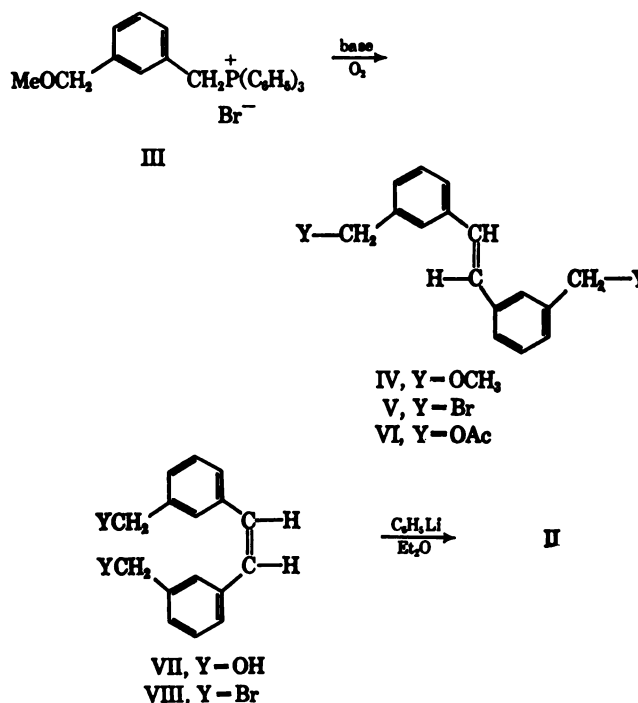
[2.2]Metacyclophane-1-ene¹ and Its Photoisomerization to 1,16-Tetrahydropyrene

Although Pellegrin² has claimed the synthesis of tacyclophane-1,9-diene (I), subsequent attempts at his preparation have been unsuccessful.^{3,4} Furthermore, even though the elegant studies of Dewar and Cram⁵ have shown that [2.2]paracyclophane can be converted to the corresponding mono- and diolefinic compounds, attempts to utilize their procedure for introduction of unsaturation into the [2.2]metacyclophane molecule have been unsuccessful.⁴ In view of our recent studies⁶ that [2.2]metacyclophane-1,9-diene derivatives

undergo spontaneous valence tautomerization to the corresponding *trans*-15,16-dihydropyrene derivatives, it has become of interest to reexamine the synthesis of [2.2]metacyclophanes having unsaturation in the bridging atoms. We now report the successful preparation of [2.2]metacyclophane-1-ene (II).



Treatment of the monophosphonium salt of *m*-xylyl dibromide with methanol readily gives the corresponding methoxy derivative III, mp 242-242.5°.⁷ The reaction of III with oxygen in the presence of base, following the procedure of Bestmann,⁸ yielded a mixture of the *cis*- and *trans*-stilbenes, IV. Cleavage of the benzylic ether linkages of IV with hydrogen bromide gave the corresponding *trans*-dibromide V, mp 161-162°, which by reaction with sodium acetate led to the *trans*-diacetate VI, mp 97-98°. Irradiation converted VI to a mixture of stereoisomers whose nmr spectrum indicated the ratio of *cis* to *trans* isomers was 3:1. On addition of ethanol the *trans* form of VI crystallized out. Hydrolysis of the remaining *cis* isomer of VI gave the corresponding diol VII as an oil, which was characterized by its analytical and spectral data. Treatment of VII with phosphorus tribromide followed by chromatography of the product gave the pure *cis*-stilbene dibromide VIII as a colorless oil.



In devising this scheme it had been anticipated that the presence of a bridging double bond, if it were in the *cis* configuration, would not interfere but might even help in a cyclization to the corresponding metacyclo-

(7) Satisfactory elemental analyses and supporting spectral data have been obtained for all new compounds reported in this communication.

(8) H. J. Bestmann, *Angew. Chem.*, 72, 34 (1960); H. J. Bestmann and O. Kratzer, *Chem. Ber.*, 96, 1899 (1963).

nomenclature used in this communication follows the suggestion of B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964, p 88.

Pellegrin, *Rec. Trav. Chim.*, 18, 457 (1899).

Baker, J. F. W. McOmie, and J. M. Norman, *J. Chem. Soc.*, 1957, 103.

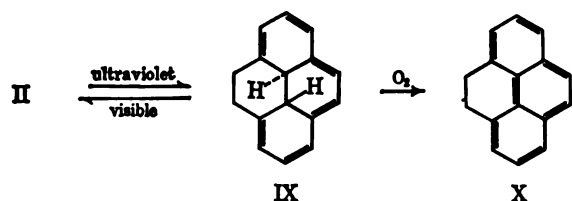
5. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *J. Am. Chem. Soc.*, 83, 943 (1961).

6. Dewar and D. J. Cram, *ibid.*, 80, 3115 (1958).

7. Blattmann, D. Meuche, E. Heilbronner, R. J. Molyneux, and V. Boekelheide, *ibid.*, 87, 130 (1965).

phane. When VIII was treated with sodium in the presence of tetraphenylethylene, the usual conditions for cyclization to form metacyclophanes, cyclization occurred, but it was accompanied by aromatization to give 4,5-dihydropyrene (X) in 50% yield. However, an investigation of other cyclization procedures led to the discovery that the treatment of VIII with phenyllithium in ether gives the desired [2.2]metacyclophane-1-ene (II) as white crystals, mp 82–83°, in 45% yield. It is of interest that in the nmr spectrum of II the signal for the two internal aromatic protons at the 8 and 16 positions is a broad singlet at τ 4.38. In [2.2]metacyclophane itself the internal 8 and 16 protons appear at τ 5.75. Thus, the orientation of the bridging double bond is such that it has a strong deshielding effect on the internal aromatic protons.

Ultraviolet irradiation of stilbene solutions in the absence of oxygen has been shown by a number of investigators to lead to 4a,4b-dihydrophenanthrenes.^{9–12} When a solution of II in benzene or carbon tetrachloride was irradiated with ultraviolet light, the solution rapidly became colored, showing the appearance of absorption bands at 237, 305, 318.5, and 500 m μ (broad).¹⁴ This spectrum is in good accord with that reported for the hexamethyldihydrophenanthrene¹³ and suggests the formation of the 4,5,15,16-tetrahydropyrene (IX). As would be expected, the formation of IX is readily reversible by visible light. Furthermore, the solutions resulting from irradiation of II are extremely sensitive to traces of oxygen and, in its presence, the product found is 4,5-dihydropyrene (X).



Thus far, attempts (catalytic dehydrogenation and NBS) to effect a dehydrogenation of IX to give *trans*-15,16-dihydropyrene have been unsuccessful and have invariably yielded pyrene. However, in the case where the internal substituents are other than hydrogen, the corresponding irradiation products should be more stable both toward oxygen and toward aromatization to pyrene. Studies on such derivatives are in progress.

(9) W. M. Moore, D. D. Morgan, and F. R. Stermitz, *J. Am. Chem. Soc.*, **85**, 829 (1963).

(10) M. V. Sargent and C. J. Timmons, *ibid.*, **85**, 2186 (1963).

(11) F. B. Mallory, C. S. Wood, and J. T. Gordon, *ibid.*, **86**, 3094 (1964).

(12) G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *ibid.*, **86**, 3197 (1964).

(13) K. A. Muszkat, D. Gegiou, and E. Fischer, *Chem. Commun.*, 447 (1965). We are indebted to Professor Fischer for his kindness in making a preprint of their detailed paper on this subject available to us prior to publication.

(14) Since the concentration of IX in the irradiated solutions is not known, extinction coefficients for their absorption bands could not be determined.

(15) We thank the Office of Naval Research for their support under Contract Nonr-2771(OR), NR-055-468, which made this investigation possible.

Heinz Blaschke, V. Boekelheide¹⁵

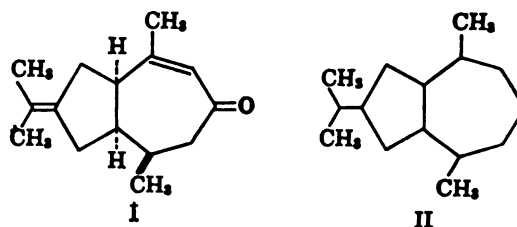
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A Stereoselective Synthesis of Hydroazulenes. Grounds for Structure Revision of the Vetivane Sesquiterpenes

Sir:

With a view toward the total synthesis of β -vetivone, a constituent of the essential oil of vetiver,¹ we formulated a new stereoselective route to substituted hydroazulenes and thereby prepared the three 6,10-dimethyl-*cis*-decahydroazulen-8-ones 12a–c. In this report we describe these synthetic studies and show that none of the aforementioned hydroazulenones corresponds to either of the epimeric desisopropylidenedihydro- β -vetivones prepared from β -vetivone. This finding invalidates not only the structure (I) heretofore accepted^{1,2} for β -vetivone but, by virtue of reported chemical correlations, the proposed carbon framework (II) of the entire class of bicyclic vetivane sesquiterpenes as well.^{2c,3}



Methylation (KO-*t*-Bu, CH₃I)⁴ of the known hydrindanone 1¹ afforded the dimethyl derivative 2 [$\lambda_{\text{max}}^{\text{film}}$ 3.28 (C=CH), 5.84 (CO), 6.09 (C=C), 8.78, 9.21, 9.58, 9.82, 9.92, and 10.05 μ ; $\delta_{\text{TMS}}^{\text{CCl}_4}$ = 5.36 (H-3, four lines, $J_{1,3}$ = 2 Hz, $J_{3,7a}$ = 2 Hz), 1.21, and 1.20 ppm (C-4 dimethyl)]. This substance yielded principally the *cis*-hydrindanone 3a [$\lambda_{\text{max}}^{\text{film}}$ 5.86 (CO), 10.14, 10.86, and 11.59 μ , purified *via* the semicarbazone derivative, mp 207–208°] upon hydrogenation over palladium on carbon in ethanol. The minor hydrogenation product was identified as the *trans*-hydrindanone 3b by comparison with an authentic sample.⁶ Bromination followed by dehydrobromination⁴ converted hydrindanone 3a to the conjugated ketone 4 [$\lambda_{\text{max}}^{\text{film}}$ 5.96 (CO), 6.18 (C=C), 8.91, 10.82, 11.80, and 12.41 μ]. Hydrogenation (Pd-C) regenerated the *cis*-hydrindanone 3a thus confirming our expectation⁴ that isomerization of the ring fusion had not occurred en route to the conjugated ketone 4 (Chart I).

Addition of methylmagnesium iodide to hydrindanone 4 in the initial presence of cupric acetate⁶ afforded the 1,4 adduct 5 [$\lambda_{\text{max}}^{\text{film}}$ 5.84 (CO), 8.90, 9.10, 9.63, and 9.95 μ ; $\delta_{\text{TMS}}^{\text{CCl}_4}$ = 1.27, 0.97 (C-4 dimethyl, two singlets), and 1.01 ppm (C-7 methyl doublet, J = 5.0 Hz)]. This

(1) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, London, 1952, pp 224–232.

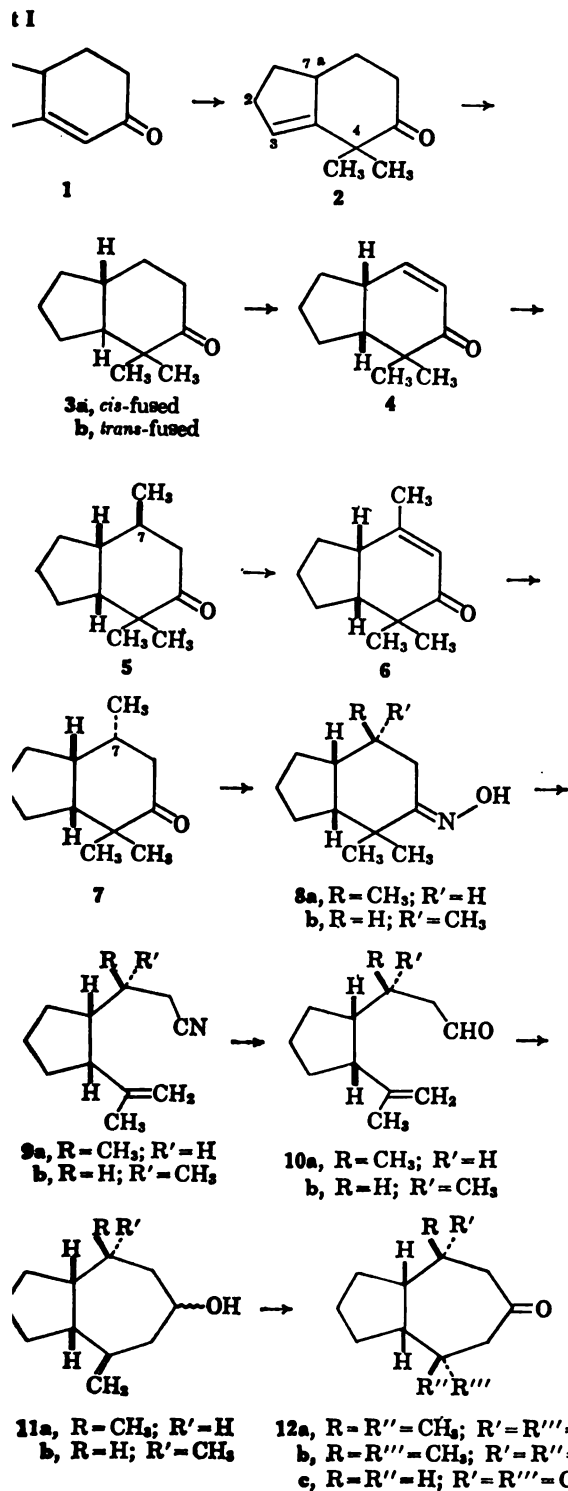
(2) (a) A. S. Pfau and P. A. Plattner, *Helv. Chim. Acta*, **23**, 768 (1940), and previous papers; (b) Y. R. Naves and E. Perrotet, *ibid.*, **24**, 3 (1941); (c) Y. R. Naves, *Bull. Soc. Chim. France*, 369 (1951); (d) M. Romaniuk and V. Herout, *Collection Czech. Chem. Commun.*, **25**, 2540 (1960); (e) I. Yosioka and T. Kimura, *Chem. Pharm. Bull. (Tokyo)*, **13**, 1430 (1965).

(3) Notably hinesol: W. Z. Chow, O. Motl, and F. Šorm, *Collection Czech. Chem. Commun.*, **27**, 1914 (1962); I. Yosioka, H. Hikano, and Y. Sasaki, *Chem. Pharm. Bull. (Tokyo)*, **9**, 84 (1961), and previous papers. Bicyclovetivenol: G. Chiurdoglu and J. Decot, *Tetrahedron*, **4**, 1 (1958). α -Isovetivenene and β -isovetivenene: ref 2d.

(4) Cf. J. A. Marshall and N. H. Andersen, *J. Org. Chem.*, **31**, 667 (1966).

(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(6) G. Stork, P. Rosen, H. Goldman, R. V. Coombs, and J. Twi, *ibid.*, **87**, 275 (1965).

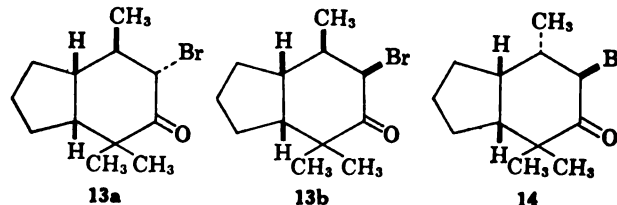


stance yielded the corresponding conjugated ketone 5. Expectedly, reduction of this conjugated ketone with lithium in ammonia⁷ regenerated the saturated ketone 5, whereas hydrogenation (Pd-C in ethanol) gave ketone 7 [$\lambda_{\text{max}}^{\text{film}}$ 5.86 (CO), 8.90, 9.48, and 11.70 μ ; ν_{max} = 1.15, 0.98 (C-4 dimethyl, two singlets), and 0.93 μ (C-7 methyl doublet, J = 5.7 Hz)], which readily yielded its conjugated ketone progenitor 6 upon bromination-dehydrobromination.⁴

Previous studies⁴ provide a basis for the *a priori* assignment of stereochemistry to ketone 5. The spectroscopic properties of the α -bromo ketones derived from 5

Cf. G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).

and 7 support this assignment. Thus ketone 5 affords bromo derivatives 13a [mp 97–98°, $\lambda_{\text{max}}^{\text{KBr}}$ 5.81 μ ; $\delta_{\text{TMS}}^{\text{CCl}_4}$ = 4.77 ppm (H-6 doublet, $J_{6,7}$ = 11.2 Hz)], an equatorial α -bromo ketone,⁴ and 13b [$\lambda_{\text{max}}^{\text{film}}$ 5.86 μ ; $\delta_{\text{TMS}}^{\text{CCl}_4}$ = 4.20 ppm (H-6 doublet, $J_{6,7}$ = 2.4 Hz)], an axial α -bromo ketone,⁴ in the ratio 6:1 upon bromination in acetic acid. In contrast, ketone 7 yields only an equatorial bromo ketone 14 [$\lambda_{\text{max}}^{\text{film}}$ 5.81 μ ; $\delta_{\text{TMS}}^{\text{CCl}_4}$ = 4.10 ppm (H-6 doublet, $J_{6,7}$ = 12.2 Hz)] under these conditions.



We recently reported⁸ the conversion of hydrindanone 5 to hydroazulenol 11a *via* fragmentation of the oxime derivative 8a (mp 150°) to nitrile 9a in pyridine containing *p*-toluenesulfonyl chloride, reduction of this nitrile with diisobutylaluminum hydride,⁹ and cyclization of the resulting aldehyde 10a with stannic chloride in benzene. The epimeric hydrindanone 7 was transformed in a similar manner to the oxime 8b (mp 98°), nitrile 9b, aldehyde 10b, and hydroazulenol 11b [$\lambda_{\text{max}}^{\text{film}}$ 2.95 (OH), 3.25 (C=CH₂), 6.11 (C=C), 9.45, 9.61, 9.75, 11.23 (C=CH₂), 12.42, and 12.55 μ]. Aldehyde 10b, like its methyl epimer 10a, afforded principally one isomer (95% according to the gas chromatogram) in the cyclization step.

Catalytic hydrogenation (Pt in ethanol) of unsaturated alcohol 11a afforded a mixture (*ca.* 1:1) of two dihydro compounds (methyl epimers) which, in turn, gave ketones 12a [$\lambda_{\text{max}}^{\text{film}}$ 5.88 (CO), 8.86, 9.12, 9.32, and 9.60 μ] and 12b [$\lambda_{\text{max}}^{\text{film}}$ 5.88 (CO), 8.85, and 9.32 μ], respectively, upon oxidation with chromic acid. Similar treatment of unsaturated alcohol 11b likewise afforded two ketones (in the ratio 40:60) of which the major component was identified by spectra comparison and gas chromatographic behavior (peak enhancement) as one of the ketones obtained from 11a. This substance must therefore possess *trans* oriented methyl groups as in 12b. The stereochemistry of the minor ketone 12c [$\lambda_{\text{max}}^{\text{film}}$ 5.90 (CO), 8.50, 8.70, 8.9, 9.21, and 9.34 μ] follows from its hydrindanone precursor 7.

(-)- β -Vetivone was secured from vetiver acetate, Java origin, and identified by its melting point,^{2a,b} optical rotation,^{2a,b} infrared spectrum,^{2c,10} and nmr spectrum.^{2c}

Following the hydrogenation-ozonolysis sequence reported by Pfau and Plattner,^{2a} we converted (-)- β -vetivone first to the *meso*-dihydro alcohol [a 65:35 mixture of alcohol epimers, mp 68–74°; $\lambda_{\text{max}}^{\text{KBr}}$ 3.1 (OH), 9.7, 10.40, 10.61, 10.93, and 12.61 μ], and then to the desisopropylidene compound [$\lambda_{\text{max}}^{\text{film}}$ 2.94 (OH), 5.77 (CO), 9.74, 10.92, and 12.18 μ]. The thioketal derivative of this hydroxy ketone afforded the alcohol upon desulfurization (H₂, Raney nickel). Oxidation with chromic acid then gave the desired ketone, *meso*-desisopropylidenedihydro- β -vetivone [$\lambda_{\text{max}}^{\text{film}}$ 5.81 (CO), 8.63, 8.75, 10.24, 10.72, and 11.67 μ]. The infrared spectrum

(8) J. A. Marshall and N. H. Andersen, *Tetrahedron Letters*, 1219 (1967).

(9) Cf. L. I. Zakharkin and I. M. Khorlina, *Dokl. Akad. Nauk SSSR*, **116**, 422 (1957); *Chem. Abstr.*, **52**, 8040f (1958).

(10) J. C. Nigam and L. Levi, *Can. J. Chem.*, **40**, 2083 (1962).

of this substance clearly differed from that of its alleged synthetic counterpart 12a and the isomers thereof (12b and c).

Reduction of (–)-β-vetivone with lithium in ammonia-ethanol afforded principally a new dihydro alcohol [40% yield, $\lambda_{\text{max}}^{\text{lim}}$ 3.00 (OH), 9.71, 10.38, and 11.05 μ] along with one of the previously obtained *meso* dihydro alcohols (15% yield) and recovered starting material. Degradation of this new dihydro alcohol along the lines described above for the *meso* compound afforded a new desisopropylidenedihydro-β-vetivone [$\lambda_{\text{max}}^{\text{lim}}$ 5.81 (CO), 8.64, and 9.6 μ] whose infrared spectrum bore no close resemblance to that of its supposed racemic counterpart 12b or the synthetic *meso* compounds 12a and c.

In view of the nonidentity of our naturally derived and synthetic ketones we must conclude that β-vetivone cannot be represented by I or a stereoisomer thereof. Evidence which supports a spiro[4.5]decane skeleton for this substance and its relatives is presented in the following paper.

Acknowledgments. We thank the Public Health Service for supporting this work through a research grant (AI04965, Division of Allergy and Infectious Diseases) and predoctoral fellowships. We are indebted to Dr. S. K. Freeman (International Flavors and Fragrances, Inc., New York, N. Y.) for generous samples of vetivert acetate.

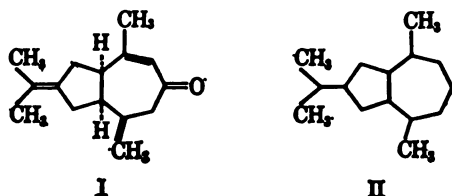
(11) (a) Alfred P. Sloan Foundation Fellow; (b) Public Health Service Fellow of the National Institute of General Medical Sciences.

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The Structure of β-Vetivone and Related Vetivane Sesquiterpenes

Sir:

The preceding report¹ summarizes synthetic and degradative work refuting the previously proposed structure (I) for β-vetivone² and those related sesquiterpenes whose carbon skeletons hinge on their correlation with "isovetivane" (II).³ In this earlier work we noted



that the carbonyl absorption (λ_{max} 5.81 μ) of dihydro-β-vetivone and desisopropylidenedihydro-β-vetivone seemed better accommodated by a cyclohexanone than a cycloheptanone as previously formulated.¹ We therefore sought alternative structures for these substances based on cyclohexanone. With this in mind and after considering the wealth of chemical and physical data recorded for β-vetivone,^{1,2} we decided on the spiro[4.5]decane III and IV as likely possibilities.

(1) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Am. Chem. Soc.*, **89**, 2748 (1967).

(2) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, London, 1952, pp 224-232.

(3) Cf. M. Romanjuk and V. Herout, *Collection Czech. Chem. Commun.*, **25**, 2540 (1960).

Chart I summarizes the transformations which v this proposal and allow us to choose III as the co structure.

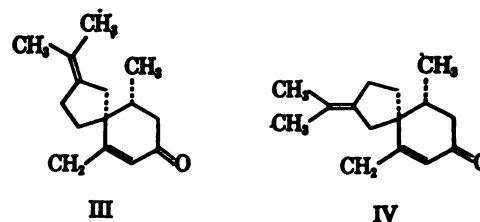
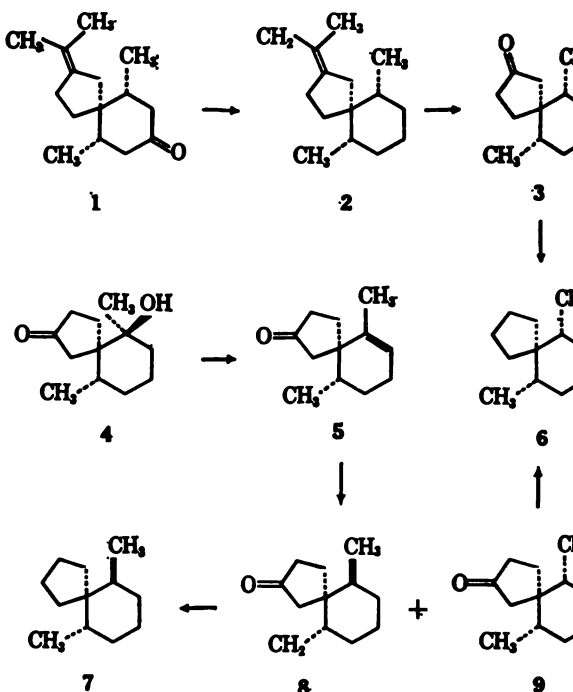


Chart I



The known *meso*-dihydro-β-vetivone (1)⁴ yields corresponding unsaturated hydrocarbon 2 [$\lambda_{\text{max}}^{\text{lim}}$ 8.71, 9.06, 9.46, 10.23, and 10.59 μ ; $\delta_{\text{TMS}}^{\text{CH}}$ = 1.60 (CH₃), 1.25 (ring H envelope), and 0.80 ppm (CH doublet, J = 5 Hz)] upon Wolff-Kishner reduction of the semicarbazone derivative, mp 192–193°. Onolysis⁴ afforded the cyclopentanone 3 [$\lambda_{\text{max}}^{\text{lim}}$ (CO), 7.11, 7.24, 8.42, 8.61, 9.44, 10.60, and 11.2 μ] which in turn gave the hydrocarbon 6 [$\lambda_{\text{max}}^{\text{lim}}$ 7.24, 9.42, 10.29, 11.00, 11.10, and 11.20 μ] after conversion to the ethylene thioketal derivative and desulfurization with W-2 Raney nickel⁶ in refluxing ethanol.

We secured an authentic sample of the spiro[4.5]decane 6 from hydroxy ketone 4,⁷ a known photochemical transformation product of *trans*-4a,8-dimethyl-5,6,7,8-tetrahydro-2(4aH)-naphthalenone. Dehydration with thionyl chloride in pyridine led to a mixture of olefins [$\lambda_{\text{max}}^{\text{lim}}$ 5.75 (CO), 7.11, 7.24, 10.12, 10.25, 10.36, 11.06, 11.79, and 12.42 μ], mixture 5 along with a minor amount of the exocyclic double bond isomer. Hydrogenation over palladium on carbon in ethanol afforded a mixture of ketones 8 [$\lambda_{\text{max}}^{\text{lim}}$ (CO), 7.11, 7.24, 8.53, 8.67, 10.20, 10.50, 11.0 and 11.25 μ] and 9 [$\lambda_{\text{max}}^{\text{lim}}$ 5.75, 7.11, 7.24, 8.53, 11.0 and 11.25 μ].

(4) A. S. Pfau and P. A. Plattner, *Helv. Chim. Acta*, **23**, 768 (1940).

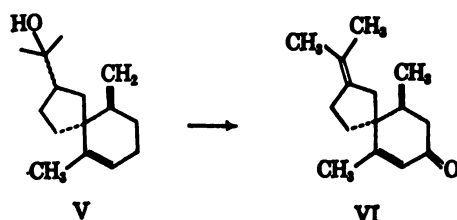
(5) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(6) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

(7) P. J. Kropp and W. F. Ertman, *J. Am. Chem. Soc.*, **85**, 181 (1963).

10.16, 10.48, 10.70, and 11.27 μ] in the ratio 2:3 judged by the gas chromatogram. The major component of this mixture should be the *meso* isomer since the double bond in unsaturated ketone 5 appears from models to be somewhat hindered by the imate methyl group.⁸ Ketones 8 and 9 differed 1:3 according to the infrared spectra and gas chromatographic behavior. However, desulfurization of thioketal derivative of ketone 9 afforded the same isocarbon 6 previously obtained from β -vetivone. Ketones 8 and 9 must therefore be epimeric at the spiro junction. Ketone 8, when similarly treated, yielded hydrocarbon 7 [$\lambda_{\text{max}}^{\text{film}}$ 7.24, 8.63, 9.42, 10.25, 11.05, 10.95, and 11.33 μ] which closely resembled 6. These hydrocarbons could be cleanly separated by chromatography.

The above transformations require that β -vetivone be formulated as III, or the mirror image. The choice I can be made from Yosioka and Kimura's work in which hinesol (now formulated as V) was converted to β -vetivone (VI).⁹ The absolute configuration of hinesol (V) follows from its degradation to (+)- α -



isovalglutaric acid by Šorm and co-workers.¹⁰

In view of the findings recorded above and in our previous report,¹ the list of sesquiterpenes containing a [4.5]decane ring system which previously contained the acrorones¹¹ and agarospirol¹² must now be amended to include β -vetivone, hinesol¹⁰ (a close relative of agarospirol¹²), bicyclovetivenol,¹³ α -isovetivene, and β -isovetivenene.⁸

Acknowledgments. We thank the Public Health Service for supporting this work through a research grant (AI04965, Division of Allergy and Infectious Diseases) and predoctoral fellowships. We are indebted to Dr. S. K. Freeman (International Flavors and Fragrances, Inc., New York, N. Y.) for generous supplies of vetivert acetate and Dr. P. J. Kropp (Procter and Gamble Company, Cincinnati, Ohio) for a supply of tetrahydronaphthalenone.

This methyl group probably prefers an axial conformation to *gauche* butane interactions with the adjacent spiro methylenes. An orientation may be particularly favored with olefin 5 because a double bond alleviates or removes the unfavorable *gauche* interaction normally associated with an axial methylcyclohexane: Cf. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., pp 42ff, 109ff.

I. Yosioka and T. Kimura, *Chem. Pharm. Bull.* (Tokyo), 13, (1965).

(1) W. Z. Chow, O. Motl, and F. Šorm, *Collection Czech. Chem. Commun.*, 27, 1914 (1962).

(2) J. Vrkoč, J. Jonas, V. Herout, and F. Šorm, *ibid.*, 29, 539 (1964).

(3) K. R. Varma, M. L. Maheshwari, and S. C. Bhattacharyya, *Tetrahedron*, 21, 115 (1965).

(4) G. Chiurdogiu and J. Decot, *ibid.*, 4, 1 (1958).

(5) (a) Alfred P. Sloan Foundation Fellow; (b) Public Health Service Fellow of the National Institute of General Medical Sciences.

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Received March 14, 1967

The Acidities of Weak Acids in Dimethyl Sulfoxide (DMSO) Solutions. III. Comments on the *H*-Acidity Scales

Sir:

There has been some apparent disparity between the acidity scale in cyclohexylamine solvent developed by Streitwieser¹ and his co-workers and one which we reported earlier² for DMSO, aqueous DMSO, and methanolic DMSO. We present here some recent results which bring the two scales into better over-all agreement but which indicate a significant difficulty in basing the scales satisfactorily on the aqueous reference state.

In our previous communication² we reported a ΔpK between fluorene (FH) and 9-phenylxanthene (PXH) of 3.7–3.8. Subsequent work showed that the actual ΔpK was too great to relate the indicators directly, and an intermediate indicator, 1,1,3-triphenylpropene (TPH), has now been used. The result is that the pK of indicators less acidic than fluorene must be increased by about 1.6 units. This gives a pK span of 9.7 units between FH and our least acidic indicator, diphenylmethane (DH), as compared to Streitwieser's span of 10.4. This is surprisingly good agreement considering the vast difference in the acidities involved and the difference in solvent systems.

A second point of inconsistency is the assignment of absolute pK values. We based our scale on 4-nitroaniline (NAH), the pK of which was reported to be 18.4 by Stewart and O'Donnell,³ a value based on the aqueous reference state. Streitwieser's scale is based on 9-phenylfluorene (PFH), the pK of which is reported to be 18.5 by Langford and Burwell⁴ and 18.6 by Bowden and Stewart.⁵ We have related FH to NAH, FH to PFH, and PFH to NAH, and find that PFH is significantly more acidic than previously reported. Ritchie has also found this to be the case.⁶ With these results our ΔpK between PFH and DH is 13.6 while Streitwieser's is 14.6—still excellent agreement. Furthermore, if both scales are based on the same reference compound the absolute pK values are within 1 pK unit throughout.

Absolute pK values have been avoided intentionally in the above discussion. The reason is that large deviations have been found between the hydrocarbon indicators, PFH and FH, and the nitroanilines in aqueous DMSO, and this causes uncertainties in basing the acidity scale on the aqueous reference state. This is shown graphically in Figure 1 where the *H*- of 10 mM KOH solutions in aqueous DMSO is plotted against $-\log [H_2O]$ using the different indicators. Values calculated from the data of Stewart, O'Donnell, and Dolman⁷ are also included. They used Me_4N^+ as the cation. The pK values of the nitroanilines are assumed to be those reported by Stewart and O'Donnell.³

(1) (a) A. Streitwieser, Jr., J. H. Hammons, E. Ciuffarin, and J. L. Brauman, *J. Am. Chem. Soc.*, 89, 59 (1967); (b) A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *ibid.*, 89, 63 (1967).

(2) E. C. Steiner and J. M. Gilbert, *ibid.*, 87, 382 (1965).

(3) R. Stewart and J. P. O'Donnell, *ibid.*, 84, 493 (1962).

(4) C. H. Langford and R. L. Burwell, *ibid.*, 82, 1503 (1960).

(5) K. Bowden and R. Stewart, *Tetrahedron*, 21, 261 (1965).

(6) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, 89, 2752 (1967).

(7) (a) R. Stewart and J. P. O'Donnell, *Can. J. Chem.*, 42, 1694 (1964); (b) R. Stewart and D. Dolman as presented in a review by K. Bowden, *Chem. Rev.*, 66, 119 (1966).

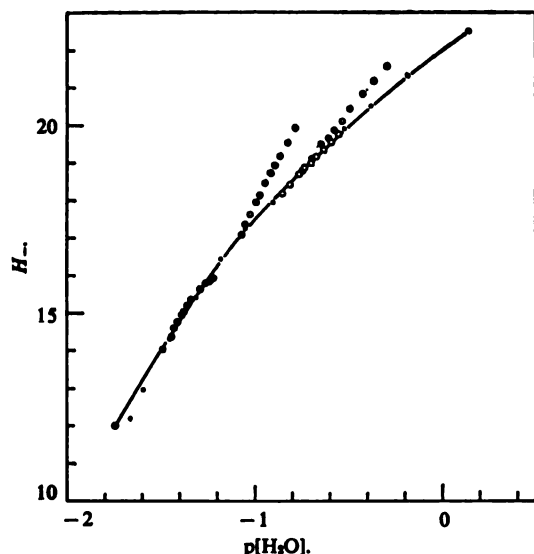
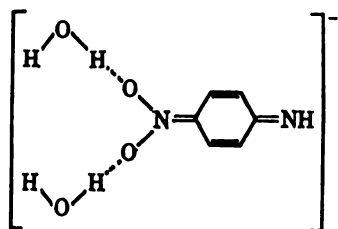


Figure 1. Base strength of aqueous DMSO solutions as a function of water concentration: \circ , 2,4-dinitrophenylamine, $[\text{KOH}] = 10 \text{ mM}$; \circ , 4-nitroaniline, $[\text{KOH}] = 10 \text{ mM}$; \bullet , calculated from data in ref 7, $[\text{Me}_4\text{N}^+\text{OH}^-] = 11 \text{ mM}$ adjusted to 10 mM ; \circ , 9-phenylfluorene ($\text{p}K = 18.1$ assumed), $[\text{KOH}] = 10 \text{ mM}$; \bullet , fluorene ($\text{p}K = 21.1$ assumed), $[\text{KOH}] = 10 \text{ mM}$.

The $\text{p}K$'s of PFH and FH are set at 18.1 and 21.1 so that H_- values measured with them conform to the aniline scale at the higher water concentrations. Clearly, the two types of indicators do not behave ideally relative to each other since the curves are not parallel. Furthermore, the $\Delta\text{p}K$ between, say, NAH and PFH will depend strongly on solvent composition, and therefore a large uncertainty is inevitable when absolute $\text{p}K$ values are assigned to the less acidic hydrocarbons. This same sort of discrepancy obtains also in methanolic DMSO, although it is not as serious. The discrepancy is negligible in ethanolic DMSO.

The causes of the deviations have not been investigated, but it seems likely that the nitro groups are an important factor. Thus if the anion of 4-nitroaniline is stabilized by hydrogen bonding to water, an increase



in water concentration would increase the acidity of NAH relative to that of PFH, as is observed. Salting out of the un-ionized hydrocarbon by water, another possible source of nonideality, should have an effect opposite to that observed. It is interesting to note that H_- data measured in methanolic DMSO with 4-nitrotriphenylmethane and with bis(4-nitrobenzyl) sulfone⁸ parallel very closely the data from the nitroanilines.

At the present time it appears to us that the nitroaniline scale is the most firmly anchored in the aqueous reference state. Furthermore, it is fairly consistent in a number of aqueous and alcoholic DMSO solutions as well as in pure DMSO. As such, it can be a useful tool. The nonideality between the anilines and the

(8) Measured in our laboratory by R. H. Imes in cooperation with Dr. F. G. Bordwell.

more acidic hydrocarbons creates large uncertainties in the $\text{p}K$ values assigned to the hydrocarbons, but since the aniline scale is the only available link between the hydrocarbons and the aqueous reference state there is little choice but to use it temporarily as the base for the hydrocarbons. If the hydrocarbon scale can be satisfactorily related directly to the pH scale, then perhaps a more valid and widely applicable H_- scale can be developed. A more detailed description of the H_- scale in a number of alcoholic DMSO mixtures will be given in a subsequent communication.

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Received February 15, 1967

Acidity in Nonaqueous Solvents. V. Acidity Scales in Dimethyl Sulfoxide Solution^{1,2}

Sir:

Using the potentiometric method recently described,³ we have determined the "absolute"⁴ acidities of several additional carbon acids in dimethyl sulfoxide solution. The new data, presented in Table I, along with some pertinent previously reported data, provide an explanation of major discrepancies between reported relative acidities in dimethyl sulfoxide and cyclohexylamine solution⁴ and provide further insight into the nature of the effect of changing solvent on the relative acidities of various acids.

Table I. Comparison of Acidities in Various Solvents

Acid	$\text{p}K(\text{DMSO})^a$	$\text{p}K(\text{H}_2\text{O})^b$	$\text{p}K(\text{CHA})^c$
9-Carbomethoxyfluorene	10.3	12.9 ^{d,e}	...
<i>p</i> -Nitrophenol	10.4 ^f	7.1	...
Acetic acid	11.6 ^f	4.8	...
Malononitrile	11.0	11.1 ^{d,e}	...
Benzoylacetone	12.1 ^f	9.6	...
Tris(<i>p</i> -nitrophenyl)-methane	12.2 ^f	14.3 ^{d,e}	...
Acetylacetone	13.4	9.0	...
2,4-Dinitroaniline	14.8 ^f	14.7 ^d	...
Nitromethane	15.9 ^f	10.2	...
9-Phenylfluorene	16.4	18.6 ^{d,e}	(16.4)
Indene	18.5	18.2 ^d	17.8
9-Methylfluorene	19.7 ^f
4,5-Methyleneph-anthrene	20.0	...	20.5
Fluorene	20.5	20.5 ^d	20.6
Triphenylmethane	~28	28.8 ^{d,h}	29.4

^a Standard state in dimethyl sulfoxide solution. Estimated accuracy: $\pm 0.3 \text{ p}K$ unit (see ref 2). All measurements at 25.0° .

^b Those values not referenced were actually determined in aqueous solution. Others have been determined by acidity function techniques. ^c Values taken from ref 4 and adjusted to $\text{p}K = 16.4$ for 9-phenylfluorene. ^d Values determined by acidity function techniques. ^e From ref 5. ^f Values from ref 2. ^g Value determined in aqueous solution and used as the standard for establishment of an H_- scale. See ref 5. ^h Personal communication from Dr. E. C. Steiner.

(1) This work was supported by Grant No. GM 12832 from the Public Health Service, National Institutes of Health.

(2) For previous papers in this series, see: C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 1721 (1967), and earlier references cited there.

(3) The word "absolute" is used in the sense that the equilibrium constants are referred to a standard state in the solvent in which they are measured.

(4) A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *J. Am. Chem. Soc.*, **89**, 63 (1967).

value of 11.14 for malononitrile in aqueous was determined by Bowden and Stewart.⁵ was then used as the "anchor compound" in an acidity scale in ethanol-dimethyl sulfures. The scale was applied to the measure- K values for a number of carbon acids, among 9-carbomethoxyfluorene, tris(*p*-nitrophenyl)- and 9-phenylfluorene. The $pK(H_2O)$ values the table for these compounds are those ob- Bowden and Stewart.

ent data clearly show the breakdown of the ale. The relative acidity of malononitrile and ethoxyfluorene changes by 2.5 pK units on n ethanol to dimethyl sulfoxide solution. The idities of 9-carbomethoxyfluorene and either ophenyl)methane or 9-phenylfluorene, how- nearly the same in both determinations.

appears probable that the agreement pre- reported² between our "absolute" pK 's and rmined by Steiner⁶ by acidity function tech- purely fortuitous. Apparently, the reference d, 4-nitroaniline, used by Steiner for determi- the other acids just happens to be one for : pK is not strongly affected by the change of Malononitrile appears to be another such d, showing the same pK in water and dimethyl

discussed in our previous paper,² four distinct e expected to influence the change in acidity d on going from water to dimethyl sulfoxide. hese effects, the greater basicity of dimethyl than water and the dispersion interaction of flored anions with solvent, would act to in- idity in dimethyl sulfoxide. The other two lectrostatic effects and hydrogen bonding of o the conjugate base, would decrease acidity yl sulfoxide. For the nitroanilines and for itrile it appears that these effects just balance. ve that this cancellation is purely fortuitous

results from different magnitudes of the in- effects in the two cases. Both hydrogen bond- he dispersion interactions are expected to be or the nitroanilines than for malononitrile. crease in acidity of 9-carbomethoxyfluorene t for malononitrile in going from ethanol to sulfoxide is most reasonably attributed to the n interactions of the substituted fluorenyl th the polarizable solvent.

onclusions pertinent to current investigations dy of acidities of hydrocarbons can be drawn present data. First, and in our opinion most it, *the data clearly show that no single H- mction applicable to acids of different structures nstructed to reach into pure dimethyl sulfoxide.* clusion is further strengthened by the results r's recent study.⁷

l, if the relative acidities of various hydro- in cyclohexylamine solution, determined by ser,⁴ are adjusted to our value of 16.4 for the -phenylfluorene, rather than to the previously

used value of 18.5, the discrepancies noted between the scales in dimethyl sulfoxide and cyclohexylamine solutions no longer appear, and, in fact, the agreement, as shown in Table I, is even better than might have been expected for two such different solvents.

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A Novel Method for the Synthesis of Isomerically Pure Vinyl Halides from Alkynes via the Hydroalumination Reaction¹

Sir:

The addition of bromine to vinylorganoboranes results in the formation of 1,2-dibromoboranes. These derivatives are converted to vinyl halides when treated with water or aqueous sodium hydroxide.² Recently, Matteson and Liedtke³ have suggested that bromine adds *trans* to unsaturated boronic esters, and they have established that deboronobromination involves a stereo-specific *trans* elimination. In concurrence with these results is the observation by Brown⁴ that bromination of *trans*-1-hex-1-enyl-bis(3-methyl-2-butyl)borane, derived from hydroboration of 1-hexyne with bis(3-methyl-2-butyl)borane,⁴ gives after hydrolysis *cis*-1-bromo-1-hexene.

We have now investigated the halogenation of vinylalanes. These derivatives are readily available by hydroalumination of alkynes with diisobutylaluminum hydride in a hydrocarbon solvent.⁵ This involves a *cis* addition of the aluminum-hydrogen bond to the triple bond, yielding *trans*-vinylalanes from 1-alkynes and *cis*-vinylalanes from disubstituted alkynes. Treatment of the *trans*-vinylalane derived from 1-hexyne in tetrahydrofuran with various halogens in a 1:1 ratio at -50° produces essentially pure *trans*-1-halo-1-hexenes. Under similar experimental conditions the *cis*-vinylalane obtained from 3-hexyne reacts with bromine or iodine to give the corresponding *cis*-3-halo-3-hexenes. The experimental results are summarized in Table I.

The fact that halogenation of unsaturated alanes proceeds with retention of configuration supports the contention that vinylalanes undergo electrophilic cleavage (1) preferentially at the vinyl carbon-aluminum bond. Formation of vinyl halides from vinylboranes, however, is the result of an addition-elimination reaction (2). It should be noted that the reaction of chlorine with the vinylalane derived from 1-hexyne gives a 70:30 mixture of *trans*- and *cis*-1-chloro-1-hexene, indicating a competition between addition to the double bond and cleavage at the vinyl carbon-aluminum bond.

(1) This research was supported by National Science Foundation Grants No. GP3521 and GP 6633.

(2) B. M. Mikhailov and P. M. Aronovich, *Izv. Akad. Nauk SSSR, Old. Khim. Nauk*, 927 (1961); *Chem. Abstr.*, 55, 24541 (1961); D. S. Matteson and K. Peacock, *J. Org. Chem.*, 28, 369 (1963); W. G. Woods and I. S. Bengelsdorf, *ibid.*, 31, 2766 (1966); H. C. Brown, private communication.

(3) D. S. Matteson and J. D. Liedtke, *J. Am. Chem. Soc.*, 87, 1526 (1965).

(4) H. C. Brown, and G. Zweifel, *ibid.*, 83, 3834 (1961).

(5) G. Wilke and H. Müller, *Ann.*, 629, 222 (1960); G. Zweifel and R. B. Steele, to be published.

owden and R. Stewart, *Tetrahedron*, 21, 261 (1965).

. Steiner and J. M. Gilbert, *J. Am. Chem. Soc.*, 87, 382

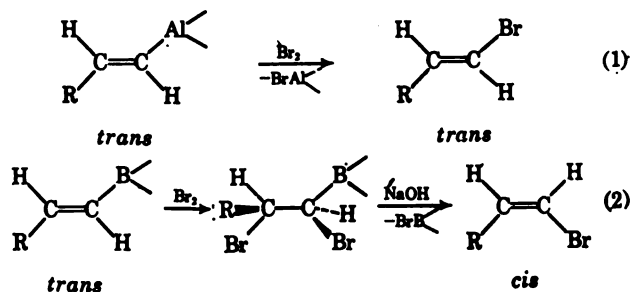
. Steiner and J. D. Starkey, *ibid.*, 89, 2751 (1967). We wish our appreciation to Dr. Steiner for furnishing us with a this paper.

Table I. Halogenation of Vinylalanes in Tetrahydrofuran

Vinylalane derived from	Halogen ^a	Vinyl halide, <i>trans</i>	% ^{b,c} <i>cis</i>
1-Hexyne	I ₂	94	<2
	ICl	76 ^d	<2
	Br ₂	72	<2
3-Hexyne	I ₂	<2	72
	Br ₂	<2	42

^a Both bromine and iodine monochloride were dissolved in methylene chloride and then added to the vinylalane. Iodine was used in tetrahydrofuran. ^b Analysis by glpc with an internal standard. ^c The assignments for the vinyl halides are based on infrared and nmr data. ^d *trans*-1-Iodo-1-hexene.

With increasing reactivity of the halogen, there is less discrimination between cleavages at the hexenyl-aluminum and isobutyl-aluminum bonds. In these cases the vinyl halide is contaminated with the isobutyl halide. In order to maximize the yield of the vinyl halide, larger amounts of halogens should be used.



The simplicity of this procedure makes it a valuable method for synthesis of isomerically pure vinyl halides. The isobutyl groups on aluminum do not interfere with the isolation of the halides since they are converted to isobutane in the hydrolysis step. It is of special importance in that 1-iodo-1-alkenes, which cannot be prepared by the addition of hydrogen iodide to 1-alkynes in the presence of peroxides, are obtained in excellent yield from the corresponding vinylalanes. A representative procedure is given below.

To 0.10 mole of 1-hexyne in 20 ml of *n*-heptane was added 0.10 mole of diisobutylaluminum hydride while maintaining the temperature below 40°. When the initial exothermic reaction had subsided, the reaction mixture was heated for 2 hr at 50°. The heptane was then removed under reduced pressure (0.5 mm), and the residue obtained was diluted with 40 ml of tetrahydrofuran. To this vinylalane solution at -50° was added 0.10 mole of iodine in 40 ml of tetrahydrofuran. After allowing the reaction mixture to warm up to room temperature, the diisobutylalane ($-\text{Al}(\text{C}_4\text{H}_9)_2$) was decomposed at 20–30° by dropwise addition of 20% sulfuric acid (exothermic reaction). When the isobutane evolution had diminished, the reaction mixture was poured into ice–20% H_2SO_4 . The vinyl iodide was extracted into pentane and the combined extracts were washed first with sodium thiosulfate, then with sodium bicarbonate. Distillation gave 15.52 g of *trans*-1-iodo-1-hexene (74%); bp 50–52° (3 mm), n_D^{25} 1.5072. A small amount of the vinyl iodide was converted to the vinyl-lithium derivative,⁶ which was hydrolyzed with deuterium oxide. The infrared and nmr spectra of the

(6) D. Seyferth and L. G. Vaughan, *J. Am. Chem. Soc.*, **86**, 883 (1964).

olefin obtained were identical with those of an authentic sample of *trans*-1-hexene-1- d_1 .

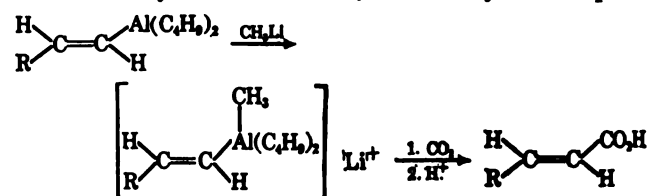
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Received March 13, 1967

A New and Convenient Method for the Preparation of Isomerically Pure α,β -Unsaturated Derivatives via Hydroalumination of Alkynes

Sir:

Relatively little attention has been directed to the utilization of organoalanes as Grignard-like reagents. Ziegler and co-workers¹ have shown that the addition of carbon dioxide to trialkylalanes at atmospheric pressure and at room temperature in hydrocarbon solvents results in the carbonation of only one carbon-aluminum bond. Similarly, we have observed that carbonation of vinylalanes in hydrocarbon solvents affords the corresponding α,β -unsaturated acids in modest yields (30–37%). Both trialkylalanes and vinylalanes, however, fail to react with carbon dioxide in ether or hydrocarbon-ether mixtures at room temperature.

We now wish to report that the *ate* complexes of vinylalanes may be utilized for Grignard-type reactions. The required vinylalanes are readily accessible via hydroalumination of alkynes with diisobutylaluminum hydride in hydrocarbon solvents.^{2,3} This involves a *cis* addition of the aluminum-hydrogen bond to the triple bond, yielding *trans*-vinylalanes from 1-alkynes and *cis*-vinylalanes from disubstituted alkynes. Treatment of the hydrocarbon solutions of vinylalanes with methyllithium in ether in a 1:1 ratio followed by carbonation gives the corresponding carboxylic acids in excellent yields. Likewise, acetaldehyde and para-



formaldehyde⁴ may be treated with the *ate* complexes at 25 and 35°, respectively, to yield α,β -unsaturated alcohols. A summary of the experimental results of these reactions is given in Table I.

Examination of the reaction mixtures by glpc revealed that the products obtained in each case were isomerically pure. Consequently, the reactions of vinylalanes with Grignard co-reagents proceed with retention of configuration. It was also noted that carbonation occurs exclusively at the vinyl-aluminum bond. The isobutyl moieties of the hydroaluminating agent are converted to isobutane in the hydrolysis step, and hence do not interfere in the isolation of the products.

(1) K. Ziegler, F. Krupp, K. Weyer, and W. Larbig, *Ann.*, **629**, 251 (1960).

(2) G. Wilke and H. Müller, *ibid.*, **629**, 222 (1960).

(3) G. Zweifel and R. B. Steele, to be published.

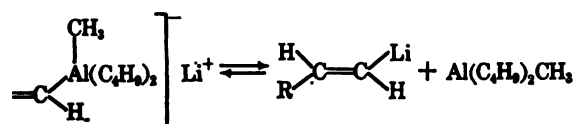
(4) It has been reported that the reaction of Grignard compounds with paraformaldehyde proceeds very slowly, whereas organolithium derivatives react at a much faster rate: A. Schaap, L. Brandma, and J. F. Arens, *Rec. Trav. Chim.*, **84**, 1200 (1965).

Reactions of Vinylalanes with
Reagents in Ether

Alkylalane d from	Reagent	Product	Yield, % ^{a,b}
1-hexyne	CO ₂	<i>trans</i> -2-Heptenoic acid	78
	HCHO ^c	<i>trans</i> -2-Hepten-1-ol	73
	CH ₃ CHO	<i>trans</i> -3-Octen-2-ol	68 ^d
hexyl- tylene yne	CO ₂	<i>trans</i> -3-Cyclohexyl-2- propenoic acid	72
	CO ₂	<i>trans</i> -2-Methyl-2-butenic acid	76
1-octyne	CO ₂	<i>trans</i> -2-Ethyl-2-pentenoic acid	78

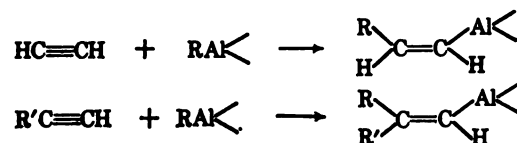
solution. ^a Yields are based on the amount of alkyne used.
maldehyde. ^d Yield 90% by glpc analysis.

ough the nature of the reactive organometallic
mediates has not been established, it is conceivable
re reactions proceed *via* the vinyl lithium deriva-
resulting from disproportionation of the vinyl-
s. The configurational stability of vinyl lithium



unds in solution, a requirement in view of the
tereospecificity of the above reactions, has been
illustrated by Seyferth and co-workers.⁵ We have
ed that tetraalkylalanes do not react with
dioxide; however, their disproportionation
lithium compounds and trialkylalanes should
modynamically unfavorable.

synthesis of vinylalanes is not confined to the
alumination reaction. Thus trialkylalanes add
tylene under mild conditions to yield *cis*-vinyl-
whereas addition of the aluminum-carbon bond
alkynes affords the corresponding disubstituted
anes.³ The availability of *cis*- and *trans*-mono-



uted vinylalanes greatly increases the versatility
above reactions.

simplicity of the present procedure for the con-
n of alkynes into α,β -unsaturated derivatives
ylalanes is illustrated by the following example.
0.10 mole of 1-hexyne in 20 ml of *n*-heptane was
by means of a hypodermic syringe 0.10 mole of
tetylaluminum hydride, while maintaining the
rature below 40°. After the initial exothermic
m had subsided, the reaction mixture was heated
r at 50°. To the vinylalane formed was added at
temperature 0.10 mole of methyl lithium in ether
l). The solution was cooled to -30°, then car-
d by introducing a stream of carbon dioxide
maintaining the temperature at -30 to -10°.
action mixture was poured slowly into an ice-
trated hydrochloric acid mixture and the car-
c acid produced was extracted into ether. Distil-

. Seyferth, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), 26,
1).

lation gave 10.0 g of *trans*-2-heptenoic acid (78%),
bp 89° (0.3 mm), n_D^{25} 1.4560, amide mp 124°.⁶

Acknowledgment. This work was supported by
National Science Foundation Grants GP-3521 and
GP-6633.

(6) P. Bruylants, *Bull. Soc. Chim. Belges*, 41, 333 (1932), reports for
trans amide mp 125°.

(7) National Institutes of Health Predoctoral Fellow, 1965-1966.

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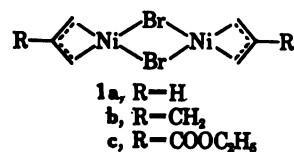
Received April 12, 1967

Organonickel Compounds as Reagents for Selective Carbon-Carbon Bond Formation between Unlike Groups

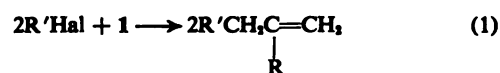
Sir:

The extension of carbon chains by the coupling of
two different groups using as reagents an organic halide,
RHal, and an alkyl- or arylmetal derivative, R'Met, is
seldom employed in synthetic practice if alternative
operations are available. This is due in part to the
fact that coupling products RR and R'R' are usually
formed in substantial amounts¹ and in part to the
intervention of a variety of other side reactions, *e.g.*,
 α - or β -elimination processes. We report here a new
and promising method for the *selective combination of*
unlike groups at carbon using organonickel reagents.

Reaction of a variety of allylic bromides with excess
nickel carbonyl in dry benzene (50°, 2-3 hr) followed by
removal of solvent and recrystallization from ether at
-70°² gives good yields of π -allylnickel(I) bromides,
for example, 1a-c, in 80-95% yield.^{3,4} These complexes
are relatively inert toward alkyl halides in either hydro-



carbon solvents or ether-type solvents (*e.g.*, tetrahydro-
furan). In more *polar, coordinating media*, *e.g.*, di-
methylformamide, N-methylpyrrolidone, or hexa-
methylphosphoramide, a facile reaction occurs between
the complexes 1 and a *wide variety* of halides, with
iodides generally being more reactive than (and pre-
ferable to) bromides.⁵ Equation 1 summarizes the
over-all reaction, and Table I presents the results ob-



(1) For example, because of fast halogen-metal exchange prior to
coupling. See D. E. Applequist and D. F. O'Brien, *J. Am. Chem. Soc.*,
85, 743 (1963).

(2) All operations with organonickel compounds have been con-
ducted with rigorous exclusion of oxygen using an argon atmosphere
either with plastic glove bag or argon-line techniques.

(3) The complex 1a, first prepared by E. O. Fischer and G. Bürger,
Z. Naturforsch., 16b, 77 (1961), was originally obtained only in ca.
10% yield; however, much higher yields are easily realized if thermal
or oxidative decomposition of the complexes is avoided.

(4) These complexes can also be obtained efficiently from allylic
bromides using bis(1,5-cyclooctadiene)nickel as reagent; see G. Wilke
et al., *Angew. Chem. Intern. Ed. Engl.*, 5, 159 (1966). However, the
synthesis from commercially available nickel carbonyl is usually more
expedient.

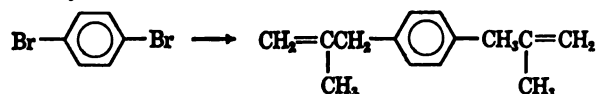
(5) Chlorides are less generally useful because of their much lower
reactivity.

Table I. Coupling of π -Methallylnickel(I) Bromide (1b) with Halides (Eq 1) in Dimethylformamide

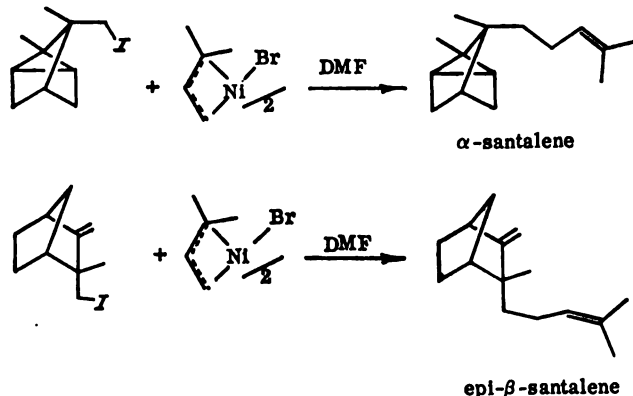
Halide	Reaction time, hr (temp, °C)	Yield, %
Methyl iodide	10 (22)	90 ^a
Methyl bromide	19 (22)	90 ^a
Cyclohexyl iodide	3 (22)	91
4-Hydroxycyclohexyl iodide	10 (22)	88 ^b
<i>t</i> -Butyl iodide	24 (22)	25 ^a
Iodobenzene	1 (22)	98
Vinyl bromide	13 (22)	70 ^a
Benzyl bromide	6 (60)	91
3-Phenylpropyl bromide	46 (65)	92
Phenyl α -chloromethyl ether	18 (60)	50
<i>p</i> -Bromophenacyl bromide	0.5 (22)	75
Chloroacetone	2 (22)	46 ^a

^a These yields were determined by quantitative vpc analysis; others are yields of isolated pure products. ^b Mixture of *cis* and *trans* isomers which are converted by chromic acid oxidation to 4-methallylcyclohexanone.

tained with 1b and a diverse collection of substrates.⁶ The reaction proceeds well not only with alkyl iodides and bromides but also with *aryl* and *vinyl* compounds. Further, the data indicate that the presence of carbonyl or hydroxyl functions in the halide partner need not interfere with coupling. Dihalides undergo disubstitution with the appropriate quantity of nickel(I) complex, as shown by the conversion of 1,6-diiodohexane with 1b (mole ratio 1:1.25) to 2,11-dimethyl-1,11-dodecadiene (95% yield) and of 1,4-dibromobenzene with 1b (mole ratio 1:1.25) to 1,4-dimethallylbenzene (97%). The latter substance is not readily accessible by conventional synthetic methods.



The new method has been employed in direct and efficient syntheses of α -santalene (2)⁷ (88% yield) and *epi*- β -santalene (3)⁸ (90% yield) using the nickel(I) complex from α,α -dimethylallyl bromide as follows.⁹



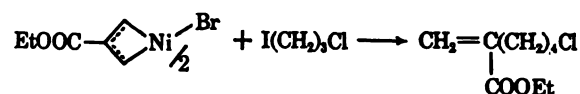
(6) The structures and products obtained by the reactions described herein have been verified by infrared, nmr, and mass spectrometric or elemental analysis. Purity was checked by vapor phase chromatography and quantitative nmr analysis.

(7) E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, **79**, 5773 (1957).

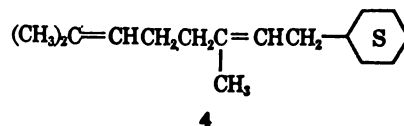
(8) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *ibid.*, **84**, 2611 (1962). The iodocamphene used in the synthesis of 3 was prepared from the corresponding bromide by successive treatment with magnesium, mercuric chloride, and iodine. The bromocamphene was derived from π -bromocamphor by reduction (BH_4^-) and dehydration with POCl_3 -pyridine.

(9) The nickel(I) π complex from α,α -dimethylallyl bromide generally undergoes preferential coupling at the primary rather than at the

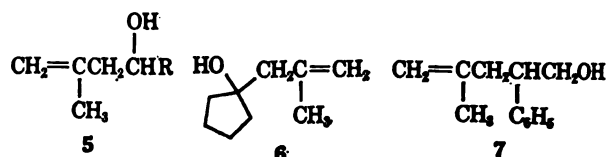
Substances of utility for further chain extension or cyclization can also be produced, for instance



In cases where substitution at C_1 and/or C_2 of the allyl group allows the possibility of geometrically isomeric coupling products, both *cis* and *trans* isomers usually result. For example, the π complex prepared from *trans*-geranyl bromide and nickel carbonyl affords with cyclohexyl iodide the coupling product 4 as a mixture of *cis-trans* isomers (40 and 60%).¹⁰



π -Allylnickel(I) complexes also can react with substances other than halides. The methallyl complex 1b reacts with benzaldehyde, acrolein, and cyclopentanone in dimethylformamide to yield 5, $\text{R} = \text{C}_6\text{H}_5$ (85%), 5, $\text{R} = \text{CH}=\text{CH}_2$ (80%), and 6 (50%), respectively, and styrene oxide affords 7 (60%). In general, these reactions are considerably slower than those of 1b with iodides, and more drastic conditions were used (50°, *ca.* 24 hr).



The more general problem of effecting cross-coupling reactions of unlike *nonallylic* groups is currently the subject of a parallel investigation in this laboratory, not only in the nickel series but also with other transition metal derivatives, for example, organocopper¹¹⁻¹³ and organosilver¹⁴⁻¹⁷ compounds.

An especially crucial part of the coupling process described above is the step in which the new carbon-carbon bond is formed and in particular the precursor for that step. Among the possibilities which presently appear as reasonable is the complex 8 which might be formed, for example, by the route¹⁸

tertiary terminal; with methyl iodide it affords pure 2-methyl-2-pentene (by vpc and nmr analysis) in *ca.* 90% yield.

(10) The interconversion of *cis-trans* forms of the allyl group could occur within the nickel complexes, *e.g.*, via reversible $\sigma-\pi$ bonding changes. See (a) J. Powell, S. D. Robinson, and B. L. Shaw, *Chem. Commun.*, 78 (1965); (b) K. G. Ramey and G. L. Statton, *J. Am. Chem. Soc.*, **88**, 4387 (1966). Alternatively, isomerization may involve equilibration of primary and tertiary allylic bromides *via* nickel(I) σ and π complexes.

(11) H. Gilman and J. M. Straley, *Rec. Trav. Chim.*, **55**, 821 (1936).

(12) R. G. R. Bacon and H. A. O. Hill, *Quart. Rev. (London)*, **19**, 95 (1965).

(13) C. E. Castro, *et al.*, *J. Org. Chem.*, **28**, 2163, 3313 (1963); **31**, 4071 (1966).

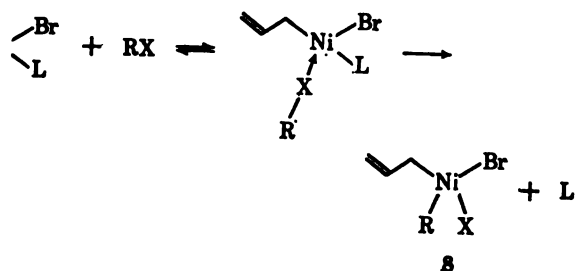
(14) E. A. Bickley and J. H. Gardner, *ibid.*, **5**, 126 (1940).

(15) G. M. Whitesides and C. P. Casey, *J. Am. Chem. Soc.*, **88**, 4541 (1966).

(16) G. Köbrich, H. Frölich, and W. Drischel, *J. Organometal. Chem. (Amsterdam)*, **6**, 194 (1966).

(17) H. C. Brown and C. H. Snyder, *J. Am. Chem. Soc.*, **83**, 1002 (1961).

(18) Experiments in progress have shown that bis- π -allylnickel(0) is unreactive toward bromobenzene and less reactive toward cyclohexyl iodide than is π -allylnickel(I) bromide (unpublished work with L. S. Hegedus and H. A. Kirst). Consequently, 8 is considered a more likely intermediate than analogs which are derived from reaction of nickel(0) complexes with RX.



L = e.g., DMF

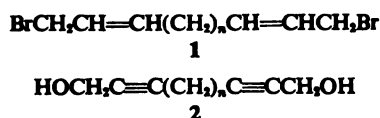
behavior of allylic halides toward π -allylnickel(I) complexes, which contrasts sharply with that of non-allylic halides such as those appearing in Table I, is detailed in due course.¹⁹

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Synthesis of Large-Ring 1,5-Dienes by Cyclization of Allylic Dibromides with Nickel Carbonyl

A method for forming cycloolefins from allylic dibromides and nickel carbonyl which has recently been described^{1,2} has now been examined in order to ascertain its scope with a series of dibromides of structure 1. Results which have been obtained suggest that this



cyclization process provides an unusually efficient route to the formation of large rings. In addition, because it is possible to cyclic 1,5-dienes, it makes available a wide variety of cyclic structures which are not obtainable in any other way *via* the acyloin reaction, currently the most commonly used general approach to large rings. Allylic dibromides 1, $n = 2, 4, 6, 8$, and 12, were cyclized in both *cis,cis* and *trans,trans* forms from the corresponding acyclic diols 2, $n = 2, 4, 6, 8$, and 12, by selective cyclization to the corresponding *cis,cis*-³ or *trans,trans*-ethylenic⁴ diols⁵ followed by reaction with phosphorus tribromide.⁶ The required acetylenic diols $n = 4, 6$, and 8, were made by alkylation of a diol, $\text{Br}(\text{CH}_2)_n\text{Br}$, with the sodio derivative of propargyl alcohol tetrahydropyranyl ether⁷ in liquid ammonia-ether⁸ ($n = 4, 6, 8$) or in tetrahydrofuran-

E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, **86**, 1641 (1964).

E. J. Corey and M. F. Semmelhack, *Tetrahedron Letters*, 6237 (1966).

Using Lindlar catalyst; see H. Lindlar and R. Dubuis, *Org. Syn.*, **46**, 1 (1966).

Using lithium aluminum hydride in tetrahydrofuran; see K. R. Ha and B. C. L. Weedon, *J. Chem. Soc.*, 1584 (1953).

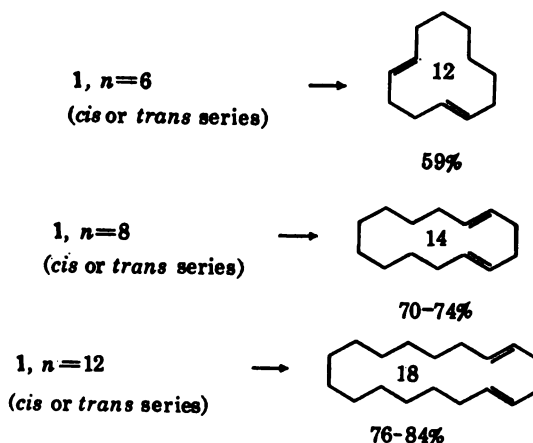
Satisfactory analytical and spectroscopic (infrared and nmr) data have been obtained for the new compounds reported herein. Stereochemical assignments to the *cis,cis*- and *trans,trans*-dibromides and the corresponding diols rest not only on the methods of synthesis (usually shown to be stereospecific) but also on the occurrence of absorption at 10.4 or 10.3 μ for the *trans,trans*-dihalides or at 13.1–13.4 μ for all the *cis,cis*-dibromides.

M. Osbond, *J. Chem. Soc.*, 5270 (1961).

L. G. Jones and M. J. Mann, *J. Am. Chem. Soc.*, **75**, 4048 (1953).

dimethyl sulfoxide ($n = 12$), and the diol 2, $n = 2$, was obtained from 1,5-hexadiyne⁹ and formaldehyde.¹⁰

The cyclization experiments were conducted by slow addition (motor-driven syringe, 12-hr period of addition) of the allylic dibromide (1 mmole) in dimethylformamide (1 ml) to a solution of nickel carbonyl (5 mmoles) in dimethylformamide (ca. 40 ml) under argon at 50°. In the cases of the dibromides 1, $n = 6, 8$, and 12, the same cyclization product was obtained starting with either *cis,cis* or *trans,trans* isomer.



In each of these cases the cyclization product was principally (95–98%) the *trans,trans*-1,5-diene, but small amounts of an isomeric compound, probably the *cis,trans* isomer, could be detected by vapor phase chromatography.¹¹ The major product from 1, $n = 6$, was identified as *trans,trans*-1,5-cyclododecadiene by spectroscopic comparison with the known substance;¹² the infrared spectrum manifested absorption at 10.4 μ due to $\text{CH}=\text{CH}$ (*trans*) and no absorption at ca. 14.2 μ which would be expected for $\text{CH}=\text{CH}$ (*cis*), and hydrogenation afforded cyclododecane, identical with an authentic sample. The principal products from 1, $n = 8$, and 1, $n = 12$, were identified by their infrared spectra (e.g., absorption at 10.4 μ but not at 14.2 μ), mass spectra, nmr spectra, and hydrogenation to cyclotetradecane, mp 54–55°,¹³ and cyclooctadecane, mp 71–72°,¹³ respectively. The predominant course of cyclization with the dibromides 1, $n = 2$, and 1, $n = 4$, was formation of six-membered ring structures by 1–6 and 3–8 coupling, respectively; again the product composition was essentially independent of the geometry of the starting dibromide. With nickel carbonyl, 1, $n = 2$, afforded 4-vinylcyclohexene (42%) and *cis,cis*-1,5-cyclooctadiene (5%); the same products were also obtained using triphenylphosphinenickel tricarbonyl,¹⁴ but the relative amount of 1,5-cyclooctadiene was somewhat greater (ca. 20% of the mixture). In the case of dibromide 1, $n = 4$, with either nickel carbonyl or triphenylphosphinenickel tricarbonyl, only

(8) H. Bader, L. C. Cross, I. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 619 (1949).

(9) R. A. Raphael and F. Sondheimer, *ibid.*, 120 (1950).

(10) F. Sondheimer, *J. Am. Chem. Soc.*, **74**, 4040 (1952).

(11) Using a column packed with Carbowax 20M (10%) on Chromosorb P at 200°.

(12) Reference spectra were furnished by Dr. Masaji Ohno, Toyo Rayon Co., Kamakura, Japan.

(13) L. Ruzicka, M. Stoll, M. W. Huyser, and H. A. Bockenoogen, *Helv. Chim. Acta*, **13**, 1152 (1930).

(14) See ref 2 for an example of ligand control of product using this reagent.

cis- and *trans*-1,2-divinylcyclohexane¹⁵ were observed, with the former reagent giving a preponderance of the *cis* isomer and the latter favoring the *trans* isomer with a ratio of *ca.* 1:2; no 1,5-cyclodecadiene^{15,16} could be detected spectroscopically or by vpc.

Although it has not yet been shown experimentally that the cyclization of allylic dibromides by nickel carbonyl can be used for the synthesis of ring sizes larger than 18, the efficiency of cyclization in the 18-membered case strongly suggests that it can.¹⁷ The formation of essentially the same cyclization product from *cis-trans* isomeric dibromides is not surprising in view of earlier findings and similar results in intermolecular coupling reactions,¹⁸ and it can be explained simply by allylic isomerization either because of allylic halogen-nickel exchange¹⁸ or allylic rearrangement within the organonickel complexes *via* σ -allylnickel structures.¹⁹

The fact that the cyclization of 1, *n* = 2 and 4, leads mainly to six-membered ring structures indicates that the formation of this ring size relative to the alternative eight- and ten-membered structures is sufficiently favorable to overcome the marked preference for the joining of primary over secondary over tertiary carbons in allylic coupling.^{18,20,21}

It is noteworthy that the efficiency of cyclization of the substrates 1, *n* = 2, 4, 6, 8, and 12, is strongly dependent on the solvent which is used; solvents such as dimethylformamide and *N*-methylpyrrolidone are much superior to, *e.g.*, tetrahydrofuran or glyme solvents. A discussion of these effects and detailed considerations of the mechanism of the cyclization process will be presented in due course.

It is apparent that the cyclization discussed herein is a very useful synthetic method. In principle it is applicable, for example, to a synthesis of elemol,²² β -maaliene,²³ or cembrene.²⁴ A total synthesis of humulene has already been accomplished using this method.^{25,26}

(15) Authentic samples of *cis*-1,2-divinylcyclohexane and *cis,trans*-1,5-cyclodecadiene were kindly provided by Dr. P. Heimbach, Max-Planck Institut, Mülheim, Germany; see P. Heimbach, *Angew. Chem. Intern. Ed. Engl.*, **3**, 702 (1964); **5**, 595 (1966).

(16) It was shown by a control experiment that *cis,trans*-1,5-cyclodecadiene was recovered unchanged after being subjected to cyclization conditions.

(17) A study of the cyclization of 1,40-dibromo-2,38-tetracontadiene which could give a 40-membered ring is now under way. The yields given for the cyclization of 1, *n* = 6, 8, 12, are probably not optimal, since only one set of reaction conditions was tried.

(18) E. J. Corey and M. F. Semmelhack, to be published.

(19) The intervention of allylnickel(I) bromide complexes in these cyclizations is clear from the development of the deep red color characteristic of such complexes during reaction. This color develops rapidly as the addition of dibromide to nickel carbonyl is started, and at the end of the addition it fades and gives way to the characteristic green color of nickel(II) bromide in dimethylformamide solution.

(20) I. D. Webb and G. T. Borchardt, *J. Am. Chem. Soc.*, **73**, 2654 (1951).

(21) E. J. Corey and M. F. Semmelhack, *ibid.*, **89**, 2755 (1967).

(22) V. Sykora, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, **20**, 220 (1955).

(23) V. Herout, *et al.*, Abstracts, IUPAC Congress on Natural Products, Stockholm, Sweden, 1966, p 57.

(24) W. G. Dauben, W. E. Thiessen, and P. R. Resnick, *J. Am. Chem. Soc.*, **84**, 2015 (1962).

(25) E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967).

(26) This work was generously supported by the National Institutes of Health (fellowships to E. Wat) and the National Science Foundation.

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Total Synthesis of Humulene

Sir:

We describe herein a total synthesis of humulene, 7 (2,6,6,9-tetramethyl-*trans,trans,trans*-cycloundeca-1,4,8-triene),¹⁻⁴ a fundamental monocyclic triisoprenoid structure which is a likely precursor of a number of other naturally occurring sesquiterpenes.⁵ The key step in the synthesis is formation of the 11-membered ring by cyclization of a 1,11-dibromo-2,5,9-undecatriene derivative using nickel carbonyl.⁶

One important intermediate in the synthesis is the phosphonium ylide 1 which was obtained starting with dimethyl *trans*-3-methylglutaconate⁷ by a sequence involving (1) reduction to the corresponding diol (2, U = V = OH) using lithium aluminum hydride-aluminum chloride (3:1)⁸ in ether; (2) conversion to the dibromide 2, U = V = Br,⁹ then selective displacement of the allylic bromine with trimethylbenzylammonium dichloroacetate in acetone to give 2, U = Br, V = OCOCHCl₂; (3) basic hydrolysis to the bromohydrin 2, U = Br, V = OH; (4) acid-catalyzed addition to dihydropyran to form 2, U = Br, V = OTHP (THP = 2-tetrahydropyranyl ether), and (5) reaction with triphenylphosphine in acetonitrile at 80° for 24 hr to form the phosphonium (bromide), U = P⁺(C₆H₅)₃, V = OTHP.

A second key intermediate is the aldehyde 3, the synthesis of which proceeded from 1-chloro-2-methyl-4-acetoxy-2-butene,¹⁰ 4, W = Cl, X = OAc, as follows: (1) displacement of chloride from 4, W = Cl, X = OAc, by trimethylbenzylammonium mesitoate in ethanol at 80° for 24 hr to form 4, W = mesitoxyloxy, X = OAc; (2) selective alkaline hydrolysis to 4, W = mesitoxyloxy, X = OH; and (3) reaction with phosphorus tribromide¹¹ in ether to give 4, W = mesitoxyloxy, X = Br, which was used to alkylate the magnesium derivative formed from *N*-(2-methylpropylidene)cyclohexylamine^{12,13} to afford an imine which yielded 3 by hydrolysis with aqueous oxalic acid at 25° for 4 hr.

Wittig condensation of the ylide 1 with the aldehyde 3 in dimethyl sulfoxide¹⁴ afforded the triene 5, Y =

(1) S. Dev, *Tetrahedron*, **9**, 1 (1960).

(2) M. D. Sutherland and O. J. Waters, *Australian J. Chem.*, **14**, 596 (1961).

(3) A. T. McPhail, R. I. Reed, and G. A. Sim, *Chem. Ind. (London)*, 976 (1964).

(4) J. A. Hartsuck and I. C. Paul, *ibid.*, 977 (1964).

(5) For example: (a) caryophyllene: E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **86**, 485 (1964), and references therein cited; (b) zarumbone: S. Dev, *Tetrahedron*, **8**, 171 (1960); (c) humulene mono- and dioxide: S. K. Ramaswami and S. C. Bhattacharyya, *ibid.*, **18**, 575 (1962); (d) humulenol: N. P. Damodaren and S. Dev, *Tetrahedron Letters*, 1941 (1963).

(6) See (a) E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, **86**, 1641 (1964); (b) E. J. Corey and M. F. Semmelhack, *Tetrahedron Letters*, 6237 (1966); (c) E. J. Corey and E. K. W. Wat, *J. Am. Chem. Soc.*, **89**, 2757 (1967).

(7) Obtained from a commercially available mixture of *trans* and *cis* isomers (ratio 45:55) by fractional distillation; any *cis* isomer remaining as an impurity in this starting material could easily be removed in the transformation to 2. U = Br, V = OH.

(8) M. J. Jorgenson, *Tetrahedron Letters*, 559 (1962).

(9) Procedure of I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 843 (1958).

(10) W. Oroshnik and R. Mallory, *J. Am. Chem. Soc.*, **72**, 4608 (1950).

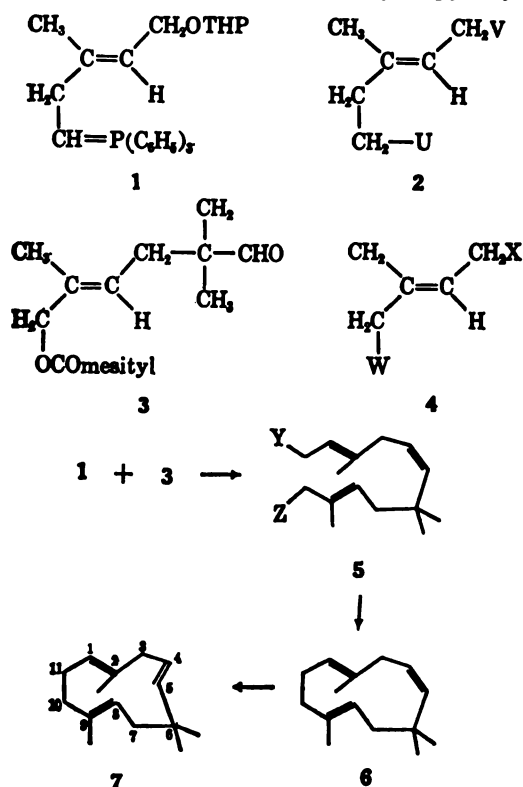
(11) J. M. Osbond, *J. Chem. Soc.*, 5270 (1961).

(12) G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2179 (1963).

(13) G. Wittig, H. D. Frommelt, and P. Suchanek, *Angew. Chem. Intern. Ed. Engl.*, **2**, 693 (1963).

(14) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

Z = mesityloxy, with the central (5,6) double *cis*.¹⁸ The mesityl and tetrahydropyranyl pro-



groups were removed by sequential treatment with aluminum hydride in ether (25°, 1 hr) and acidic methanol at 25° to give the diol 5, Y = OH, which was converted by phosphorus tri-
 de¹¹ to the dibromide 5, Y = Z = Br.

4,5-*cis* isomer of humulene (6) was formed as the product when a solution of the dibromide 5, Z = Br, in N-methylpyrrolidone was added (automatic syringe drive) to 4 mole equiv of carbonyl in the same solvent at 50° under argon with three other volatile products (0.7, 0.5, 4 parts per part of 6). Irradiation of the crude reaction product (>350 mμ) and diphenyl disulfide¹⁶ in hexane at 25° for 2.5 hr caused isomerization of humulene (7) which was obtained from the mixture extraction with 50% aqueous silver nitrate.¹⁸ Isolation of pure humulene from the only contaminant readily accomplished by preparative vapor phase chromatography (fluorosilicone column, 150°). The synthetic product behaved exactly as did natural humulene¹⁹ upon vpc analysis with fluorosilicone, diethylene glycol succinate, and Carbowax 20M columns

The *cis* geometry for the 5,6-double bond in 5 is indicated by the observation of the absorption characteristic of *trans*-CH=CH- at 10.3 μ by the ready photoisomerization using diphenyl disulfide¹⁶ to which 5 did exhibit infrared absorption at 10.3 μ, and finally by observation that the model reaction of pivalaldehyde with *n*-oct-5-en-2-yl and β-phenylethylidene triphenylphosphorane in dimethyl ether afforded olefinic product of >98% *cis* content.¹⁷ The subsequent transformations also allow the *cis* assignment.

J. Moussebois and J. Dale, *J. Chem. Soc.*, 260 (1966).
 J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, 88, 166 (1966).

P. Hildebrand and M. D. Sutherland, *Australian J. Chem.*, 14, 1, have described an efficient purification of naturally occurring humulene by this technique. In the present case the extraction removes humulene and any unisomerized 4,5-*cis*-humulene (6) from the

We are indebted to Drs. F. Sorm, S. Dev, and M. D. Sutherland for the analysis of natural humulene for comparison.

(which cleanly resolve a large number of sesquiterpenes). Identity was further established by the correspondence of infrared, nuclear magnetic resonance, and mass spectra.²⁰

(20) This work was supported by a grant from the National Science Foundation.

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Structures of Two Compounds Containing Strong Metal-to-Metal Bonds

Sir:

It has been established that the $\text{Re}_2\text{Cl}_8^{2-}$ and $\text{Re}_2\text{Br}_8^{2-}$ ions have an eclipsed structure¹ with a quadruple bond between the metal atoms.² It has been shown that ligand substitution reactions of various kinds proceed readily with these ions.³ In particular, a compound of empirical formula $\text{Re}_2\text{Cl}_8\text{P}(\text{C}_6\text{H}_5)_4$ was obtained^{3a} by treating $\text{Re}_2\text{Cl}_8^{2-}$ with $\text{P}(\text{C}_6\text{H}_5)_3$. Unfortunately this compound, which was shown^{3a} not to be of the $\text{Re}_2\text{Cl}_8\text{L}_2$ type obtained⁴ from Re_2Cl_8 , was too insoluble to permit positive structural characterization. It was postulated, however, that it is the dinuclear, 1,2-disubstituted derivative, $(\text{C}_6\text{H}_5)_4\text{PReCl}_2\text{ReCl}_2\text{P}(\text{C}_6\text{H}_5)_4$. In order to obtain direct evidence on this, and particularly to see if such a compound retains the short Re-Re bond and the eclipsed configuration which is a consequence² of the δ component of the quadruple bond, a soluble, crystallizable analog was sought. The $\text{P}(\text{C}_6\text{H}_5)_3$ analog proved satisfactory; its structure has been determined by single-crystal X-ray methods and is described here.

$\text{Re}_2\text{Cl}_8[\text{P}(\text{C}_6\text{H}_5)_3]_2$ crystallizes in the space group $\text{P2}_1/\text{n}$ with unit cell dimensions $a = 7.644 \pm 0.003$, $b = 10.985 \pm 0.005$, $c = 14.206 \pm 0.006$ Å; $\beta = 96.5 \pm 0.1^\circ$; $Z = 2$. Intensities were recorded using a counter diffractometer and Cu Kα radiation (Ni filtered) within a sphere limited by $\theta = 55^\circ$. The structure was solved by conventional Patterson and Fourier syntheses and has been refined to an R value⁵ of 0.066 neglecting statistically unreliable reflections.

The molecule, shown in Figure 1, lies on a crystallographic inversion center and possesses the expected eclipsed configuration. Important bond lengths and angles are: Re-Re, 2.222 ± 0.003 Å; Re-Cl, 2.35 ± 0.01 Å; Re-Cl₂ and Re-Cl₃, 2.30 ± 0.01 Å; Re-P, 2.46 ± 0.01 Å; Re-Re-Cl, $116.3 \pm 0.2^\circ$; Re-Re-Cl₂, $104.0 \pm 0.2^\circ$; Re-Re-Cl₃, $103.0 \pm 0.2^\circ$; Re-Re-P, $97.4 \pm 0.2^\circ$. While the significant difference in Re-Cl distances may be explained in terms of the *trans* effect, there is no immediately apparent reason for the observed angular distortions.

This is the first substitution product (not involving oxidation or reduction) of an $\text{Re}_2\text{X}_8^{2-}$ ion which has

- (1) (a) F. A. Cotton and C. B. Harris, *Inorg. Chem.*, 4, 330 (1965); (b) V. G. Kuznetsov and P. A. Koz'min, *Zh. Strukt. Khim.*, 4, 55 (1963); (c) V. G. Koz'min, V. G. Kuznetsov, and Z. V. Popova, *ibid.*, 6, 651 (1965); (d) W. R. Robinson, Thesis, MIT, 1966.
- (2) F. A. Cotton, *Inorg. Chem.*, 4, 334 (1965).
- (3) (a) F. A. Cotton, N. F. Curtis, and W. R. Robinson, *ibid.*, 4, 1696 (1965); (b) F. A. Cotton, N. F. Curtis, B. F. G. Johnson, and W. R. Robinson, *ibid.*, 4, 326 (1965); (c) F. A. Cotton, C. Oldham, and W. R. Robinson, *ibid.*, 5, 1798 (1966).
- (4) F. A. Cotton, S. J. Lippard, and J. T. Mague, *ibid.*, 4, 508 (1965).
- (5) Defined as $\sum ||F_o| - |F_c|| / \sum |F_o|$.

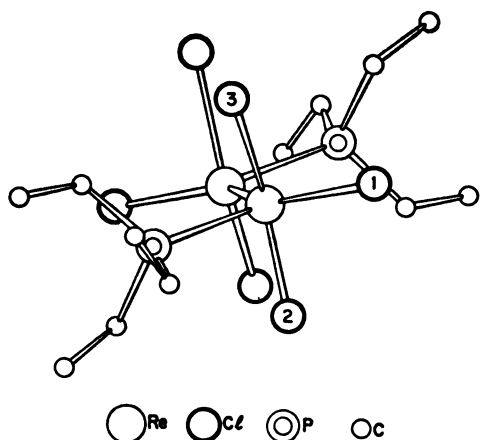


Figure 1. The structure of $\text{Re}_2\text{Cl}_4[\text{P}(\text{C}_2\text{H}_5)_3]_2$.

been structurally characterized in a direct and definitive way. It shows that such substitutions can indeed be carried out with preservation of the Re-to-Re quadruple bond with its attendant structural consequences. This result is to be compared with the extensive structural changes (see below) which are sometimes found when $\text{Re}_2\text{X}_8^{2-}$ species are subjected to redox reactions.

It has recently been reported that a crystalline form of rhenium(IV) chloride exists, from which many chemical reactions produce the $\text{Re}_2\text{Cl}_8^{2-}$ ion or derivatives thereof.⁶ These observations would suggest that the rhenium(IV) chloride contains dinuclear structural units, and one interesting possibility is that such a unit might have a structure similar to that of $\text{Re}_2\text{Cl}_8^{2-}$ except that the rotational configuration would be staggered and the Re-Re bond longer because of the absence of a δ bond, as in the recently reported⁷ structure of $\text{Re}_2\text{Cl}_4(\text{CH}_3\text{SCH}_2\text{CH}_2\text{SCH}_3)_2$. A single-crystal X-ray study of the structure of the rhenium(IV) chloride has been undertaken. Though dinuclear units are present, they are of an entirely different structure, being of the $\text{W}_2\text{Cl}_8^{2-}$ type, strung together in infinite chains *via* bridging by one of each set of terminal Cl atoms. Thus, conversion of rhenium(IV) chloride to $\text{Re}_2\text{Cl}_8^{2-}$ and its derivatives takes place with very extensive rearrangement, *but* the Re-Re unit remains intact.

Rhenium(IV) chloride forms monoclinic crystals belonging to one of the space groups Pc or P2/c. Unit cell dimensions are $a = 6.366 \pm 0.005$, $b = 6.282 \pm 0.006$, $c = 12.165 \pm 0.006$ Å; $\beta = 93.17 \pm 0.10^\circ$. Three-dimensional data were collected using nickel-filtered Cu K α radiation on a GE XRD-5 diffractometer, within the sphere limited by $2\theta \leq 101^\circ$. The 425 significant reflections were corrected for Lorentz-polarization effects and absorption. Conventional Patterson and Fourier techniques revealed the structure shown in Figure 2.

Refinement of this structure has been hampered by several severe and seemingly inescapable difficulties, although there is no reason to doubt that, qualitatively, this structure is correct. As reported⁶ before, the ReCl_4 crystals are only metastable and the preparation of them has not been successfully duplicated. The available crystals are relatively large (giving transmission factors for Cu K α radiation ranging from 0.027

(6) F. A. Cotton, W. R. Robinson, and R. A. Walton, *Inorg. Chem.*, **6**, 223 (1967).

(7) M. J. Bennett, F. A. Cotton, and R. A. Walton, *J. Am. Chem. Soc.*, **88**, 3866 (1966).

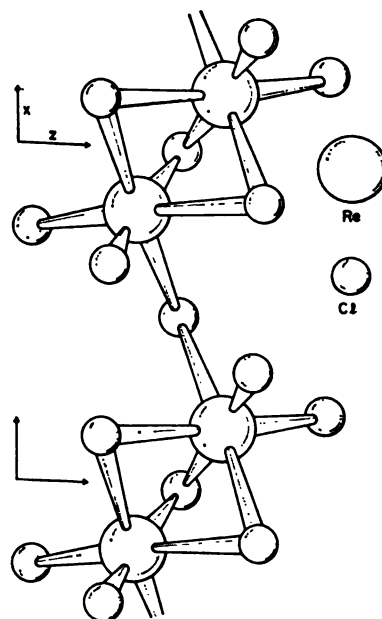


Figure 2. A portion of the ReCl_4 structure projected down the b axis.

to 0.160) and irregularly shaped so that absorption corrections could not be accurately applied. Attempts to reduce the size or improve the shape of the crystals using either solvents or mechanical grinding failed because of their chemical instability and brittleness. There is also evidence in Laué photographs for disorder. Difference Fourier maps have contained too much noise ($\sim 2e/\text{\AA}^3$) to allow an unambiguous test of the several disorder models which have been postulated. Two independent sets of data on different crystals have been used, each refining (full-matrix, least-squares, P2/c) to $R \sim 18\%$. Use of the average of the two sets leads to $R = 17\%$. Use of space group Pc makes no significant difference in the course of the refinement. It is possible that by recollecting the data using Mo K α radiation, absorption errors might be minimized enough to permit clarification of the disorder.

The Re-Re distance presently available is 2.73 ± 0.03 Å, which indicates metal-metal bonding. This distance and in fact the entire structure is in marked contrast to that of TcCl_4 . The latter⁸ also contains polymeric chains of MX_4 octahedra, but joined on edges with Tc-Tc distances of 3.62 Å. Moreover, the Tc atoms are actually displaced away from each other, a good sign⁹ that there is no metal-metal bonding. Thus for the four-valent group VII metals, the tendency to form metal-metal bonds becomes dominant only with the third-row metals. However, even a slight lowering of the oxidation state causes Tc as well as Re to form such bonds, as in the $\text{Tc}_2\text{Cl}_8^{2-}$ ion.^{10,11}

(8) M. Elder and B. R. Penfold, *Inorg. Chem.*, **5**, 1197 (1966).

(9) F. A. Cotton, *Rev. Pure Appl. Chem.*, in press.

(10) F. A. Cotton and W. K. Bratton, *J. Am. Chem. Soc.*, **87**, 921 (1965).

(11) These studies were supported, in part, by Contract No. AT(30-1)-1965 with the U. S. Atomic Energy Commission.

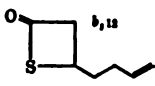
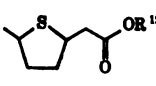
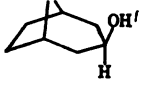
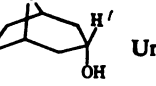
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ysis of γ -Keto Sulfides

ultraviolet spectra of β -keto sulfides,¹⁻³ the cyclic sulfide thiacyclohexan-4-one¹⁻³ (1), and the δ -keto sulfide thiacyclooctan-5-one^{4,5} show evidence for charge transfer in the excited state as well as perturbation of the n, π^* state of the carbonyl group.

Yields of Products from Photolysis of 4

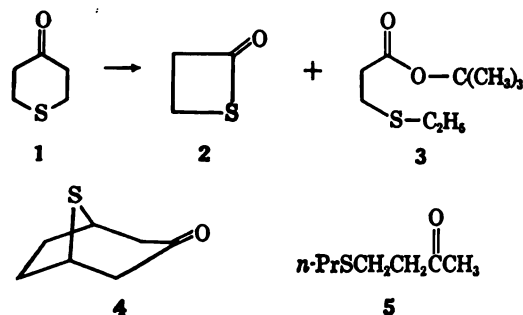
Solvent	Time, hr	Concn, % (g/ml)					Unreacted 4
butyl alcohol	39	0.20	49 (84)	(0)	(6)	(1)	6 (9)
butyl alcohol	95	1.20	43 (67)	0.5 (3) ^c	15	2	36 (33)
ethanol	62.3	0.20	(2)	(4) ^{d,e}	(42)	(6)	(45)
cyclohexane	74	0.20	(0)		15	4	70
Freon-113	15.3	0.40	32			0	50

e numbers not in parentheses are isolated yields determined by column chromatography on 80-100 mesh silicic acid followed by distillation or sublimation; the yields in parentheses are determined by gas chromatography as described in ref 9. ^b $\nu_{\text{max}}^{\text{CHCl}_3}$ 1782 (s), 1637 (w),

n), 910 (m) cm^{-1} ; nmr (CCl_4): δ 1.7-2.6 (multiplet, 4 H, $-\text{CH}_2\text{CH}_2-$), 3.2-4.4 (multiplet, 3 H, $-\text{CH}-\text{CH}_2-\text{CO}-\text{S}-$), 4.8-5.2 (multiplet, $=\text{CH}_2$), 5.4-6.3 (multiplet, 1 H, $-\text{CH}=\text{CH}-$). ^c R = $\text{C}(\text{CH}_3)_3$. ^d R = CH_3 . ^e Structure not established; structure based on retention time by gas chromatography. ^f R. E. Ireland and N. H. Smith, *Chem. Ind. (London)*, 1252 (1959).

have undertaken a study of the photochemistry of these systems and related systems to investigate possible applications of these reactions. This communication reports the results of our initial studies with γ -keto sulfides.

Photolysis⁶ of 1^{7,8} as a 0.21% (w/v) solution in *t*-butyl alcohol for 26.4 hr yielded 46.5%⁹ β -thiolactone 2, 49% ester 3,^{12,13} and 5%⁹ unreacted 1. Photolysis of 1⁸ as a 0.29% solution in Freon-113 for 48.2



duced 2 in 51% yield.⁹

1. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949).
2. Bergson and A.-L. Delin, *Arkiv Kemi*, **18**, 489 (1961).
3. Bergson, G. Claesson, and L. Schotte, *Acta Chem. Scand.*, **16**, 1962.
4. N. J. Leonard, T. L. Brown, and T. W. Milligan, *J. Am. Chem. Soc.*, **81**, 504 (1959).
5. N. J. Leonard, T. W. Milligan, and T. L. Brown, *ibid.*, **82**, 4075 (1960).

Hanovia Type L 450-w lamp with Pyrex filter. $\lambda_{\text{max}}^{\text{Freon-113}}$ 230 m μ (ϵ 640), 291 m μ (ϵ 21); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 237 m μ (ϵ 435), 287 m μ (ϵ 21).

C. Barkenbuss, V. C. Midkiff, and R. M. Newman, *J. Org. Chem.*, **26**, 1951.

Not isolated yield; the mixture was analyzed by gas chromatography on a 6-ft column of 10% Carbowax on Chromosorb P at 110°. Samples were collected on a 2.5-ft column at 110° for spectral analysis or comparison with an authentic sample.

British Patent 840,658 (1960); *Chem. Abstr.*, **55**, 1452 (1961). $\nu_{\text{max}}^{\text{CHCl}_3}$ 1776 cm^{-1} ; nmr (CCl_4): δ 3.05 and 4.02 ppm, triplets, 1.5 cps.

Satisfactory analyses have been obtained for all new compounds reported.

The isolated yield of 3 was 36%; isolated by column chromatography on 80-100 mesh silicic acid followed by distillation.

Similar studies of the photolysis⁶ of 8-thiabicyclo-[3.2.1]octan-3-one^{14,15} (4) in a variety of solvents yielded the products indicated in Table I.

The ultraviolet spectrum of the acyclic γ -keto sulfide 5 shows no charge-transfer band.^{16,17} Photolysis of 5 in Freon-113 with a Pyrex, Corex, or Vycor filter yields only polymeric material; photolysis in *t*-butyl alcohol yields predominately polymeric material plus

at least six other products, formed in a total yield of less than 5%.

Since the charge-transfer bands for 1 and 4 extend beyond 280 m μ and overlap with the n, π^* band, our results do not enable us to conclude whether charge transfer or n, π^* excitation is responsible for the observed products.¹⁸

(14) $\lambda_{\text{max}}^{\text{Freon-113}}$ 232 m μ (ϵ 570), 294 m μ (ϵ 20); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 238 m μ (ϵ 399), 287 m μ (ϵ 21).

(15) V. Horak, J. Zavada, and A. Pishala, *Acta Chim. Hung.*, **21**, 97 (1959).

(16) $\lambda_{\text{max}}^{\text{Freon-113}}$ 283 m μ (ϵ 28); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 280 m μ (ϵ 34).

(17) Similar results are reported for other acyclic γ -keto sulfides; see ref 1-3.

(18) This research has been supported by National Science Foundation Grant No. GP-5761.

(19) Alfred P. Sloan Fellow, 1963-1967.

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Photochemistry of Isothiochroman-4-one

Sir:

We wish to report an interesting photochemical rearrangement of the isothiochroman-4-one system.

Photolysis¹ of 1^{2,3} in cyclohexane (0.20% w/v) for 6-7 hr produced in 20% yield a liquid isomer identified as thiochroman-3-one (3) by analysis,⁴ spectral data,⁵ and the synthesis of an authentic sample by Dieckmann cyclization of 4 followed by acid hydrolysis and decar-

(1) Hanovia Type L 450-w lamp with Pyrex filter.

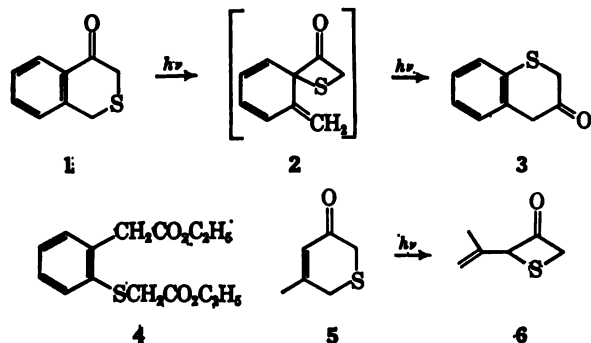
(2) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Am. Chem. Soc.*, **85**, 2278 (1963); J. von Braun and K. Weissbach, *Ber.*, **62**, 2416 (1929); P. Cagniant and D. Cagniant, *Bull. Soc. Chim. France*, 2225 (1961).

(3) $\lambda_{\text{max}}^{\text{isoctane}}$ 244.5 m μ (ϵ 10,400), 289 (1540), 348 (149).

(4) Satisfactory analyses have been obtained on all new compounds reported.

(5) $\nu_{\text{max}}^{\text{CCl}_4}$ 1723, 1468, 1443, 1385, 1253, 1236, 951, 500, 440 cm^{-1} ; $\lambda_{\text{max}}^{\text{isoctane}}$ 254 m μ (ϵ 6900), 357 (150); nmr: δ 3.15 (2 H, singlet, $-\text{SCH}_2-\text{CO}-$), 3.55 (2 H, singlet, $\text{ArCH}_2\text{CO}-$), 6.9-7.8 (4 H, multiplet, ArH).

boxylation. Photolysis of 1 under similar conditions in a Rayonet reactor, 3500-A source,⁶ resulted in very slow decomposition to polymeric material, indicating excitation of only the long-wavelength band is not sufficient for the reaction.



We believe that the initial photoproduct is the triene 2 which undergoes a further photochemically induced rearrangement to 3. In an effort to obtain evidence for the intermediacy of 2 in the reaction, 5^{4,7} was irradiated under similar conditions in the hope of isolating 6, which should not undergo further photochemical rearrangement if excitation of the triene system is responsible for further photochemical rearrangement of 2. Photolysis¹ of 5 in cyclohexane produced 6⁸ in 30% yield. This observation and the appearance of an absorption band at 1770 cm⁻¹ in the infrared spectrum of a solution of 1 in cyclohexane which had been photolyzed for a short period of time suggest that 2 is a reasonable intermediate in the formation of 3.

8-Methyl-, 7-methoxy-, 3-methyl-, and 3,3-dimethylisothiochroman-4-one also undergo this photochemical rearrangement in yields varying from 20 to 40%.⁹

(6) The Southern New England Ultraviolet Co., Middletown, Conn.

(7) λ_{max} 231.5 m μ (ϵ 9340), 270 (302), 347 (97.8).

(8) $\nu_{\text{max}}^{\text{C=O}}$ 1780, 1641, 1448, 1397, 1374, 1168, 1127, 910 cm⁻¹; $\lambda_{\text{max}}^{\text{C=O}}$ 245 m μ (ϵ 912), 330 (166); nmr: δ 4.1 (2 H, broad singlet, -SCH₂C(=)-), 1.85 (3 H, broad singlet, CH₃-), 5.0, 5.1, 5.25 (3 H, broad singlets, CH₂=C- and >CCH(S-CO)-).

(9) This research has been supported by National Science Foundation Grant No. GP-5761.

(10) Alfred P. Sloan Fellow, 1963-1967.

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Inhibited Pseudo-Rotation in a Cyclic Monoalkylphosphorane¹

Sir:

Methyl ethylene phosphate undergoes hydrolysis, both to open the ring and to lose the methoxyl group, at a rate about a million times as great as that for trimethyl phosphate.² The driving force for the rapid reactions is presumably ring strain.³ However, to explain the unexpected rapid hydrolysis of the ester group external to the ring in methyl ethylene phosphate and various other cyclic compounds^{3,4-8} we recently

(1) This research was supported by the National Science Foundation under Grant GP-2098.

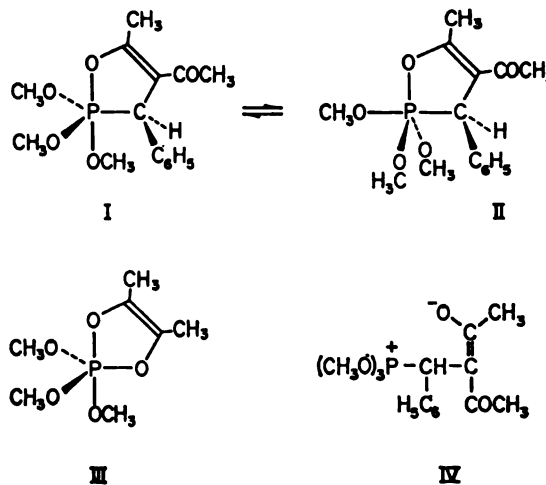
(2) F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 1773 (1963).

(3) E. T. Kaiser, M. Panar, and F. H. Westheimer, *ibid.*, **85**, 602 (1963); D. A. Usher, E. A. Dennis, and F. H. Westheimer, *ibid.*, **87**, 2320 (1965).

(4) P. C. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961).

postulated⁷ that the hydrolysis of phosphate esters may, and in some cases must, proceed with pseudo-rotation^{8,9} of trigonal-bipyramidal intermediates. In contrast to methyl ethylene phosphate, the methyl ester of the five-membered cyclic phosphinic acid hydrolyzes at a rate comparable to that of the ester of diethylphosphinic acid.^{6,10} This fact can be explained by postulating that, in analogy with the known chemistry of the alkylfluorophosphoranes,¹¹ oxygen atoms preferentially occupy the apical, and alkyl groups the equatorial positions in the trigonal-bipyramidal intermediates formed during hydrolysis. Under these assumptions, the hydrolysis of the ester of the cyclic phosphinic acid is slow, despite the presumed strain in the ring, because, in order to form a trigonal-bipyramidal intermediate, an alkyl group must be forced into an unfavorable axial position, or else the ring angle must be expanded to 120°. Both kinetic^{4,7} and X-ray crystallographic¹² evidence as well as theory⁸ argue against this latter choice. The chemistry of phosphonates⁷ can also be rationalized on the assumption of preferential placement of alkyl groups in equatorial positions in trigonal-bipyramidal intermediates in hydrolysis. Ramirez and his co-workers¹³ have prepared many cyclic phosphoranes, including¹⁴ I, where an alkyl group is part of a five-membered ring system. According to our postulates,⁷ this compound should exist preferentially in a structure where the alkyl group is equatorial, and where therefore the methoxyl groups occupy different positions. However, the nmr spectrum of I, determined at room temperature,¹⁴ shows only one kind of methoxyl group.

We now report that, at low temperatures, the nmr spectrum of I corresponds to that expected for the structure as shown. At room temperature, the three



(5) M. G. Newton, J. R. Cox, Jr., and J. A. Bertrand, *ibid.*, **88**, 1503 (1966).

(6) E. A. Dennis and F. H. Westheimer, *ibid.*, **88**, 3431 (1966).

(7) E. A. Dennis and F. H. Westheimer, *ibid.*, **88**, 3432 (1966).

(8) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).

(9) D. Hellwinkel, *Ber.*, **99**, 3628, 3660 (1966), has demonstrated similar pseudo-rotations for pentaarylphosphoranes by stereochemical studies.

(10) G. Aksnes and K. Bergesen, *Acta Chim. Scand.*, **20**, 2508 (1966).

(11) E. Muetterties and R. A. Schonm, *Quart. Rev. (London)*, **20**, 245 (1966); R. Schmutzler, *Angew. Chem. Intern. Ed. Engl.*, **4**, 496 (1965).

(12) W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *J. Am. Chem. Soc.*, **87**, 127 (1965).

(13) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964).

(14) F. Ramirez, O. P. Madan, and S. R. Heller, *J. Am. Chem. Soc.*, **87**, 731 (1965).

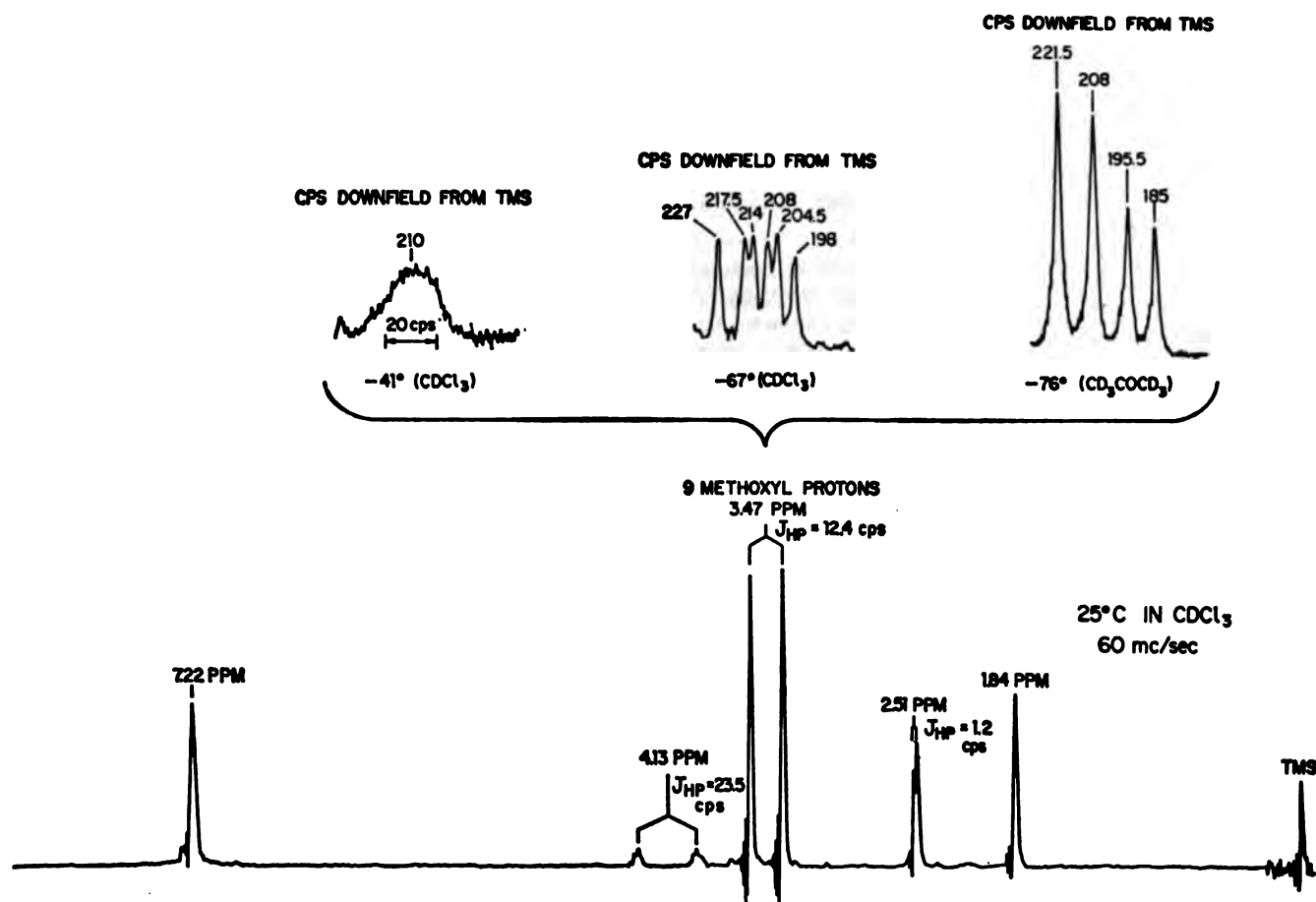


Figure 1. The proton nmr spectrum, at 60 Mc, for I at 25, -41° , and -67° in deuteriochloroform, and -76° in deuterioacetone.

methoxyl groups appear as a doublet; the signal is split by ^{31}P with $J = 12.5$ cps. In either deuteriochloroform or in deuterioacetone, the doublet observed at room temperature collapses, at about -40° , to a broad band, and at -65° this band is again resolved (Figure 1). In deuterioacetone, the nmr spectrum of the methoxyl groups shows two separate doublets, with $J = 13.5$ and 10.5 ppm and with integrated intensities of 1:2, corresponding to one apical and two equatorial methoxyl groups, whereas in deuteriochloroform the spectrum shows three partially separated doublets, two with $J = 13$ and one with $J = 10$ cps. These again correspond to one apical and two equatorial methoxyl groups. Since the two equatorial methoxyl groups in I differ in their relationship to the phenyl ring, it is the acetone spectrum, rather than that in chloroform, that is somewhat unexpected. In contrast to I, the pentaoxyphosphorane III shows only one kind of methoxyl groups (a sharp doublet, $J = 13$ cps) all the way down to -100° . For III, pseudo-rotation necessarily generates unstrained structures with apical oxygen atoms; the equivalence of positions in this compound resembles that^{8,11} of PF_5 .

The low-temperature nmr spectra in Figure 1 show that I is stable with equatorial alkyl group. The constancy of the average chemical shift for the methoxyl groups and of the coupling constants shows that, at high temperature, exchange occurs among equivalent structures. Pseudo-rotation about an equatorial methoxyl group as pivot will convert I to II; two methoxyl groups of II are equivalent, and the pseudo-rotation from II to I can utilize a different

methoxyl group as pivot than that for its formation. Further pseudo-rotations can complete the exchange process. Although II is energetically unfavorable with respect to I, its formation in minute amount and reversion to I is apparently sufficiently rapid at room temperature to catalyze the exchange of the methoxyl groups; II functions as does the boat form of cyclohexane in the interconversion of equivalent chair forms. An alternative mechanism for exchange of the methoxyl groups allows the opening of the five-membered ring¹⁶ to form IV, followed by mixing of the methoxyl groups by rotation and reclosure of the ring. Even if such a mechanism is operative, it does not in any way affect the conclusion that, at low temperatures, the structure of I is frozen as drawn, that pseudo-rotation is inhibited, and that in derivatives of phosphorane alkyl groups preferentially occupy equatorial and oxygen atoms apical positions. But the explanation involving ion pairs is relatively unlikely. First, the enolate ion in IV must be more stable than the corresponding enolate in an ion pair derived from III; if the formation of ion pairs were the only mechanism for exchange, I should undergo the reaction more readily, rather than less readily, than III. But further, the temperature at which the doublet for I coalesces is about -41° in deuteriochloroform and -37° in deuterioacetone, but about -60° in deuteriotoluene. If the exchange among the methoxyl groups occurred by way of an ion pair, this exchange should prove more facile, rather than less facile, in the more

(15) F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.*, **85**, 3252 (1963).

polar solvents. Further studies of these spectra are in progress.

The experiments were carried out with a Varian A-60 nmr spectrometer, equipped with a Varian Associates V-6031B variable low-temperature probe.

Acknowledgment. We gratefully acknowledge the skilled technical assistance of Mr. Hampar Janjigian in the nmr measurements.

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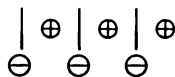
Contact and Solvent-Separated Ion Pairs of Carbanions. III. Reactivities in Proton-Abstraction Reactions

Sir:

It was recently shown¹ that changes in the absorption spectra of solutions of carbanions and radical ions upon varying the solvent composition and temperature could be interpreted in terms of two kinds of ion pairs, *i.e.*, contact and solvent-separated ion pairs. We have now studied the reactivity behavior of these species in proton-abstraction reactions and have made a number of interesting observations.

Alkali salts of the fluorenyl carbanion were allowed to react with 1,2- or 3,4-benzofluorene in dioxane, tetrahydrofuran, or 1,2-dimethoxyethane as solvent. The progress of the reaction was followed spectrophotometrically, and the rate constants were calculated from the initial slopes of the recorder tracings. In a number of instances a flow system was used, but even then some of the reactions were too rapid to obtain accurately the initial slopes. In these cases calculation of the rate constants was based on the half-life of the reaction. Although this will somewhat affect the accuracy of the data, the differences between the observed second-order rate constants for the various systems are large enough to justify a comparison. The results are reported in Table I.

The data for fluorenyllithium show a strong dependence of the rate constants on the carbanion concentration in all three solvents. The same is true of fluorenylsodium in dioxane. This suggests the presence of unreactive aggregates, $[F^-, M^+]_n$, in these solutions, and the kinetic measurements lead to an average aggregation number of 5 or even higher. This strong association, even in solvents like THF and DME, is surprising since no such association was observed for the less charge delocalized polystyryl salts in either THF or dioxane.² It is likely that the association of the fluorenyl salts is favored by the planar structure of the carbanion. This may lead to a sandwich-type aggregate in which many ion pairs are stacked up



An additional attractive force, particularly important for the lithium salts, may result from a tendency of the counterion to complex with the highly polarizable π cloud of the fluorenyl ring.

(1) T. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.*, **87**, 669 (1965); **88**, 307 (1966).

(2) D. N. Bhattacharyya, C. L. Lee, J. Smid, and M. Szwarc, *J. Phys. Chem.*, **69**, 612 (1965).

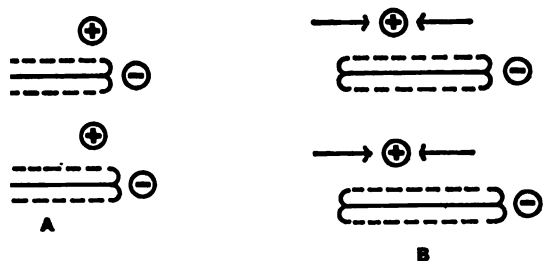
Table I. Observed Rate Constants for the Reaction
Fluorenyl⁻, M⁺ + 1,2- or 3,4-Benzofluorene at 25°

[F ⁻ , M ⁺]			[F ⁻ , M ⁺]		
Solvent	$\times 10^{-4}$, M	k_{obsd} , M ⁻¹ sec ⁻¹	Solvent	$\times 10^{-4}$, M	k_{obsd} , M ⁻¹ sec ⁻¹
F⁻, Li⁺ + 3,4-Benzofluorene					
THF	370	2.86	THF	40	1.6
	140	3.16		4.7	12.3
	61	5.0		4.2	19.9
	26.8	9.2		0.67	51.6
	10.8	29.0		15.0	6.8
	3.3	60.0		4.5	14.4
	1.36	158.0		0.9	103
F⁻, Na⁺ + 1,2-Benzofluorene					
Dioxane	42	183	THF	32	3800
	20	294		1.5	3960
	8.1	660		1.3	3500
	2.8	1660		24	~80,000
	1.2	4200	DME	22	~80,000
				0.92	~50,000
F⁻, Cs⁺ + 1,2-Benzofluorene			F⁻, N⁺Bu₄ + 1,2-Benzofluorene		
Dioxane	46	860	THF	43	800
	11	1300		46	700
	2.8	1560		35	810
THF	42	960	DME	35	930
	43	1080			
	1.9	1570			
			F⁻, Na⁺ + 1,2-Benzofluorene in THF + CH₃O(CH₂CH₂O)_nCH₃		
			40		
			40		
			40		
			650		
			575		

Aggregation persists, at least for the lithium salts, even in THF and DME, where the ion pairs are solvent separated. This suggests that in the solvent-separated ion pair of fluorenyllithium the counterion is not fully surrounded by solvent molecules, since aggregation would then be sterically unfavorable and expected to be less than for the poorly solvated fluorenylcesium. Apparently, the lithium ion assumes a new average position in the solvent-separated ion pair; away from the carbanion but yet still close to the π -electron cloud of the ring system (see Figure 1). Such a position, made possible because of increased association with solvent molecules, would also lead to the observed red shift in the spectrum as compared to the contact ion pair and would at the same time energetically be favorable because of π complexing. Rate measurements with dioxane solutions of fluorenyllithium containing varying quantities of dimethyl sulfoxide again point to strong association of both contact and solvent-separated ion pairs in these systems. This type of association may well be responsible for the large discrepancies observed in the values for proton-transfer rate constants in solutions of fluorenyllithium in dimethyl sulfoxide,³ in which different techniques and different carbanion concentrations were used.

Another interesting observation concerns the role of the counterion in proton-abstraction reactions. At low concentrations (*i.e.*, under conditions where aggregation vanishes), fluorenylsodium is as reactive or even more so in dioxane than in THF, while a strong increase in the rate constant is observed in DME. In the first two solvents the sodium salt is a contact ion pair, while in DME it is essentially solvent separated. Hence, less energy is needed in the latter case to transfer

(3) J. I. Brauman, D. F. McMillen, and Y. Kanazawa, *J. Am. Chem. Soc.*, **89**, 1728 (1967); C. D. Ritchie and R. E. Uschold, *ibid.*, **89**, 1730 (1967).



1. A represents an aggregate of contact ion pairs $(F^-, M^+)_n$ that of solvent-separated ion pairs. The arrow denotes g molecules inducing a shift of the counterion to a new position away from the center of negative charge.

unterior to the new carbanion. For the tetrammonium salt, the reactivity is found to be the in THF as in DME. No solvent-separated ion are observed for this salt in either solvent! How the Coulomb interaction between carbanion and cation is not the only rate-determining factor, since cesium would then be expected to have a higher reactivity than fluorenylsodium in both dioxane and

The reverse is true, which suggests that the cation activates the benzofluorene molecule and rates the proton-abstraction process (see Figure 2) such an activation has been suggested in other reactions involving organometallic reagents.⁴ The effect will rapidly decrease with increasing size of the cation and may be essentially absent for cesium tetrabutylammonium (the association of the lithium prevented us from obtaining the rate constant for lithium ion pair).

It is significant that addition of the strongly dissociable $NaB(C_6H_5)_4$ does not decrease the rate of the reaction but seems to even increase the rate slightly. Presently, the free carbanion is not more, and probably even less, reactive than the contact ion pair. This would also explain the concentration independence of rate constants for the sodium and cesium salts [F] in spite of the increased free ion formation at low concentration.⁵ These results are in agreement with the catalyzing role assigned to the counterion.

In a solvent-separated ion pair, where Coulomb interaction has greatly weakened, would be highly reactive as the counterion can effectively activate the fluorene molecules. This appears to be the case in dimethoxyethane. However, when the solvating agent prevents a close approach between the benzofluorene molecule and the counterion, the solvent-separated ion pair reactivity is expected to be less than that of the contact ion pair and may approach that of the free ion. Such appears to be the case in the system fluorenylsodium-tetrahydrofuran to which small quantities of tetraethylene glycol dimethyl ether were added. In the presence of this powerful solvating agent⁶ the system shows complete solvent-separated ion pair formation, yet the rate of proton abstraction is slower in the absence of this reagent. Its high solvating power arises from the fact that probably all five oxygens are utilized in the solvation of the sodium ion and therefore effectively shield this ion from interaction with the fluorene molecule.

6. A. Morton, "Solid Organoalkalimetal Reagents," Gordon and Breach Science Publishers Inc., New York, N. Y., 1964.

7. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.*, **88**, 318 (1966).

8. L. Chan and J. Smid, to be published.

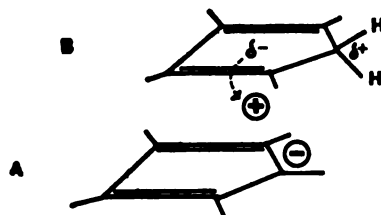


Figure 2. Activating role of the positive ion in proton-abstraction reactions. A and B represent the fluorenyl carbanion and the benzofluorene molecule, respectively.

The behavior of these carbanion salts in proton-abstraction reactions is the more interesting when the results are compared with those of addition reactions involving carbanions. In the anionic polymerization of styrene in THF² the free polystyryl ion was found to be about 800 times more reactive than the sodium contact ion pair, while the solvent-separated ion pair reactivity approaches that of the free ion.⁷ In dioxane the ion pair reactivity increases substantially in the order $Li < Na < Cs$.⁸ Both results indicate that in these reactions the Coulombic interaction between the carbanion and the counterion is of far greater importance than any possible interaction between the counterion and the reacting monomer, at least in ethereal solvents. Other types of carbanions and substrates will be investigated in order to establish whether the behavior of fluorene and its derivatives in proton abstraction reactions is unique in this respect.

Acknowledgment. The support of this research through a grant from the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(7) T. Shimomura, K. J. Tölle, J. Smid, and M. Szwarc, *J. Am. Chem. Soc.*, **89**, 796 (1967).

(8) D. N. Bhattacharyya, J. Smid, and M. Szwarc, *J. Phys. Chem.*, **69**, 624 (1965).

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Indirect ^{15}N - 1H Spin-Spin Couplings in Quinoline- ^{15}N , Its Ethiodide, and Its N-Oxide. Relative Signs and Solvent Dependence

Sir:

Previous observations,^{1,2} of some interest, on the spin couplings between a nitrogen-15 nucleus in an aromatic ring and ring protons have prompted us to report here the correlation of indirect ^{15}N - 1H couplings with the electronic nature of the ^{15}N atom as studied by using quinoline- ^{15}N (I), its ethiodide (II), and its N-oxide (III).³ Coupling constants, J , in these compounds were obtained by comparing the pmr spectra of the ^{15}N compounds with those of the corresponding ^{14}N compounds in a variety of solvents (see Table I).⁴ A pair of the pmr spectra of quinoline- ^{14}N and - ^{15}N in acetone- d_6 is shown in Figure 1 as an example.

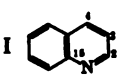
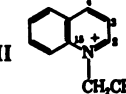
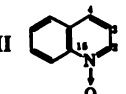
(1) Y. Kawazoe, M. Ohnishi, and N. Kataoka, *Chem. Pharm. Bull. (Tokyo)*, **13**, 396 (1965).

(2) B. W. Roberts, J. B. Lambert, and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 5439 (1965).

(3) For the synthesis of III (97 atom %), see ref. 1. I and II were successively prepared from III in the usual way.

(4) Pmr spectra were taken with a Varian HA-100 spectrometer operating at 100 MHz in the frequency-swept and TMS-locked mode,

Table I. Summary of ^{15}N - ^1H Spin-Coupling Constants (in Hz)

Compound		Solvent		
		Aprotic solvents ^a	CH_3COOD	D_2SO_4 and CF_3COOD
I		$J_{^{15}\text{N},\text{H}(2)}$ $J_{^{15}\text{N},\text{H}(3)}$	-11.1 -1.4	-4.5 -3.1
				-2.0 -4.5
II		$J_{^{15}\text{N},\text{H}(2)}$ $J_{^{15}\text{N},\text{H}(3)}$	-1.6 ^b -4.3 ^b	-1.6 -4.3
				... ^c -4.4
III		$J_{^{15}\text{N},\text{H}(2)}$ $J_{^{15}\text{N},\text{H}(3)}$	~0 -5.0	~+1 -5.5
				+1.2 -6.0

^a Aprotic solvents used were cyclohexane, CCl_4 , C_6D_6 , $\text{C}_5\text{D}_5\text{N}$, CH_3CN , dioxane, acetone- d_6 , and/or DMSO- d_6 . Other solvents used as protic ones were CDCl_3 , D_2O , and/or D_2O -dioxane (1:1)-DCl system. ^b Values obtained in D_2O . ^c Obscured by overlapping of other signals.

Since coupling constants between ring protons in quinoline were already found to have a positive sign,⁵ the relative sign of $J_{^{15}\text{N},\text{H}(2)}$ and $J_{^{15}\text{N},\text{H}(3)}$ was determined in an acetone- d_6 solution by using partial spin-decoupling technique. The ^{15}N , H(2), H(3), and H(4) nuclei can be treated as an isolated first-order, four-

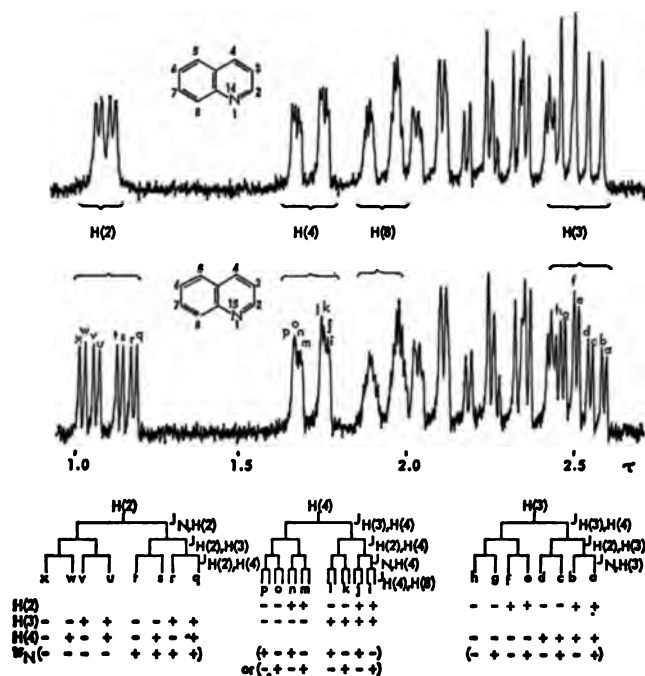


Figure 1. PMR spectra of quinoline- ^{15}N and ^{15}N in acetone- d_6 at 100 MHz and the spin-state diagram.

spin system by neglecting $J_{\text{H}(4),\text{H}(3)}$. On double irradiation on the lines q, r, s, and t, the lines a and c and the lines e and g collapse to two single peaks, whereas irradiation on the lines u, v, w, and x causes collapsing of the lines b and d, and the lines f and h (see Figure 1). These results can be well explained by the spin states shown in Figure 1 (bottom); this indi-

cates that $J_{^{15}\text{N},\text{H}(2)}$ and $J_{^{15}\text{N},\text{H}(3)}$ are of the same sign although the sign of these J 's relative to $J_{^{15}\text{N},\text{H}(4)}$ could not be determined because of the small magnitude of the latter, $J_{\text{H}(2),\text{H}(4)}$, and $J_{\text{H}(4),\text{H}(3)}$.⁶ Since the magnetogyric ratio of the ^{15}N nucleus has a negative sign, the absolute sign of these J values can reasonably be assumed to be negative by analogy with the fact that the $J_{^{15}\text{N}-\text{C}-\text{C}-\text{H}}$ values in trimethylvinylammonium bromide⁷ and alkyl isonitriles⁸ have a positive sign.⁹

Since coupling constants between ring protons in quinoline were already found to have a positive sign,⁵ the relative sign of $J_{^{15}\text{N},\text{H}(2)}$ and $J_{^{15}\text{N},\text{H}(3)}$ was determined in an acetone- d_6 solution by using partial spin-decoupling technique. The ^{15}N , H(2), H(3), and H(4) nuclei can be treated as an isolated first-order, four-

spin system by neglecting $J_{\text{H}(4),\text{H}(3)}$. On double irradiation on the lines q, r, s, and t, the lines a and c and the lines e and g collapse to two single peaks, whereas irradiation on the lines u, v, w, and x causes collapsing of the lines b and d, and the lines f and h (see Figure 1). These results can be well explained by the spin states shown in Figure 1 (bottom); this indicates that $J_{^{15}\text{N},\text{H}(2)}$ and $J_{^{15}\text{N},\text{H}(3)}$ are of the same sign although the sign of these J 's relative to $J_{^{15}\text{N},\text{H}(4)}$ could not be determined because of the small magnitude of the latter, $J_{\text{H}(2),\text{H}(4)}$, and $J_{\text{H}(4),\text{H}(3)}$.⁶ Since the magnetogyric ratio of the ^{15}N nucleus has a negative sign, the absolute sign of these J values can reasonably be assumed to be negative by analogy with the fact that the $J_{^{15}\text{N}-\text{C}-\text{C}-\text{H}}$ values in trimethylvinylammonium bromide⁷ and alkyl isonitriles⁸ have a positive sign.⁹

The large negative value for $J_{^{15}\text{N},\text{H}(2)}$ was obtained for I as for pyrimidine derivatives in aprotic solvents.³ However, this value increases algebraically to a great extent with an increase in the acidity of the solutions, whereas the value for $J_{^{15}\text{N},\text{H}(3)}$ decreases reversely, as summarized in Table I. These J values were plotted against pH values of the aqueous solutions examined (D_2O -dioxane-DCl system) to obtain the proportional correlation of the J values with the degree of protonation toward the ^{15}N atom in question. The J values in II and III, where the ^{15}N atom is cationic even in aprotic solvents, depend a little upon the solvent acidity. The variation in the J values in going from I through III is such that the J values in II and III are brought to values which I would show in far more strongly acid media than have been examined here. On the basis of such presumption, the $J_{^{15}\text{N},\text{H}(2)}$ in III, which is about 0 Hz in aprotic solvents, may reasonably be inferred to increase finally to +1.2 Hz in strongly acid media, while the $J_{^{15}\text{N},\text{H}(3)}$ value decreases to -6.0 Hz. Thus it was revealed that either N oxygenation, quaternization, protonation, or hydrogen bonding, which changes the s character of the ^{15}N -atom bonding orbitals to carbon, results in a remarkable increase in the $J_{^{15}\text{N},\text{H}(2)}$ value and a decrease in the $J_{^{15}\text{N},\text{H}(3)}$ value simultaneously. The s character of the ^{15}N -atom bonding orbitals to carbon, which is supposed to increase in the order of $\text{>N} < \text{>N}^+-\text{H} < \text{>N}^+-\text{C} < \text{>N}^+-\text{O}^- < \text{>N}^+-\text{OH}$,

(6) The determination of relative signs of $J_{^{15}\text{N},\text{H}}$ to $J_{\text{H},\text{H}}$ is impossible solely from pmr spectra; see E. W. Randall and J. D. Baldeschwieler, *J. Mol. Spectry.*, **8**, 365 (1962).

(7) (a) M. Ohtsuru and K. Tori, *Chem. Commun.*, 750 (1966); (b) J. M. Lehn and R. Seher, *ibid.*, 847 (1966).

(8) (a) See footnote 12 in ref 10a; (b) J. P. Maher, *J. Chem. Soc., Sect. A*, 1855 (1966).

(9) Refer to A. J. R. Bourn, D. G. Gillies, and E. W. Randall, "Nuclear Magnetic Resonance in Chemistry," B. Pesce, Ed., Academic Press Inc., New York, N. Y., 1965, p 277.

it play a significant role in these facts, although the contribution due to changes in π -electron structures cannot completely be excluded. Further, this conclusion is supported by the similar behavior reported on $J_{\text{HP-C-H}}$ and $J_{\text{HP-C-C-H}}$,¹⁰ when the reduced coupling constants are compared. The former J value decreases algebraically whereas the latter, which is always positive, increases as the ^{31}P atom becomes more cationic ($\text{P} \rightarrow \text{P}^+$).

It should also be noted that whenever the signals concerned were separately observed, the presence of small couplings (about 1 Hz or less), although not experimentally measured, were clearly discernible for $|J_{\text{HN,H(4)}}|$ and $|J_{\text{HN,H(3)}}|$, which are considerably smaller than $|J_{\text{HN,H(1)}}|$ in all the cases examined (see Figure 1, for example).¹¹

(a) S. L. Manatt, G. L. Juvinall, and D. D. Elleman, *J. Am. Chem. Soc.*, **85**, 2664 (1963); (b) A. R. Cullingworth, A. Pidcock, and R. Smith, *Chem. Commun.*, 89 (1966); (c) S. L. Manatt, G. L. Juvinall, I. Wagner, and D. D. Elleman, *J. Am. Chem. Soc.*, **88**, 2689 (1966); (d) W. McFarlane, *Chem. Commun.*, 58 (1967).

We thank the referee for his valuable comments on the sign of the coupling constants.

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Synthesis of N⁴-Acetyl-3,4,5,6-tetrahydrocytidine Copolymers of Cytidylic Acid and N⁴-Acetyl-3,4,5,6-tetrahydrocytidylic Acid

Recent studies of the optical rotatory dispersion of poly C^{1,2} and poly U³ at neutral pH, and of the reduction of poly C³ and poly A⁴ with formaldehyde, led to the conclusion that intra- or interstrand hydrogen bonding plays a negligible role in the stabilization of the secondary structure of these polymers. It has been suggested for these polymers that a single-stranded helical structure is stabilized by interactions of the reduced bases. Polynucleotides containing residues of a saturated and therefore nonplanar heterocyclic nucleoside are suitable model compounds for studying this thesis. Saturated nucleotides are unlikely to participate in base stacking due to their stereochemistry and their shortened π -electron system.⁵ Copolymers containing saturated nucleotide residues are also suitable model compounds for yeast transfer RNA, where 5,6-dihydrouridine has been detected as a minor constituent.⁶ We wish to report the synthesis of N⁴-acetyl-3,4,5,6-tetrahydrocytidine and copolymers of cytidylic acid containing varying amounts of N⁴-acetyl-3,4,5,6-tetrahydrocytidylic acid as nonplanar constituents.

While cytidine is completely resistant toward sodium borohydride in the dark,⁷ N⁴-acetylcytidine is reduced

Abbreviations: polyuridylic acid, poly U; polycytidylic acid, poly C; polyadenylic acid, poly A.

G. D. Fasman, C. Lindblow, and L. Grossman, *Biochemistry*, **3**, 1964.

A. M. Michelson and C. Monny, *Proc. Natl. Acad. Sci. U. S.*, **56**, 1966.

C. L. Stevens and A. Rosenfeld, *Biochemistry*, **5**, 2714 (1966).

P. Cerutti, H. Miles, and J. Frazier, *Biochem. Biophys. Res. Commun.*, **22**, 466 (1966).

J. T. Madison and R. W. Holley, *ibid.*, **18**, 153 (1965).

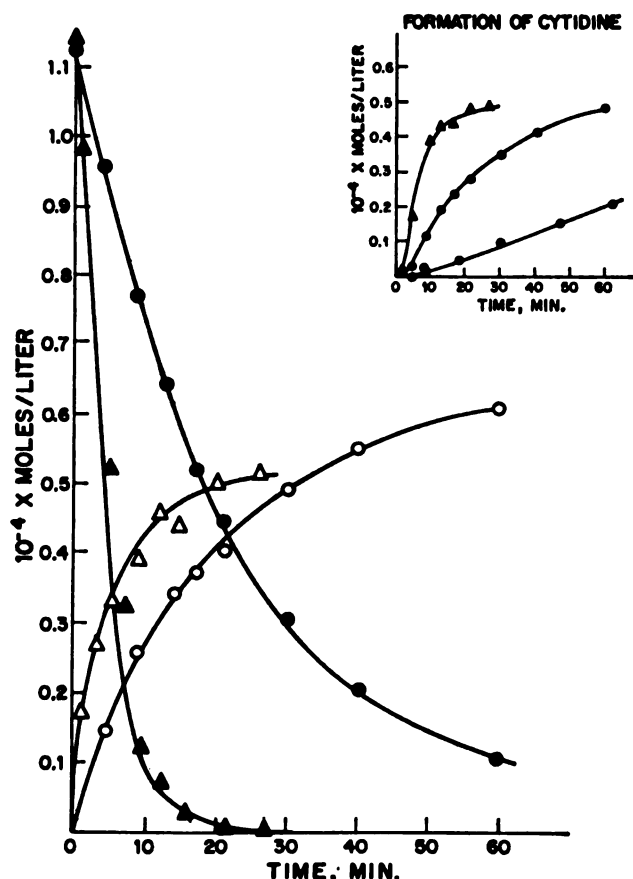


Figure 1. The reduction and deacetylation of N⁴-acetylcytidine in the presence of sodium borohydride in the dark. Disappearance of N⁴-acetylcytidine calculated from the absorbance at 310 m μ in 1 N HCl (●, 14 M excess NaBH₄; ▲, 140 M excess NaBH₄; ϵ_{310} N⁴-acetylcytidine 18×10^3); formation of N⁴-acetyl-3,4,5,6-tetrahydrocytidine, orcinol assay (○, 14 M excess NaBH₄; △, 140 M excess NaBH₄). Inset: formation of cytidine calculated from the absorbance at 310 m μ and 270 m μ in 1 N HCl (●, 14 M excess NaBH₄; ▲, 140 M excess NaBH₄; ϵ_{310} N⁴-acetylcytidine 18×10^3 , ϵ_{270} N⁴-acetylcytidine 23×10^3 , ϵ_{310} cytidine 0, ϵ_{270} cytidine 10×10^4); deacetylation of N⁴-acetylcytidine in the absence of NaBH₄ at pH 10 (○, from the disappearance of the absorbance at 310 m μ measured in 1 N HCl; ϵ_{310} N⁴-acetylcytidine 18×10^3).

to N⁴-acetyl-3,4,5,6-tetrahydrocytidine and partially deacetylated to cytidine in the presence of sodium borohydride at pH 10. The rate of the reduction and deacetylation⁸ are both dependent on the concentration of sodium borohydride. N⁴-Acetylcytidine is also deacetylated at a slower rate at pH 10 in the absence of the reducing agent. The extent of the reduction can be determined with the orcinol assay for ribose due to the labilization of the N-glycoside bond upon saturation of the 5,6 double bond in N⁴-acetylcytidine. The disappearance of N⁴-acetylcytidine and the formation of cytidine can be followed spectrophotometrically and the composition of the reaction mixture calculated at each point of the reaction from the absorbance at 310 and 270 m μ in 1 N HCl⁹ (see Figure 1). The final yield of N⁴-acetyl-3,4,5,6-tetrahydrocytidine was 54% if a 14 M excess of sodium borohydride was used and 45% at a 140 M excess of the reducing agent. In both cases

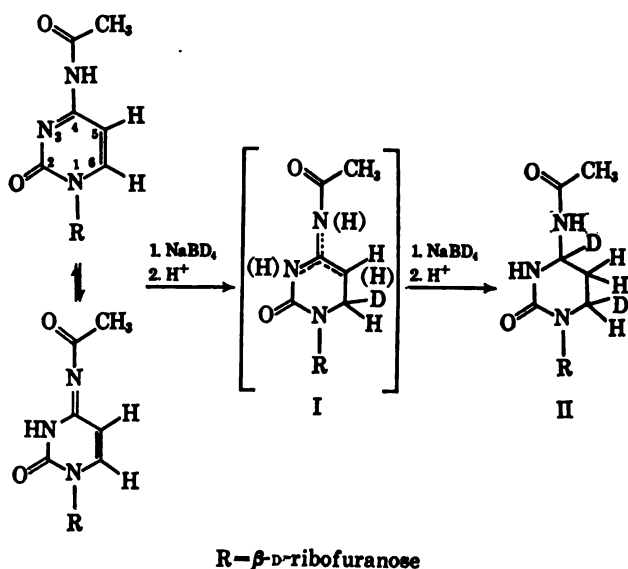
(7) P. Cerutti and N. Miller, *J. Mol. Biol.*, in press.

(8) The deacetylation reaction is reminiscent of the reductive deacetylation of N-acylindoles and carbazoles with NaBH₄ (K. Banholzer, T. W. Campbell, and H. Schmid, *Helv. Chim. Acta*, **35**, 1577 (1952)).

(9) N⁴-Acetyl-3,4,5,6-tetrahydrocytidine has no appreciable absorption at wavelengths longer than 250 m μ .

44% cytidine was formed. If the reaction was carried out under ultraviolet irradiation (2537 Å) the yield for the reduction product was 76% and for cytidine 21% (14 M excess of NaBH_4).¹⁰

The two components of the reduction mixture, cytidine and N^4 -acetyl-3,4,5,6-tetrahydrocytidine, were separated by column chromatography on Dowex 50W-X8 (H^+). The structure of the reduction product was derived from the nmr spectrum (in D_2O). A triplet at 5.30 ppm ($J = 4.5$ cps, 1 H) was attributed to the proton at C_4 and a multiplet centered at 3.39 ppm (2 H) to the methylene protons at C_5 . A multiplet at higher field was superimposed by a singlet originating from the methyl group of the acetyl substituent (singlet at 1.99 ppm) and was attributed to the methylene protons at C_6 . The signal at 5.30 ppm disappeared and the multiplet at 3.39 ppm was simplified and lowered in intensity if the reduction was carried out with sodium borodeuteride. The product of the reduction with sodium borodeuteride is therefore N^4 -acetyl-3,4,5,6-tetrahydrocytidine- d_4, d_6 (II). The isotope distribution in II suggests the following reaction steps: (1) 1,4 addition of a hydride (deuteride) ion (at C_4) and a proton (at N^3 or N^4) to an α, β -unsaturated imine, and (2) further reduction of the intermediate N^4 -acetyldihydrocytidine (I) by the attack of a second hydride (deuteride) ion at C_4 .



This novel reaction was used for the synthesis of copolymers of cytidylic acid and N^4 -acetyl-3,4,5,6-tetrahydrocytidylic acid by the reduction of copolymers of cytidylic acid and N^4 -acetylcytidylic acid.¹¹ The polymers were exposed to a large excess of sodium borohydride in 0.05 M sodium carbonate buffer at pH 9.8 for 40 min at room temperature. The polymers were purified by repeated precipitation with cold ethanol and by passage through Sephadex G-25. The composition of the polymers was determined spectrophotometrically and with the orcinol assay after total digestion with pancreatic ribonuclease. In contrast to the behavior of the monomer no significant deacetylation was observed. Polymers containing 8, 16, and 29%

(10) No spectral changes were detected if N^4 -acetylcytidine was irradiated under the analogous conditions for 70 min in the absence of NaBH_4 .

(11) A. M. Michelson and M. Grunberg-Manago, *Biochim. Biophys. Acta*, 91, 92 (1964).

N^4 -acetyl-3,4,5,6-tetrahydrocytidylic acid were prep by this method, and their physical properties are being investigated. The characterization of the polymers is given in Table I. The presence of N^4 -acetyl-3,4,5,6-tetrahydrocytidine in the reduced polymer demonstrated in experiments using sodium borotris as a reducing agent. The components of the nuclease digest were separated on Dowex 50W

Table I. Characterization of the Polymers

Compn before reduction, %		Compn after reduction, %	
Cytidine 3'-phosphate ^a	N^4 -Acetylcytidine 3'-phosphate ^a	Cytidine 3'-phosphate ^b	N^4 -Acetyl-3,4,5,6-tetrahydrocytidine 3'-phosphate ^b
68	26	73	29
81	18	84	16
90	7	90	8

^a The amounts of cytidine 3'-phosphate and N^4 -acetylcytidine 3'-phosphate were calculated from the absorbance of the nucleotide mixture obtained from the digestion of the polymers with creatic ribonuclease in 0.05 M NH_4HCO_3 , pH 7.5, at 270 m μ (ϵ_{270} cytidine 3'-phosphate 9×10^3 ; ϵ_{270} N^4 -acetylcytidine 3'-phosphate 4.4×10^3 ; ϵ_{270} N^4 -acetylcytidine 3'-phosphate 8.6×10^3). To accomplish complete deacetylation the samples were then kept for 6 hr at 65–70°C. The cytidine 3'-phosphate content was determined from the absorbance at 280 m μ ($\epsilon = 1.3 \times 10^4$, pH 1). This value was taken 100% for the calculation of the base composition of the polymer. ^b The amount of cytidine 3'-phosphate was determined from the absorbance of the nucleotide mixture obtained from the digestion of the reduced polymers with pancreatic ribonuclease at 280 m μ ($\epsilon = 1.3 \times 10^4$, pH 1). The content of N^4 -acetyl-3,4,5,6-tetrahydrocytidine 3'-phosphate was measured with the orcinol assay. The polymer phosphate was determined according to B. N. Ames and D. T. Dubin, *J. Biol. Chem.*, 235, 769 (1960), and taken as a basis for the calculation of the base composition of the polymer.

(H^+). The fractions containing radioactive material were treated with alkaline phosphomonoesterase and their content was compared to authentic N^4 -acetyl-3,4,5,6-tetrahydrocytidine by thin layer chromatography (silica gel G, 85% 2-propanol). Identical R_f values were found for the radioactive compound derived from the polymer and for N^4 -acetyl-3,4,5,6-tetrahydrocytidine obtained from the reduction of the monomer. Radioactivity was found in the eluates containing cytidylic acid.

Attempts are now being made to synthesize copolymers of cytidylic acid and 3,4,5,6-tetrahydrocytidylic acid by the reduction of N^4 -formylated and N -fluoroacetylated polycytidylic acid followed by deacetylation.

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Rate Constants and the Mechanism for the Transfer of Triplet Excitation Energy

Sir:

The intramolecular transfer of triplet excitation energy from one chromophore to another has been measured

s I and II shown in Figure 1. The triplet donor is ester of benzophenone-4-carboxylic acid, and triplet donor in II is the carbazole chromophore. The acceptor in both cases is the naphthalene chromophore. The absorption spectrum of each molecule is the sum of the absorption spectra of their components. The lowest singlet state of both donors is lower in energy than the lowest singlet state of naphthalene. This makes it possible to excite donors with long wavelength radiation which is absorbed by the naphthalene chromophore. All measurements were made at 77°K in a rigid matrix.¹

The phosphorescence spectrum of a very dilute solution ($10^{-5} M$) of II shows emission from both the carbazole chromophore ($\sim 63\%$) and the naphthalene chromophore ($\sim 37\%$). The intensity of phosphorescence from II is about 67% as strong as the intensity of phosphorescence of an equimolar mixture of naphthalene and III at the same concentration. The lifetime of the carbazole emission from II is 5.7 sec,² while the lifetime of the carbazole emission from III is 7.2 sec. The difference of the first-order rate constants (calculated from lifetimes) indicates that 21% of the triplet energy is transferred and that the rate constant for the transfer process is about 0.04 sec^{-1} . The agreement between these three completely different measurements for the amount transferred is excellent. The first method is the least accurate but it involves a knowledge of the phosphorescence quantum yields for the two chromophores, and it involves intensity measurements at different wavelengths.

No corrections were made for the change in sensitivity of the apparatus as a function of wave-

length. The phosphorescence spectrum of a very dilute solution ($10^{-4} M$) of I shows emission from both the naphthalene and the benzophenone chromophore. The lifetime of the phosphorescence from the benzophenone chromophore is almost 1000 times shorter than the phosphorescent lifetime of the naphthalene chromophore. A measurement of the ratio of the intensities of the fast and slow components of I indicated that 70% of the triplet excitation energy was transferred to the naphthalene chromophore. The phosphorescence from I is about 65% as intense as the phosphorescence from an equimolar mixture of IV and naphthalene.

This indicates that about 35% of the triplet energy is transferred. The lifetime of the naphthalene emission from I is $4.9 \times 10^{-8} \text{ sec}$ and the lifetime of the benzophenone emission from I is $5.6 \times 10^{-8} \text{ sec}$. The difference of the first-order rate constants indicates that 12% of the triplet energy is transferred and that the rate constant for the transfer process is 25 sec^{-1} . The agreement between the two sets of measurements is not quite as good for

butyl alcohol and 70% isopentane.

The decay was very slightly nonexponential at very short times. The decay is due to a distribution in the distances between the chromophores. The lifetime quoted was from the exponential part of the decay.

The quantum yields of naphthalene and carbazole were assumed to be the same for this calculation. The intersystem quantum yields for the two compounds were found to be the same by A. A. Lamola and J. N. Pitts, "Photochemistry," John Wiley and Sons, Inc., New York, 1952, p 209.

Corrections were made for the sensitivity of the apparatus as a function of wavelength. The phosphorescent quantum yield of the benzophenone chromophore was assumed to be ten times the phosphorescent quantum yield of the naphthalene chromophore.

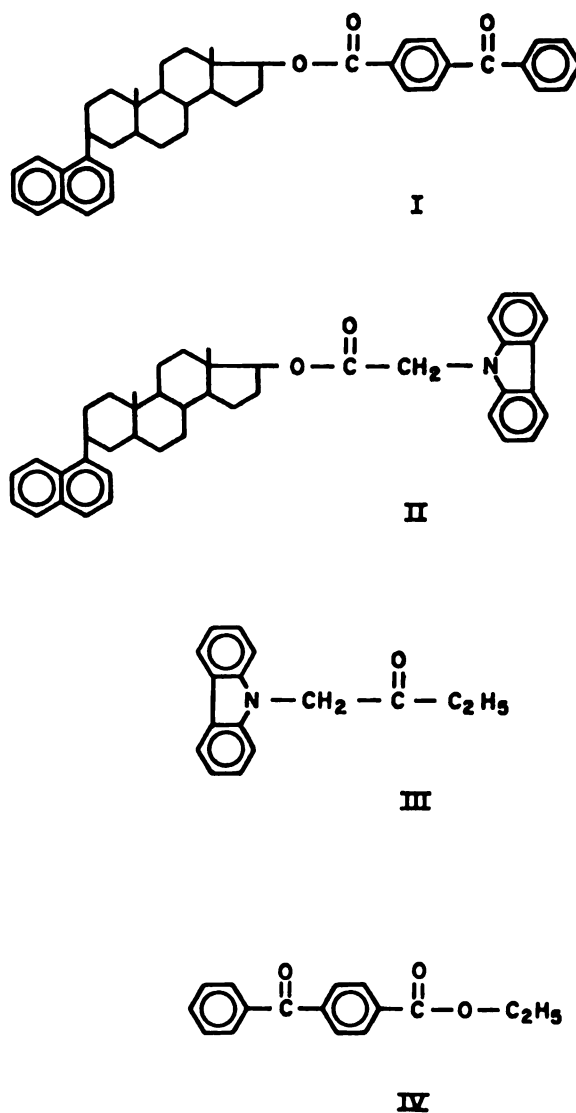


Figure 1. Molecules studied: (I) 3-(α -naphthyl)-5 α -androstan-17 β -ol 17-*p*-benzoylbenzoate, (II) 3-(α -naphthyl)-5 α -androstan-17 β -ol 17-(9-carbazole)acetate, (III) ethyl (9-carbazole)acetate, (IV) ethyl *p*-benzoylbenzoate.

I as it is for II, but all measurements agree within a factor of 3. The lifetime measurement is probably the most accurate because it does not involve a comparison of two intensities or an assumption of quantum yields.

The transfer of singlet excitation energy from the naphthalene chromophore to the two donor chromophores was measured by comparing the intensity of the naphthalene emission from an equimolar mixture of naphthalene and either III or IV to the intensity of the naphthalene emission from I or II; 2985-Å radiation was used for excitation. These measurements indicated that in I, 70% of the singlet excitation energy is transferred and in II, 95% of the singlet excitation energy is transferred. A dipole-dipole coupling mechanism was assumed to be responsible for the transfer of singlet excitation energy and Förster's equation⁵ was used to calculate the distance between the chromophores. The distances were found to be 14 Å for I and 15 Å for II. These numbers agree very well with

(5) Th. Förster, *Discussions Faraday Soc.*, 27, 7 (1959). The exponent on r should be 5 instead of 6; see S. A. Latt, H. T. Cheung, and E. R. Blout, *J. Am. Chem. Soc.*, 87, 995 (1965).

measurements of the distances made on molecular models.

In summary, the rate constant for triplet excitation transfer in I (25 sec^{-1}) is about 1000 times greater than in II (0.040 sec^{-1}). The transfer distance is about the same in both cases. The mechanism suggested by these results involves spin-orbital coupling to the singlet system in the donor chromophore combined with dipole-dipole coupling between the singlet systems of the two chromophores and spin-orbital coupling back to the triplet system in the acceptor chromophore. The difference of 1000 in the rate constant for transfer is the result of the large difference in spin-orbital coupling between III and IV which is exemplified by the large difference (again a factor of 1000) in their phosphorescent lifetimes. A mechanism involving exchange integrals would not be expected to lead to such a large difference in the transfer properties of the two compounds. Also, it is unlikely that an exchange integral mechanism could be operative at such large distances.

A more complete description of these measurements is currently in preparation.

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Received March 30, 1967

(6) Alfred P. Sloan Research Fellow. L. J. D. gratefully acknowledges financial support from the Public Health Service Carrier Program Award 1-K3-NB-28, 105 from the National Institute of Neurological Diseases and Blindness.

Preparation and Properties of Monocesium Chloroxenate (CsClXeO_3)¹

Sir:

We wish to report preparation of a stable, crystalline cesium xenon(VI) compound containing chloride similar to the cesium fluoroxenate (CsFXeO_3) reported by Selig² and Spittler, *et al.*³ The crystalline cesium chloroxenate can be prepared either from aqueous solutions at pH 8 to 9 or from acetonitrile. A crystalline precipitate is obtained by mixing ice-cold solutions of approximately 2.0 ml of 1.5 *M* cesium chloride with 0.4 ml of 1.5 *M* xenon trioxide or by adding xenon trioxide to cesium chloride dropwise until permanent turbidity appears. Then the solution is left in the icebox for approximately 3 hr. The supernatant solution is sucked off, and the crystals first are washed with several portions of ice-cold water and finally with acetonitrile. The contents are dried in a vacuum desiccator. Preparation of cesium chloroxenate must be carried out in slightly alkaline medium otherwise chloride is oxidized to chlorine oxides and forms highly explosive solutions. Crystalline cesium chloroxenate also can be prepared by mixing approximately equal volumes of 0.1 *M* cesium chloride and 0.1 *M* xenon trioxide dissolved in moist acetonitrile. The precipitation in acetonitrile is less dependent on pH, but is more subject to coprecipitation

(1) This work is supported by the grant from the National Science Foundation (GP-5045).

(2) H. Selig, *Inorg. Chem.*, **5**, 183 (1966).

(3) T. M. Spittler, B. Jaselskis, and J. L. Huston, presented at the 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967.

of the reagent which is present in excess. The resulting precipitate compares well to the aqueous preparations: infrared spectra and analyses are almost identical.

The chloride in the cesium chloroxenate is determined by Fajans method after the decomposition of xenate with dilute hydrogen peroxide. Cesium is determined either as cesium perchlorate or indirectly as cesium chloride titrimetrically, and the oxidation equivalent is determined iodometrically by "hi-lo" titration. The analyses of chloride, cesium, and oxidation equivalent yield the empirical formula weight 347, 348, and 344, respectively, as compared to the calculated formula weight 346.5 for CsClXeO_3 .

Cesium chloroxenate is considerably more stable than xenon trioxide. It loses some xenon and oxygen at approximately 150° and on further heating evolution of xenon and oxygen diminishes. At temperatures higher than 190° , xenon and oxygen are evolved rather rapidly and the sample explodes at approximately 205° *in vacuo*, leaving cesium chloride residue. Cesium chloroxenate is shock sensitive and should be handled with care. Cesium chloroxenate, upon addition to concentrated sulfuric acid, yields chlorine, chlorine oxides, oxygen, and xenon.

Crystalline cesium chloroxenate shows a number of infrared bands at 818 (s), 793 (s), 766 (m), 749 (m), 663 (w), and 400 (m) cm^{-1} . The strong bands at 818 and 749 cm^{-1} are similar to cesium fluoroxenate at 807 and 757 cm^{-1} as reported by Selig.² The X-ray powder diffraction pattern is different from cesium chloride and xenon trioxide calculated *d* values.⁴ However, the general pattern of lines resembles that of CsFXeO_3 , as prepared in our laboratory.³ The *d* spacings for the CsClXeO_3 are: 4.03 (w), 3.82 (m), 3.34 (m), 3.20 (w), 2.68 (m), 2.34 (m), 2.00 (s), and 1.74 (w) Å. (Some of these weak lines may be due to the decomposition of crystals in the X-ray beam as has been observed in the study of various xenon(VI) compounds.)

We are continuing our investigations on the nature of the halide interactions with xenon trioxide.

(4) D. H. Templeton, A. Zalkin, J. D. Forrester, and S. M. Williamson, "Noble Gas Compounds," H. H. Hyman, Ed., University of Chicago, Chicago, Ill, 1963, p 229.

Bruno Jaselskis, T. M. Spittler, J. L. Huston
Department of Chemistry, Loyola University
Chicago, Illinois 60626
Received February 1, 1967

Dibenzoequinene. A Novel Heptacyclic Hydrocarbon from the Photolysis of [2.2]Paracyclonaphthane

Sir:

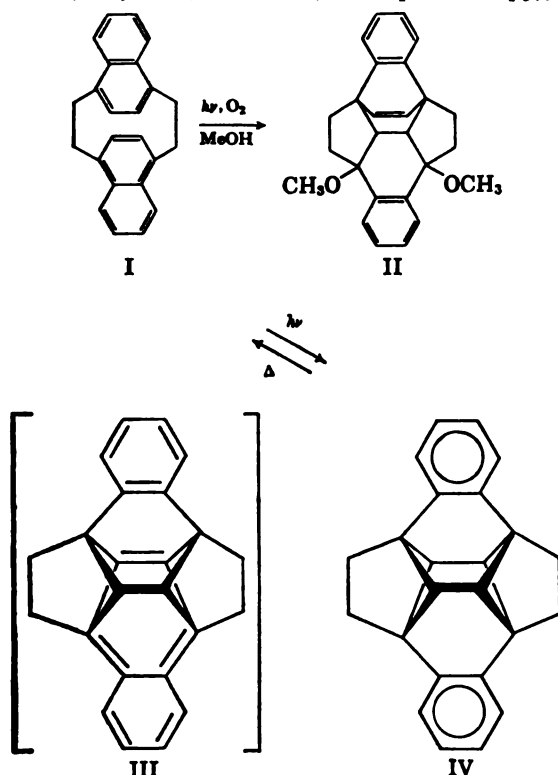
In a recent communication¹ we reported that [2.2]paracyclonaphthane (I)² undergoes photosensitized autoxidation to form the dibenzo dimethoxy polycyclic system II. We have now found that, in the presence of ultraviolet light,³ I is converted to the novel hydrocarbon IV, "dibenzoequinene."⁴

(1) H. H. Wasserman and P. M. Koehn, *J. Am. Chem. Soc.*, **88**, 4522 (1966).

(2) D. J. Cram, C. K. Dalton, and G. R. Knox, *ibid.*, **85**, 1068 (1963).

(3) In our initial dye-photosensitized autoxidation studies we used a 150-w floodlamp as light source. This was replaced by a sunlamp in order to decrease reaction time and improve yields. Compound IV was observed as a minor product in the photosensitized autoxidations

Ultraviolet irradiation⁶ of [2.2]paracyclonaphthene (I) in degassed benzene-methanol (1:1) for 10 days yielded IV (50%), after chromatography on silica gel and recrystallization from hexane. *Anal.*⁷ Calcd for $C_{24}H_{20}$: C, 93.46; H, 6.54; mol wt, 308. Found: C, 93.53; H, 6.20; mol wt (mass spectroscopy), 308.

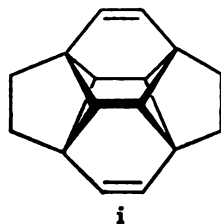


The photolysis product did not exhibit a sharp melting point. At about 190–200° a change in the crystalline structure was observed, and melting finally took place at 294–298° dec. (The reported melting point of I is 299–301°.) Examination of the ultraviolet spectrum of the material which had been heated to 200° clearly showed that a thermal reversal of IV to I had taken place.

Further spectroscopic examination of product IV revealed the following. (i) The infrared spectrum ($CHCl_3$) contains broad (CH) absorption in the 2800–3000- cm^{-1} range with no bands in the regions associated with alcohol or ether groups. (ii) The mass spectrum (like the spectrum of I) shows only a base peak

carried out in the presence of ultraviolet light, but it was the main product in the purely photochemical reaction in the absence of oxygen.

(4) We suggest the trivial name "equinene" for the parent $C_{14}H_{10}$ bicyclic diene (i) which has not yet been prepared. As has been pointed out earlier,⁸ this hydrocarbon would be formed if [2.2]-paracyclonaphthene were to undergo a twofold intramolecular Diels-Alder reaction.



(5) R. C. Helgeson and D. J. Cram, *J. Am. Chem. Soc.*, **88**, 509 (1966).

(6) An air-cooled Rayonet Photochemical Reactor (Southern New England Ultraviolet Co., Middletown, Conn.) and a Pyrex reaction vessel were used. The light source consisted of 16 lamps at 3500 Å.

(7) We thank Dr. Robert Rittner of the Olin Mathieson Chemical Corp. for assistance in obtaining the microanalytical data.

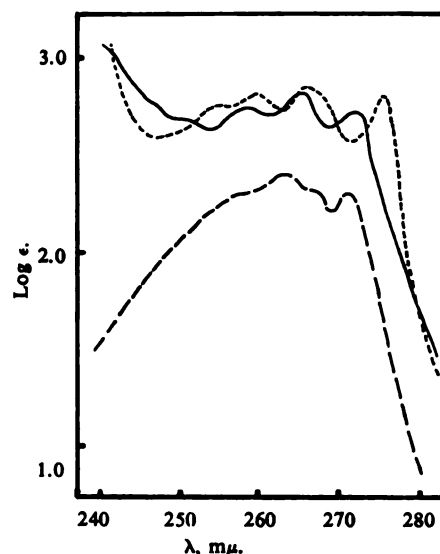
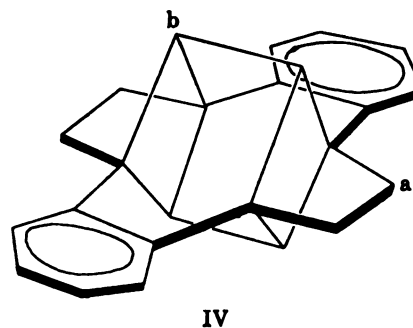


Figure 1. Ultraviolet spectrum of dibenzoequinene (IV) in hexane (----); the dimethoxy polycyclic system (II) in ethanol (—); and *o*-xylene in hexane (-.-).

at m/e 154 and a molecular ion peak at m/e 308, suggesting a hydrocarbon of molecular formula $C_{24}H_{20}$ which has a high degree of symmetry. (iii) The ultraviolet spectrum of the hydrocarbon (Figure 1) bears a very close resemblance to the spectrum of II, and also to that of *o*-xylene. (iv) The nmr spectrum is remarkably uncomplicated, showing three sharp singlets, in the ratio 2:2:1, at τ 2.65 (8 aromatic H), 7.60 (8 H at positions a), 8.36 (4 H at positions b). The upfield shift of the four protons at b is in accord with previous observations on the chemical shifts of equatorial hydrogens on the four-membered rings of bicyclo[2.1.1] systems.⁹



The structural representation for the $C_{24}H_{20}$ hydrocarbon which is clearly in accord with all of the above information is the hydrocarbon IV. This product appears to form by a light-induced intramolecular cyclization⁹ possibly through the intermediate III. Other products formed in this photochemical reaction are under investigation.

An independent X-ray structure determination on dibenzoequinene is in progress by Dr. Albert Fratini of the U. S. Naval Research Laboratories, Washington, D. C.^{9a}

(8) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Am. Chem. Soc.*, **84**, 1594 (1962).

(9) Recent studies on [2.2]paracyclonaphthene⁴ have shown that, on irradiation with ultraviolet light, this system undergoes ring opening without formation of i.

(9a) NOTE ADDED IN PROOF. Dr. Fratini has recently informed us that he has confirmed structure IV by X-ray analysis.

Acknowledgments. This work was supported by Grant GM 13854 from the National Institutes of Health. We wish to thank Drs. S. Lipsky and W. McMurray for help in determining the mass spectra of products formed in this and related work. We also thank B. von Klock for technical assistance.

(10) National Institutes of Health Predoctoral Fellow, 1966-1967.

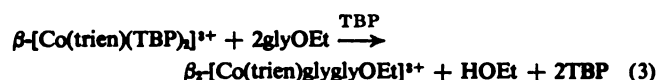
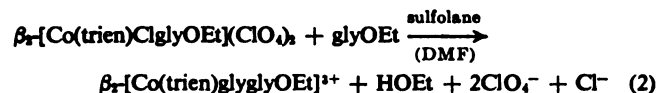
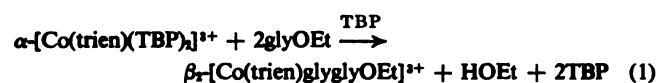
Harry H. Wasserman, Philip M. Keehn¹⁰
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New Haven, Connecticut 06520
Received January 21, 1967

Peptide Bond Formation and Subsequent Hydrolysis at a Cobalt(III) Center

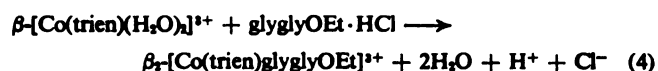
Sir:

We wish to report the rapid formation of a peptide bond in nonaqueous solutions at room temperature using the $\text{Co}(\text{trien})^{3+}$ (trien = triethylenetetramine) moiety as a N-terminal protecting group and as an activating center. This discovery was made during a preparative study of cobalt(III) complexes containing monodentate amino acid amides and esters.

Treatment of α - or β - $[\text{Co}(\text{trien})(\text{TBP})_2]^{3+}$ or β_2 - $[\text{Co}(\text{trien})\text{Cl}(\text{glyOEt})(\text{ClO}_4)_2]^{3+}$ with glycine ethyl ester in dry TBP, and sulfolane or dimethylformamide solutions, respectively, results in the rapid condensation of two glycine ester residues and the formation of the β_2 - $[\text{Co}(\text{trien})\text{glyglyOEt}]^{3+}$ ion. The reactions (eq 1-3) are complete within 2 min at 25°.



Chromatography on cation ion-exchange paper (Whatman cellulose phosphate P81) showed almost quantitative formation of the dipeptide ester complex, and analytically pure β_2 - $[\text{Co}(\text{trien})\text{glyglyOEt}](\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$ was isolated in high yield (~80%) from each of the reactions. (*Anal.* Calcd: C, 21.17; H, 4.74; N, 12.35. Found: C, 20.86; H, 4.82; N, 12.16). An identical product was isolated following treatment of β - $[\text{Co}(\text{trien})(\text{H}_2\text{O})_2]^{3+}$ with glycylglycine ethyl ester in aqueous solution at pH 7.5-8.0 for 1 hr at 25° and addition of NaClO_4 (reaction 4).

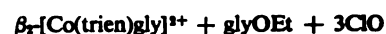


The equivalence of the products isolated from reactions 1-4 was established by comparisons of pmr (δ 1.3 (triplet), 4.36, 4.27, and 4.25 ppm (masked quartet); intensity ratio 3:2:2:2), infrared (1735 cm^{-1} ester carbonyl, 1630 cm^{-1} coordinated amide carbonyl), and visible (ϵ_{248} 153; ϵ_{478} 141) spectra, as well as by their chromatographic behavior and analytical data. The

(1) α and β refer to the geometrical arrangement of triethylenetetramine about the metal atom: G. H. Searle and A. M. Sargeson, *Inorg. Chem.*, **4**, 45 (1965). TBP = tri(*n*-butyl) phosphate.

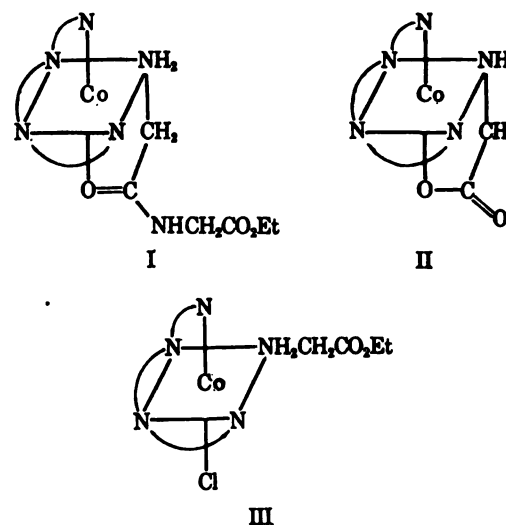
(2) Subscripts β_1 and β_2 are used to distinguish between the two non-equivalent positions in the β structure; see II and III below.

compound β_2 - $[\text{Co}(\text{trien})\text{glyglyOEt}](\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$ is recrystallized without change from neutral or acidic solutions, but undergoes hydrolysis in basic solution (pH ≥ 8) liberating 1 equiv of glycine ethyl (reaction 5). The resulting glycine chelate β_2 - $[\text{Co}(\text{trien})\text{glyglyOEt}](\text{ClO}_4)_3 + \text{OH}^- \longrightarrow$



$\text{gly}]^{2+}$ ion was isolated as its I^- and ClO_4^- salts (Calcd for $[\text{CoC}_8\text{H}_{22}\text{O}_2\text{N}_6](\text{ClO}_4)_2 \cdot 0.5\text{H}_2\text{O}$: C, 19.82; H, 4.75; N, 14.38. Found: C, 19.82; H, 4.75; N, 14.33) and is identical with that obtained in the action of β - $[\text{Co}(\text{trien})(\text{H}_2\text{O})_2]^{3+}$ with glycine (ϵ_{248} 134; ϵ_{478} 134).³ In view of reactions 4 and 5 and structure I below, it is now proposed that the β_2 - $[\text{Co}(\text{trien})\text{glyglyOEt}]^{3+}$ ion is the intermediate in the hydrolysis of peptide esters and amides catalyzed by the β - $[\text{Co}(\text{trien})(\text{OH})(\text{H}_2\text{O})]^{3+}$ ion.⁴

An X-ray structural study of β_2 - $[\text{Co}(\text{trien})\text{glyglyOEt}](\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$ establishes its geometrical configuration as I⁵ in which glycylglycine ethyl ester func-



as a bidentate ligand by attachment to cobalt through the terminal amino nitrogen and peptide carbonyl oxygen atoms. This, together with the experimental evidence below, establishes the geometrical structure of the hydrolyzed product, β_2 - $[\text{Co}(\text{trien})\text{gly}]^{2+}$, and reactions 4 and 5, as II and III, respectively, in agreement with previous assignments.³

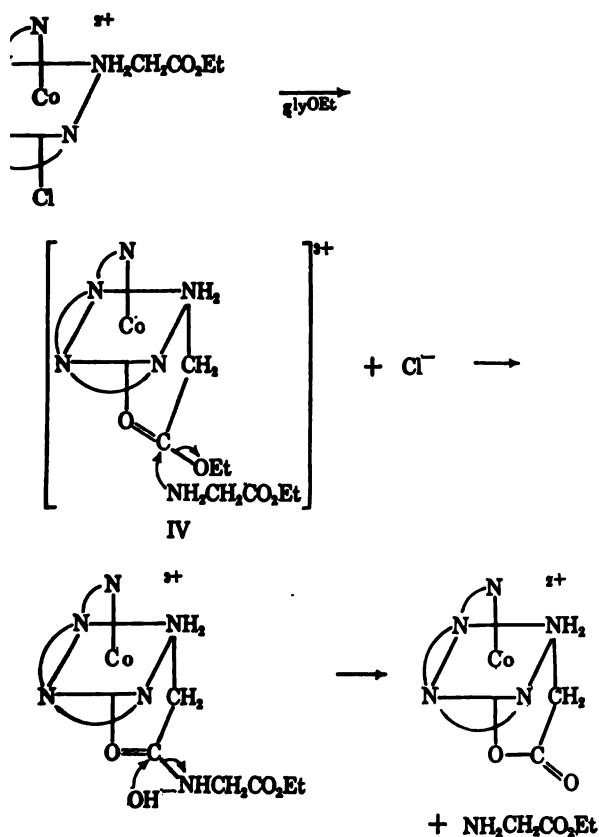
To establish that formation of the peptide bond occurs at the cobalt(III) center, β_2 - $[\text{Co}(\text{trien})\text{Cl}(\text{glyOEt})(\text{ClO}_4)_2]^{3+}$ (1 g) (*Anal.* Calcd: C, 22.13; H, 5.02; N, 12.91. Found: C, 21.98; H, 5.12; N, 12.99) containing C^{14} -labeled glycine ethyl ester (4850 ± 17 mg of complex) was treated with 2 equiv of freshly prepared inactive glycine ethyl ester (0.4 g) in sulfolane (10 ml) and the reaction quenched after 2 min by addition of ethanol and ether. The β_2 - $[\text{Co}(\text{trien})\text{glyglyOEt}](\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$ obtained after two recrystallizations from hot water (*Anal.* Calcd: C, 21.17; H, 4.74; N, 12.35. Found: C, 21.25; H, 4.42; N, 12.35) and unreacted glycine ethyl ester recovered by chromatography were analyzed for their C^{14} content.

(3) L. G. Marzilli and D. A. Buckingham, *Inorg. Chem.*, **6**, 1082 (1967).

(4) D. A. Buckingham, J. P. Collman, D. A. R. Happer, and Marzilli, *J. Am. Chem. Soc.*, **89**, 1082 (1967).

(5) M. Fehlmann, H. Freeman, D. A. Buckingham, and Sargeson, to be published.

results of 3890 ± 10 cpm/mg and approximately 200 ± 50 cpm/mg, respectively, establish no significant exchange of coordinated and free ethyl ester has occurred during the reaction. Formation of the peptide bond must involve coordination of the coordinated ester and must occur on complex. Subsequent hydrolysis of the C^{14} -labeled β -[Co(trien)glyglyOEt](ClO₄)₂·H₂O at pH $\approx 10.25^\circ$ and examination of the β -[Co(trien)gly](ClO₄)₂·H₂O isolated from the resulting solution (4930 ± 50 cpm/mg) shows 96% retention of activity in chelated glycine residue, and indicates a similar retention in the N-terminal glycine of the β -[Co(trien)glyOEt]²⁺ ion. These results are consistent with, but do not unequivocally establish, the following mechanism for peptide formation and subsequent hydrolysis. Formation of the peptide bond prior to coordination is also allowed by the results, but prior coordination of the incoming ester followed by condensation is excluded.



preliminary results indicate that the intermediate condenses with dipeptide esters to give a coordinated peptide ester, which leads to the possibility that this reaction may be useful as a general method for N-terminal addition of integral amino acid residues to peptide esters. Experiments to distinguish between mechanistic possibilities are presently being conducted. Also the scope and versatility of this reaction are being investigated.

Acknowledgment. The authors are grateful to Dr. Rosenberg, Department of Biochemistry, John Curtin School of Medical Research, for a gift of C^{14} -labeled glycine and use of the Packard Scintillation Counter

and to the Microanalytical Department for C, H, and N analyses.

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Received February 20, 1967

Chlorosilyl Derivatives of Transition Metals and Evidence for a Conformational Effect on Metal Carbonyl Stretching Bands

Sir:

The chemistry of silicon-transition metal compounds has been developed to a much smaller extent than that of germanium, tin, and lead; this situation may result in part from a lack of suitable preparative methods. We reported recently¹ that triphenylsilane, known² to react readily with cobalt carbonyl, would react under more vigorous conditions with the carbonyls of manganese and rhenium, affording $(C_6H_5)_3SiM(CO)_5$ ($M = Mn, Re$). We now communicate further studies showing that the silane-metal carbonyl reaction is a rather general one, providing a convenient route to new compounds both expected and unexpected. The reactions of trichlorosilane are particularly interesting, and a number are summarized in Table I. Yields vary widely,

Table I. Trichlorosilane Reactions^a

Reactant	Product ^b	Mp, °C ^c	CO stretching fundamentals, cm ⁻¹ ^d
$Mn_2(CO)_{10}$	$Cl_3SiMn(CO)_5$	130–131	2123, 2035
$Re_2(CO)_{10}$	$Cl_3SiRe(CO)_5$	169–169.5	2139, 2037, 2028
$Fe(CO)_5$	$[Cl_3SiFe(CO)_4]_2$	Dec >200	2094, 2053, 2048, 2038
$Fe_2(CO)_9$	$(Cl_3Si)_2Fe(CO)_4$	94–96	2125, 2078, 2071, 2061
$[C_6H_5(CO)_2Mo]_2$	$Cl_3SiMo(CO)_2C_6H_5$	149–151	2041, 1976, 1959
$[C_6H_5(CO)_2Fe]_2$	$Cl_3SiFe(CO)_2C_6H_5$	128–130	2039, 1995
$[C_6H_5(CO)_2Ni]_2$	$Cl_3SiNi(CO)_2C_6H_5$	38–40	2062

^a In sealed tubes in the 100–180° temperature range using excess Cl_3SiH . ^b Products characterized by elemental analysis and mass spectrum. In several cases other products are formed which have not yet been fully characterized. ^c Kofler hot-stage microscope. ^d In cyclohexane solution.

but the formation of $Cl_3SiMn(CO)_5$ is almost quantitative. On the basis of their infrared spectra, the products are structurally analogous to known derivatives of germanium, tin, and lead. It may be noted that silicon-molybdenum and silicon-nickel bonds have not been reported previously.

The trichlorosilyl derivatives of Table I are of interest in view of the numerous compounds of the trichlorostannyl ligand now known. The latter is regarded as a strong π acceptor and a weak σ donor.³ Strong π -acceptor character for the Cl_3Sn ligand is also consistent with trends in CO stretching force constants in $Cl_3SnMn(CO)_5$ and related compounds, as we have pointed

(1) W. Jetz, P. B. Simons, J. A. J. Thompson, and W. A. G. Graham, *Inorg. Chem.*, **5**, 2217 (1966).

(2) A. J. Chalk and J. F. Harrod, *J. Am. Chem. Soc.*, **87**, 1133 (1965).

(3) R. V. Lindsay, Jr., G. W. Parshall, and V. G. Stolberg, *ibid.*, **87**, 658 (1965); G. W. Parshall, *ibid.*, **88**, 704 (1966).

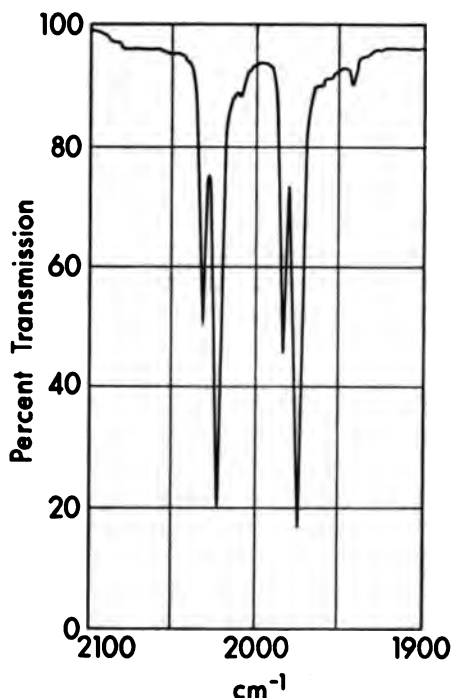


Figure 1. Carbonyl region of the infrared spectrum of $\text{CH}_3\text{Cl}_2\text{SiFe}(\text{CO})_2\text{C}_6\text{H}_5$. Precise band positions are 2031, 2022, 1983, and 1973 cm^{-1} (cyclohexane solution, about 1 mg/ml, 0.5-mm cells).

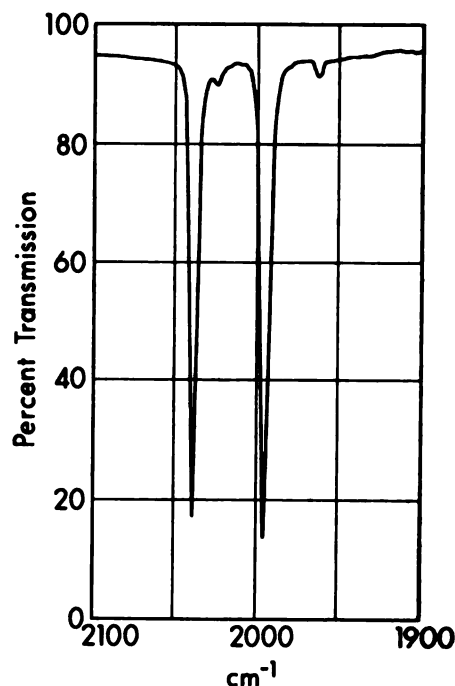


Figure 2. Carbonyl region of the infrared spectrum of $\text{Cl}_2\text{SiFe}(\text{CO})_2\text{C}_6\text{H}_5$. Precise band positions are 2039 and 1995 cm^{-1} (cyclohexane solution, about 1 mg/ml, 0.5-mm cells).

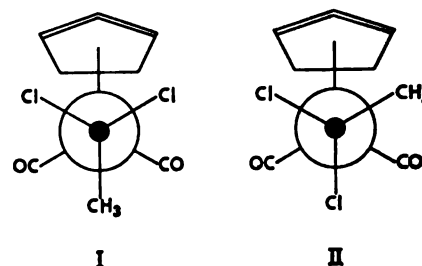
out.¹ We have now extended the force constant approach to the corresponding Cl_2Si and Cl_2Ge^4 compounds and conclude that *there is little difference among Cl_2Si , Cl_2Ge , and Cl_2Sn as ligands.*⁵ We suggest that the Cl_2Sn group is not unique, except for the ease with which it may be generated in reactions with tin(II) chloride.

Reactions with methyldichlorosilane yield methyldichlorosilyl analogs of many of the compounds of Table I. The infrared spectra of these methylsilyl derivatives reveal some unexpected features in the form of "extra" terminal carbonyl bands. The most striking example is provided by $\text{CH}_3\text{Cl}_2\text{SiFe}(\text{CO})_2\text{C}_6\text{H}_5$, of which the spectrum is shown in Figure 1. The spectrum of $\text{Cl}_2\text{SiFe}(\text{CO})_2\text{C}_6\text{H}_5$ is shown in Figure 2 for comparison. Repeated crystallization and fractional sublimation of the methyl derivative does not alter its spectrum, and its molecular weight in cyclohexane is normal (calculated, 291; found (osmometer), 294). Moreover, the nmr spectrum at 33° shows only two sharp peaks at τ 6.2 and 9.3 in a 5:3 ratio.⁶

The appearance of more than two CO stretching bands for a compound having only two CO groups leads one to postulate that isomers are present. We believe that these are most likely to be the two conformations of the molecule shown in Newman projection as I and II. Rapid interconversion would account for the

simple nmr spectrum. The phenomenon is being studied in greater detail, and a similar effect has been observed in organotin derivatives such as $\text{CH}_3\text{Cl}_2\text{SnFe}(\text{CO})_2\text{C}_6\text{H}_5$.⁷

Isomerism of the tautomeric type, involving equilibria between bridged and nonbridged forms, is well established in metal carbonyls and certain of their deriva-



tives.⁸ The present communication, however, is the first report of a *conformational* effect on terminal metal carbonyl frequencies.^{9,10} The generality of this phenomenon remains to be established, but it should evidently be borne in mind when a choice between structures is being made on the basis of predicted and observed numbers of carbonyl stretching bands.

(7) Research in progress in this laboratory by Mr. James Hoyano.

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(9) The doubling of acyl carbonyl frequencies in compounds of the type $\text{CXH}_2\text{COMn}(\text{CO})_5$ (F. Calderazzo, K. Noack, and U. Schaefer, *ibid.*, **6**, 265 (1966)) is entirely analogous to that produced by rotational isomerism in conventional organic ketones.

(10) A referee has drawn attention to the fact that four strong carbonyl bands were observed by R. B. King in the compound $\pi\text{-C}_6\text{H}_5\text{Fe}(\text{CO})_2\text{Mo}(\pi\text{-C}_6\text{H}_5)$: *Inorg. Chem.*, **5**, 2242 (1966). This was attributed by King to a kind of *cis-trans* isomerism involving a bidentate π -allyl group. We agree with the referee's suggestion that isomerism in the π -allyl case may arise from a conformational effect very similar to what is suggested here; i.e., in I and II, replace Cl by CH_3 , CH_3 by H, Si by C, and Fe by Mo. This viewpoint implies that the π -allyl group is monodentate in character, presumably with some freedom of rotation about the π -allyl-metal bond.

(4) The compound $\text{Cl}_2\text{GeMn}(\text{CO})_5$ has been prepared from Cl_2GeH and $\text{Mn}_2(\text{CO})_{10}$: A. N. Nesmeyanov, K. N. Anisimov, N. E. Kolobova, and A. B. Antonova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1284 (1965). We prepared it by reaction of chlorine with $(\text{C}_6\text{H}_5)_2\text{GeMn}(\text{CO})_5$, and observe $\nu(\text{CO})$ at 2130 (m), 2048 (s), 2038 (m) cm^{-1} in cyclohexane.

(5) Actual values of the approximate force constants (mdynes/A) are: $\text{Cl}_2\text{SiMn}(\text{CO})_5$, $k_1 = 16.86$, $k_2 = 17.17$, $k_t = 0.222$; $\text{Cl}_2\text{GeMn}(\text{CO})_5$, $k_1 = 16.90$, $k_2 = 17.36$, $k_t = 0.210$; $\text{Cl}_2\text{SnMn}(\text{CO})_5$, $k_1 = 16.91$, $k_2 = 17.31$, $k_t = 0.204$. For an explanation of nomenclature and fuller discussion, see ref 1.

(6) Attempts to measure the low-temperature nmr spectrum have not as yet been successful because of the tendency of solutions of the compound to become very viscous at about -20° .

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**Crystal Structure of $\text{HRe}_2\text{Mn}(\text{CO})_{14}$:
Neutral, "Electron-Deficient," Polynuclear
Carbonyl Hydride¹**

The reduction of $\text{Mn}_2(\text{CO})_{10}$ or $\text{Re}_2(\text{CO})_{10}$ with NaBH_4 subsequent acidification has given rise to an unusual group of polynuclear carbonyl hydrides: $\text{H}_2\text{Re}_2(\text{CO})_{12}$,² $\text{H}_2\text{Mn}_2(\text{CO})_{12}$,³ $\text{H}_7\text{B}_2\text{Mn}_2(\text{CO})_{10}$,³ and $\text{H}_2\text{Re}_2(\text{CO})_{14}$.^{4a} Only one of these complexes, $\text{H}_7\text{B}_2\text{Mn}_2(\text{CO})_{10}$, has so far been examined crystallographically,³ although attempts have been made to determine the structure of $\text{H}_2\text{Re}_2(\text{CO})_{12}$.⁶ We now wish to report the structure of $\text{HRe}_2\text{Mn}(\text{CO})_{14}$,^{4b} which no doubt will be closely related to $\text{HRe}_2(\text{CO})_{14}$.⁷

$\text{HRe}_2\text{Mn}(\text{CO})_{14}$ crystallizes in the monoclinic space group $\text{P}2_1/\text{n}$ (No. 14) with $a = 9.31$, $b = 15.82$, $c = 10.14$ Å, $\beta = 106.4^\circ$, $V = 2032$ Å³; $\rho_{\text{obsd}} = 2.64$ g/cm³ ($\rho_{\text{calcd}} = 2.68$ g/cm³ for $Z = 4$, $M = 820$). A single-crystal X-ray crystallographic analysis, based on complete three-dimensional data (Mo $\text{K}\alpha$; $\sin \theta_{\text{max}} = 25^\circ$) was collected with a Buerger automated diffractometer, and to the location of all nonhydrogen atoms. The final discrepancy index is $R_F = 10.39\%$ for the 2100 unique reflections. The over-all geometry of the molecule is shown in Figure 1. The metal atoms are in a non-linear configuration, the $\text{Re} \cdots \text{Re}-\text{Mn}$ angle is 98.1° . The $\text{Re}-\text{Mn}$ bond length of 2.960 Å is in good agreement with the value of 2.97 Å predicted from the $\text{M}-\text{M}$ distances in $\text{M}_2(\text{CO})_{10}$ ($\text{Mn}-\text{Mn} = 2.93$ Å, $\text{Re}-\text{Re} = 3.02$ Å). However, the $\text{Re} \cdots \text{Re}$ distance of 3.39 Å in $\text{HRe}_2\text{Mn}(\text{CO})_{14}$ is ~ 0.37 Å longer than a normal $\text{Re}-\text{Re}$ single bond. It is proposed that the hydrogen atom known¹⁰ to be present in $\text{HRe}_2(\text{CO})_{14}$ occupies a bridging position between the two rhenium atoms. The otherwise normal octahedral coordination of the rhenium atoms leads us to believe

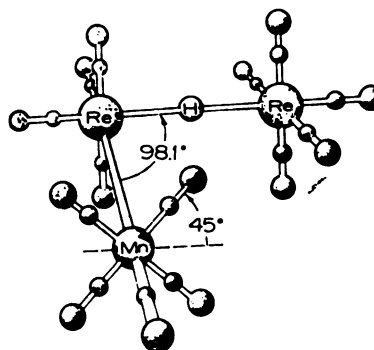


Figure 1. The stereochemistry of $\text{HRe}_2\text{Mn}(\text{CO})_{14}$.

that the $\text{Re}-\text{H}-\text{Re}$ bridge is probably linear [a similar scheme has been suggested for the $\text{HCr}_2(\text{CO})_{10}^-$ ion¹¹]. If a symmetrical, linear $\text{Re}-\text{H}-\text{Re}$ linkage is assumed, then the resulting $\text{Re}-\text{H}$ distance of 1.695 Å is in remarkably good agreement with the $\text{Re}-\text{H}$ distance of 1.68 ± 0.01 Å determined by a neutron-diffraction study¹² of K_2ReH_6 .

An interesting observation in the present study is that the carbonyls in the $(\text{OC})_4\text{Re}-\text{Mn}(\text{CO})_6$ portion of the molecule are in a strictly staggered conformation (as are those in $\text{Mn}_2(\text{CO})_{10}$,⁸ $\text{Cr}_2(\text{CO})_{10}$,¹³ and, presumably, the isomorphous⁹ $\text{Re}_2(\text{CO})_{10}$), whereas the carbonyl groups in the hydrogen-bridged portion of the molecule are in an eclipsed configuration. (The author's drawing of the $\text{HCr}_2(\text{CO})_{10}^-$ ion¹¹ indicates that this too adopts an eclipsed configuration.) Furthermore, the sets of radial carbonyl groups in the $(\text{OC})_4\text{Mn}-\text{Re}(\text{CO})_6$ moiety bend slightly toward each other, a feature noted also for $\text{Mn}_2(\text{CO})_{10}$ ⁸ and $\text{Cr}_2(\text{CO})_{10}$.¹³

The structure of $\text{HRe}_2\text{Mn}(\text{CO})_{14}$ taken together with the chemistry (treatment of this compound with CO gives $\text{HRe}(\text{CO})_6$ and $\text{MnRe}(\text{CO})_{10}$)⁴ suggests a description of the bonding which correlates the two. The $\text{HRe}(\text{CO})_6$ unit might be regarded as a neutral ligand in a radial position on $\text{LMnRe}(\text{CO})_9$ held through hydrogen bridging *via* a two-electron three-center bond.¹⁴ More extensive studies on $\text{HRe}_2(\text{CO})_{14}$ strengthen this idea: ¹³C-enriched CO reacts with $\text{HRe}_2(\text{CO})_{14}$ to produce $\text{Re}_2(^{13}\text{CO})_8(^{13}\text{CO})_2$, with the ¹³CO group in the radial position.¹⁵ CH_3CN and $(\text{C}_6\text{H}_5)_3\text{P}$ similarly give monosubstituted derivatives $\text{LRe}_2(\text{CO})_9$ but with $(\text{C}_6\text{H}_5)_3\text{P}$ axial substitution is observed.¹⁶

The concept of a neutral transition metal hydride acting as a ligand in metal complexes suggests the formulas of a large class of electron-deficient polynuclear metal hydrides. A few such possibilities based on known complex hydrides and known carbonyls would be: $(\text{OC})_6\text{ReH}\cdot\text{M}(\text{CO})_6$ and $(\pi\text{-C}_5\text{H}_5)_2\text{ReH}\cdot\text{M}(\text{CO})_6$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$), $(\text{OC})_4\text{CoH}\cdot\text{Fe}(\text{CO})_4$, or $\text{L}_2(\text{X})\text{PtH}\cdot\text{M}(\text{CO})_{n-1}$ [where $\text{M}(\text{CO})_n$ is any of a number of known carbonyls]. These compounds would be

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(12) S. C. Abrahams, A. P. Ginsberg, and K. Knox, *Inorg. Chem.*, **3**, 558 (1964).

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a) W. Fellmann and H. D. Kaesz, *Inorg. Nucl. Chem. Letters*, **2**, 166. (b) $\text{HRe}_2\text{Mn}(\text{CO})_{14}$ is obtained in 10% yield by acidification of a mixture of $\text{NaMn}(\text{CO})_6$ and a salt containing lower carbonyl of rhenium (obtained from the treatment of $\text{Re}_2(\text{CO})_{10}$ with C_4H_8 in tetrahydrofuran).

H. D. Kaesz, W. Fellmann, G. R. Wilkes, and L. F. Dahl, *J. Am. Chem. Soc.*, **87**, 2753 (1965).

We have examined crystals of $\text{H}_2\text{Re}_2(\text{CO})_{12}$, but have not yet found one which gives an interpretable diffraction pattern. Professor Dahl has informed us that he has encountered similar difficulties with $\text{H}_2\text{Re}_2(\text{CO})_{12}$ and $\text{H}_2\text{Mn}_2(\text{CO})_{12}$.

The structure of $\text{HRe}_2(\text{CO})_{14}$ is under investigation in the laboratory of Professor L. F. Dahl.

L. F. Dahl and R. E. Rundle, *Acta Cryst.*, **16**, 419 (1963).

L. F. Dahl, E. Ishishi, and R. E. Rundle, *J. Chem. Phys.*, **26**, 1750

The number of hydrogen atom(s) in this and the above-mentioned complexes has been confirmed by calibrated mass spectra: J. M. K. Mehner, and H. D. Kaesz, *J. Am. Chem. Soc.*, **89**, 1759

related by loss of a proton to the corresponding polynuclear carbonyl anions¹⁷ and could, therefore, in some cases be very strong proton-releasing acids. The electron-deficient polynuclear carbonyl hydrides would also be isoelectronic with polynuclear protonated metal carbonyl species such as $(\pi\text{-C}_5\text{H}_5)(\text{CO})_2\text{FeHMn}(\text{CO})_5^+$ or $(\pi\text{-C}_5\text{H}_5)(\text{CO})_2\text{WHW}(\text{CO})_2(\pi\text{-C}_5\text{H}_5)^+$ reported by Wilkinson and co-workers.¹⁸ The question of the placement of the hydrogen atoms is the same in these two classes of compound.

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(19) Work performed during the temporary residence of R. B. and sabbatical leave residence of H. D. K. at Harvard University.

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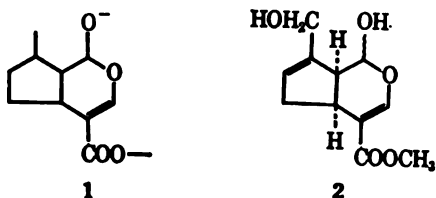
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The Total Synthesis of Racemic Genipin

Sir:

Since the pioneering work of Schmid on the structure of plumieride,¹ the group of monoterpenes containing part structure 1 has rapidly expanded. The suggestion² that such compounds are intermediates in the biosynthesis of indole alkaloids has recently been supported by preliminary experiments³ which, however, need confirmation with multiply labeled compounds. Until now no member of this class of natural products has been prepared from the elements, but the present communication reports on a synthesis of genipin (2).⁴



The bicyclic ethyl ester 3⁵⁻⁷ on base hydrolysis was transformed to the acid 4, mp 53–55° (lit.⁸ mp 51–52°). Reduction with lithium in liquid ammonia followed by esterification with methanol in the presence of *p*-toluenesulfonic acid afforded a mixture of methyl esters containing approximately 90% of 5.

When the diene 5 was treated with osmium tetroxide in dimethylformamide and the resulting osmate ester cleaved with hydrogen sulfide,⁹ a crystalline tetrol (6), mp 163–165°, was formed in 50% yield. Although

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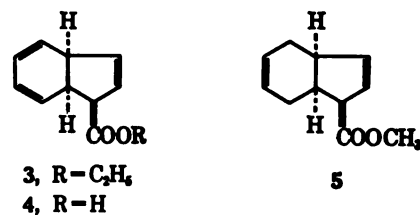
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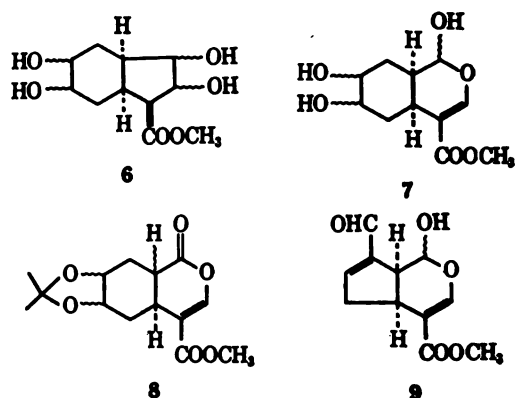
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this material was a mixture of two epimers it was directly for further transformation. Taking advantage of earlier work which demonstrated that *cis*-cyclopentane-1,2-diols are cleaved much more rapidly than *cis*-1,2-cyclohexanediols,¹⁰ a mixture of tetrols 6 was exposed to 1 equiv of this agent in glacial acetic acid solution. Oxidation complete within seconds and chromatography of the resulting mixture of products gave three triols: 7a [11%; mp 156–157°; infrared absorptions (KBr) 3550, 1700, 1640 cm^{-1} ; ultraviolet absorption (EtOH) 240 $\text{m}\mu$ (ϵ 10,500), in 0.01 *N* NaOH 273 (ϵ 19,000)], 7b [12%; mp 176–177°; infrared absorptions (KBr) 3500, 3355, 1690, 1635 cm^{-1} ; ultraviolet absorptions same as those of 7a], and 7c [22%; mp 202–208°; infrared absorptions (KBr) 3425, 1690, 1635 cm^{-1} ; ultraviolet absorptions same as those of 7a]. Investigations aimed at clarifying configurations of the three triols 7 are incomplete. Isomers 7a and 7b on consecutive treatments with tone and with dicyclohexylcarbodiimide–dimethyl oxide¹¹ yielded the same lactone, 8, mp 109–110° having infrared and ultraviolet absorptions identical with those of 7a. This tentatively indicates that the triols differ only in the configuration of the hemiacetal carbon atom. Triol 7c did not yield an acetonide and was quantitatively cleaved by periodic acid.



The resulting crude dialdehyde was cyclized by the agency of piperidine acetate,¹² and the desired bicyclic aldehyde 9 was obtained in 68% yield in the form of a liquid with infrared absorptions (CHCl_3) at 2800, 1670, 1630 cm^{-1} . Reduction of the aldehyde 9 with lithium tri-*t*-butoxyaluminumhydride¹³ in ether afforded racemic genipin (2), mp 116–117°. Identity with natural genipin¹⁴ was established by comparison of infrared

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(14) We are grateful to Professor C. Djerassi, Stanford University, for a sample of natural genipin.

violet, mass,¹⁵ and proton spectra as well as by the use of genipin to produce an inefaceable blue color applied to skin.¹⁶ An identical series of reactions served in the transformation of triol 7b to racemic in (2).

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Mass spectra were measured in the laboratory of Professor K. L. McEwen, Massachusetts Institute of Technology. C. Djerassi, J. D. Gray, and F. A. Kincl, *J. Org. Chem.*, **25**, 1960).

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Luminescence of Iridium(III) Chelates with 2,2'-Bipyridine and with 1,10-Phenanthroline

A few complexes of transition metal ions having a partially filled d shell are luminescent in fluid solutions. A notable exception is the tris(1,10-phenanthroline)iridium(II) ion; this species and several other Ru(II) complexes with some similar ligands were first reported to be luminescent by Brandt and co-workers.^{1,2} Paris and Brandt³ assigned the bands in the absorption spectrum of the tris(2,2'-bipyridine)ruthenium(II) ion and concluded that the emission accompanied a ligand-to-metal charge-transfer ($\pi^* \rightarrow d$) transition. Later, weak absorption bands at 539 m μ (18,550 kK) and at 664 m μ (15,000 kK) were reported for the latter species and led to assignment of the luminescence as fluorescence associated with a ligand-field ($^1T_1 \rightarrow ^1A_1$) radiative transition.³ More recently other workers have concluded that there is no compelling reason to assign the luminescence of the tris(2,2'-bipyridine)ruthenium(II) ion to a ligand-field transition; indeed, there are several reasons against such an assignment.⁴

The present work describes luminescence from fluid solutions of the analogous iridium(III) chelates: tris(2,2'-bipyridine)iridium(III) ion, [Ir(bipy)₃]³⁺, and tris(1,10-phenanthroline)iridium(III) ion, [Ir(phen)₃]³⁺. A group theoretical classification of these chelates is given. The metallic ion is in an octahedral environment; however, these species are diamagnetic: the metallic ion has the low-spin d⁶ configuration and geometry analogous to the ruthenium(II) chelates. The emission is assumed to accompany charge-transfer transitions from ligand to the metal ion ($\pi^* \rightarrow d$), i.e., similar in kind to those assigned by Paris and Brandt for the luminescence of the Ru(II) chelates.¹

The ultraviolet-visible absorption spectra for the above species are shown in Figure 1. The absorption spectrum of 2,2'-bipyridine in concentrated sulfuric acid is included in Figure 1 because the diprotonated

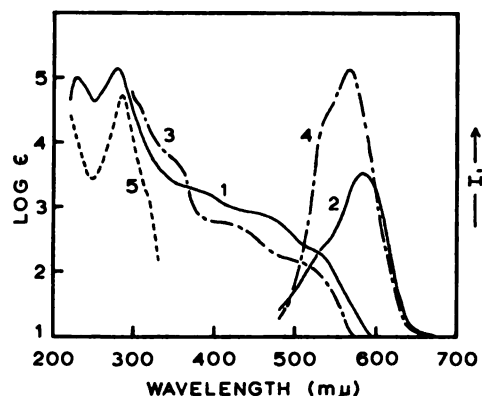


Figure 1. Absorption and luminescence spectra: (1) [Ir(bipy)₃]³⁺ absorption spectrum in DMF; (2) [Ir(bipy)₃]³⁺ luminescence spectrum in DMF, 370-m μ excitation; (3) [Ir(phen)₃]³⁺ absorption spectrum in DMF; (4) [Ir(phen)₃]³⁺ luminescence spectrum in DMF, 475-m μ excitation; (5) 2,2'-bipyridine absorption spectrum in concentrated H₂SO₄. I_L = luminescence intensity (in arbitrary units and corrected for variation of detector response with wavelength).

form most nearly approximates chelated 2,2'-bipyridine with respect to the energies of the intraligand ($\pi^* \leftarrow \pi$) transitions. Assignments of the absorption bands are given in Table I.

Table I. Absorption Band Assignments for 2,2'-Bipyridine and 1,10-Phenanthroline Chelates of Ir(III)

Compound	λ_{max} , m μ ^a	Log ϵ ^b	Assignment
2,2'-Bipyridine ^c [Ir(bipy) ₃] ³⁺ ^d	285	4.83	$\pi^* \leftarrow \pi$
	235	4.89	$\pi^* \leftarrow d$
	284	5.08	$\pi^* \leftarrow \pi$
	370 (s)	3.2	$\pi^* \leftarrow d$
	480 (s)	2.8	$\pi^* \leftarrow d$
[Ir(phen) ₃] ³⁺ ^d	515 (s)	2.3	$\pi^* \leftarrow d$
	<300	>4.7	$\pi^* \leftarrow \pi$
	310 (s)	4.4	$\pi^* \leftarrow \pi$
	350 (s)	3.7	$\pi^* \leftarrow d$
	430 (s)	2.7	$\pi^* \leftarrow d$
	520 (s)	2.1	$\pi^* \leftarrow d$

^a s = shoulder. ^b ϵ is molar absorptivity. ^c Solvent, concentrated H₂SO₄. ^d Solvent, dimethylformamide.

Jørgensen attributed bands in the range 285-345 m μ in the absorption spectra of 20 Ir(III)-pyridine complexes to ($\pi^* \leftarrow d$) charge-transfer transitions.⁵ Spectral studies of the tris(ethylenediamine)iridium(III) ion, [Ir(en)₃]³⁺, in solution show the lowest energy singlet $d^* \leftarrow d$ ($^1T_1 \leftarrow ^1A_1$) transition at 249 m μ and the lowest energy triplet ($^3T_1 \leftarrow ^1A_1$) transition at 302 m μ .⁶ Both 2,2'-bipyridine and 1,10-phenanthroline are placed above ethylenediamine in the spectrochemical series.⁷ Therefore, in [Ir(bipy)₃]³⁺ and [Ir(phen)₃]³⁺ the splitting of the several ligand field states will be larger than in [Ir(en)₃]³⁺, and more energy will be required to effect the $^1T_1 \leftarrow ^1A_1$ and $^3T_1 \leftarrow ^1A_1$ transitions. The energy required for a ligand-field transition in the 2,2'-bipyridine and 1,10-phenanthroline chelates of Ir(III) is estimated as approximately equal to the energy necessary for an intraligand ($\pi^* \leftarrow \pi$) transition and thus is greater than that for a charge-transfer ($\pi^* \leftarrow d$) transition. The luminescence of these Ir(III) chelates is therefore assigned to a $\pi^* \rightarrow d$ transition.

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Spectra of these Ir(III) complexes were obtained in dimethylformamide (DMF) and in ethyl alcohol solution. Solutions were prepared by dissolving the solid chelates $[\text{Ir}(\text{bipy})_2(\text{ClO}_4)_3]$ was prepared as previously described;⁸ $[\text{Ir}(\text{phen})_2(\text{ClO}_4)_3]$ was prepared in an analogous manner] and also by heating the stoichiometric amounts of the ligand and the metal ion (from iridium chloride) in refluxing ethyl alcohol for 96 hr or in refluxing DMF for 48 hr. Wavelengths of maximum absorption and emission of these Ir(III) chelates did not depend on the method of preparation or on the solvent. Relative luminescence quantum yields for the chelates (in DMF) were about an order of magnitude less than quinine fluorescence in 0.1 *N* H_2SO_4 ; the intensity of $[\text{Ir}(\text{phen})_2]^{3+}$ was approximately twice the intensity of $[\text{Ir}(\text{bipy})_2]^{3+}$.

Acknowledgment. The authors are grateful to the National Science Foundation for financial support (Grant GP-5449).

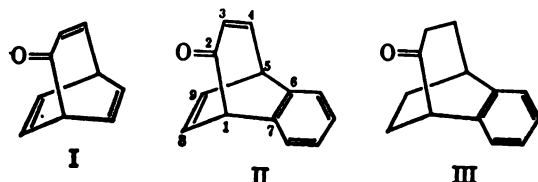
(8) B. Martin and G. M. Waind, *J. Chem. Soc.*, 4284 (1958).

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Reaction of Tropone with Benzyne. Formation and Photoisomerization of 6,7-Benzobicyclo[3.2.2]nona-3,6,8-trien-2-one

Sir:

As a vinylog of norbornadiene the bicyclo[3.2.2]nona-2,6,8-triene system and its unknown keto derivative I ("homobarrelenone") have elicited recent synthetic interest.¹ We wish to report the practical one-step synthesis of 6,7-benzobicyclo[3.2.2]nona-3,6,8-trien-2-one (II) by thermal addition of benzyne to tropone, and describe herewith a photochemical rearrangement of this adduct.



The thermal decomposition of a suspension of ~40 mmoles of *o*-benzenediazoniumcarboxylate² in a solution of 38 mmoles of tropone³ in anhydrous tetrahydrofuran at 36–37° under nitrogen for 17 hr produced after solvent removal a dark oil. Chromatography over magnesium silicate (benzene–ether) afforded a colorless crystalline adduct in 40% yield,^{4,7} purified by sublimation under reduced pressure (50–60°, 0.10 mm) or recrystallization from hexane, mp 83–84°. Structure II is assigned on the basis of the following data: mass

(1) M. J. Goldstein and A. H. Gevirtz, *Tetrahedron Letters*, 4413 (1965).

(2) The benzyne intermediate was generated *in situ* according to the Friedman⁵ modification of the Stiles⁴ procedure.

(3) L. Friedman, private communication.

(4) M. Stiles, R. G. Miller, and U. Burckhardt, *J. Am. Chem. Soc.*, 85, 1792 (1963).

(5) P. Radlick, *J. Org. Chem.*, 29, 960 (1964).

(6) A second uncharacterized product, isolated from the hexane–benzene eluates, was shown to be a 2:1 benzyne–tropone adduct by mass spectrometry (*m/e* 258).⁷

(7) The chromatographic medium used was Florisil synthetic adsorbent, a product of the Floridin Co.

Table I. Nuclear Magnetic Resonance Data

Positional assignment ^a	Chemical shift, ppm from TMS	Coupling constants, cps
5 (broad triplet)	4.19	$J_{5,4} =$ $J_{5,6} =$ $J_{5,8} =$ $J_{5,9} =$
1 (doublet of triplets)	4.59	$J_{1,2} =$ $J_{1,3} =$ $J_{1,4} =$ $J_{1,5} =$
3 (doublet of quartets)	5.17	$J_{3,4} =$ $J_{3,1} =$ $J_{3,5} =$ $J_{3,6} =$
8 (septet)	6.49	$J_{8,9} =$ $J_{8,1} =$ $J_{8,5} =$ $J_{8,6} =$
9 (septet)	6.84	$J_{9,8} =$ $J_{9,5} =$ $J_{9,6} =$ $J_{9,1} =$
4 (doublet of doublets)	7.15	$J_{4,3} =$ $J_{4,5} =$
Aromatics (4 H) (complex pattern)	~7.13	

^a The positional assignments for hydrogens 8 and 9 were by spin decoupling measurements with hydrogens 1 and 5, tively. ^b The reported *J* values determined from 100-cps width spectra are accurate to ± 0.1 cps.

spectral data: *m/e* 182, 181, 154, 153, 152, 128 (cm^{-1}) 3070 (m), 3040 (m), 2970 (m), 1675 (s), 1614 (m), 1455 (w), 1375 (m), 1320 (w), 1280 (cm^{-1}) 225 (ϵ 5720), 263 (704), 351 (137); $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ (m μ) 225 (ϵ 5720), 263 (704), 351 (137); 210 (18,700), 225 (sh) (5620), 263 (743), 331 (sh) 344 (113), 357 (151), 373 (136), 388 (sh) (64); nmr (CDCl_3), see Table I.⁸ Anal. Calcd for C_{11}H_8 , C, 85.70; H, 5.53; mol wt, 182. Found: C, H, 5.41; mol wt, 188 (osmometric in CHCl_3).

Chemical evidence for structure II was provided by rapid uptake of 2 molar equiv of hydrogen in the presence of palladium on carbon as catalyst to afford the hydro derivative III as a colorless oil.⁹ mass spectral data: *m/e* 186, 142, 130, 129, 128; $\nu_{\text{max}}^{\text{CCl}_4}$ (cm^{-1}) (w), 3025 (w), 2930 (s), 2870 (m), 1710 (s), 1490 (w), 1465 (m), 1430 (w); $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ (m μ) 264 (ϵ 465), 271 (308); $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 259 (sh) (378), 264 (454), 272 (308), 282 (174), 292 (192), 301 (198), 311 (160), 322 (174), 292 (192), 301 (198), 311 (160), 322 (174); nmr (CCl_4) (ppm): 1.94 (6 H, multiplet), 2.14 (multiplet, $-\text{CH}_2\text{C}(\text{O})-$), 3.23 (1 H, broad multiplet, position 5), 3.47 (1 H, multiplet, position 1), 7.13 (singlet, aromatics). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{O}$, C, 83.83; H, 7.57. Found: C, 84.06; H, 7.58.

The 1,4 addition of benzyne to tropone is consistent with the reported reaction of maleic anhydride with phenylmaleimide with tropone.¹⁰ On the other hand, the reaction of dimethyl acetylenedicarboxylate with tropone proceeds through the bicyclo[4.1.0]heptadienone tautomer.¹¹

(8) The nmr spectra were recorded with a Varian A-60-A spectrometer equipped with a Model V-6058A spin decoupler. Mass spectra were recorded on a Hitachi RMU-6D spectrometer. The infrared and ultraviolet data were taken on a Perkin-Elmer Model 337 spectrophotometer and a Cary Model 14 spectrophotometer, respectively. The A-60-A and RMU-6D spectrometers were purchased through a National Science Foundation major equipment grant to Brown University.

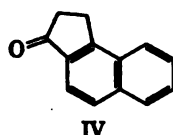
(9) Purified by short-path distillation at 130° (1.1 mm).

(10) J. Meinwald, S. L. Emerman, N. C. Yang, and G. J. Am. Chem. Soc., 77, 4401 (1955).

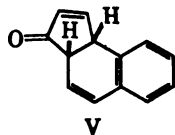
(11) H. J. Dauben and T. J. Pratt, Abstracts of Papers, 153rd Meeting of the American Chemical Society, Miami, Fla., Apr 1967.

irradiation of adduct II by a medium-pressure mercury lamp (glass filter, acetonitrile solvent, 20°, nitrogen atmosphere) resulted in the gradual formation of a carbonyl maximum near 1704 cm^{-1} with a concomitant decrease in the original carbonyl peak at 1675 cm^{-1} . Silica gel chromatography of the reaction products, followed by sublimation at 80° of the principal chromatographic fraction, gave a new crystalline compound: mp $119\text{--}120^\circ$; mass spectrum: m/z 182, 153, 126, 76; $\nu_{\text{max}}^{\text{CHCl}_3}$ 1707 cm^{-1} ; $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 250 (ϵ 61,800), 274 (8700), 284 (10,200), 296 (6600), 2930 , 342 (3250); nmr spectrum: A_2B_2 pattern with δ_A 2.85, δ_B 3.32, and an aromatic multiplet at δ 7.5–8.2. Anal. Calcd for $C_{13}H_{10}O$: C, 85.70; H, 5.33; mol wt, 182. Found: C, 85.99; H, 5.75. Consistent with the fact that sodium borohydride reduction of the photoproduct generated the ultraviolet spectrum of 1,2-dialkyl-naphthalene, the above data require the photoisomer to contain a conjugated ketone within a five-membered ring fused to the naphthalene nucleus.

Three such ketones are possible; all are known except isomer IV (lit. mp $120\text{--}121^\circ$) is compatible with the observed melting point. Moreover, the highly purified ultraviolet spectrum of the photoproduct is impossible with that depicted for authentic ketone and identity was confirmed by comparison with authentic sample.



IV



V

It can be shown spectroscopically that ketone IV is present in the photolysis solution during irradiation and can be instantly generated therein by addition of

We propose that the primary step in the photoisomerization is the rearrangement of II to the diolefinic isomer V,¹² with ultimate isomerization to the aromatic ketone taking place during the work-up procedure. Further studies of the ground-state and excited-state chemistry and its derivatives are in progress.

R. Huisgen and U. Rietz, *Tetrahedron*, **2**, 274 (1958). We are indebted to Professor Huisgen for providing us with a sample of ketone prepared by Friedel-Crafts cyclization of β -(1-naphthyl)propionic

The photoequilibrium between 1,4,4-trimethylbicyclo[3.2.0]hept-2-one and 4,4,6-trimethylbicyclo[3.2.0]hept-6-en-2-one described by G. Büchi and E. M. Burgess (*J. Am. Chem. Soc.*, **82**, 4333) may offer formal analogy to this type of isomerization.

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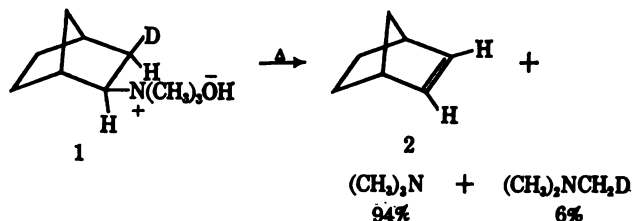
Hofmann Elimination. I. An Example of a *cis*-E2 Mechanism¹

Hofmann elimination of quaternary ammonium hydroxides to give olefins has long been thought to

This work was supported in part by a Public Health Service Research Grant, HE 07050, from the National Heart Institute, U. S. Health Service.

proceed by a *trans* elimination.² Only two proven exceptions to this have been reported. One of these involves a *cis*-E2 elimination of N,N,N-trimethyl-*trans*-2-phenylcyclohexylammonium hydroxide to give 1-phenylcyclohexene.³ This *cis* elimination presumably takes place because of the activating influence of the phenyl group on the β proton (increased acidity). The other exception involves a predominantly *cis*-ylide elimination of N,N,N-trimethyl-2-*t*-butyl-3,3-dimethylbutylammonium-2-*d*₁ hydroxide to give trimethylamine-*d*₁.⁴

We wish to report an example of a *cis*-E2 elimination mechanism involving a trimethylammonium hydroxide in which there is no activating group other than the trimethylammonium group. It has been shown⁵ that N,N,N-trimethyl-*exo*-2-norbornylammonium hydroxide is smoothly converted to norbornene on heating. We have examined this reaction and find that it proceeds by a *cis*-E2 elimination, as deduced from the following evidence. 2-*exo*-Norbornylamine-3-*exo*-*d*₁ (bp $159\text{--}163^\circ$ (760 mm); n_D^{25} 1.4752; acetamide mp $141.5\text{--}142.5^\circ$) was prepared from norbornene using diborane-*d*₆ and chloramine⁶ and was then converted consecutively by standard procedures to N,N-dimethyl-2-*exo*-norbornylamine-3-*exo*-*d*₁ (bp $50\text{--}52^\circ$ (6 mm); n_D^{25} 1.4690), N,N,N-trimethyl-2-*exo*-norbornylammonium-3-*exo*-*d*₁ iodide (mp $297\text{--}299^\circ$), and then to the hydroxide 1. Compound 1 was heated (as the dry solid) at 120° under vacuum until trimethylamine could just be detected in the vapors. This initially produced trimethylamine was analyzed by mass spectrometry⁷ and was found to contain 6% trimethylamine-*d*₁. When the pyrolysis was carried to completion the total trimethylamine was found to contain 17% trimethylamine-*d*₁, with the last traces of vapors containing 21% trimethylamine-*d*₁. This increase in incorporation of deuterium into the trimethylamine after the initial stages of the reaction has been studied by Cope and co-workers⁸ and is due to exchange between the methyl hydrogens of the quaternary hydroxide and the water (containing some deuterium) produced during the reaction. In another experiment the pyrolysis of 1 was carried to completion and the norbornene (2) that was formed was purified and examined by nmr and mass



- (2) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960).
- (3) G. Ayrey, E. Buncel, and A. N. Bourns, *Proc. Chem. Soc.*, 458 (1961); A. C. Cope, G. A. Berchtold, and D. L. Ross, *J. Am. Chem. Soc.*, **83**, 3859 (1961); S. J. Cristol and F. R. Stermitz, *ibid.*, **82**, 4692 (1960); J. Weinstock and F. G. Bordwell, *ibid.*, **77**, 6706 (1955); R. T. Arnold and P. N. Richardson, *ibid.*, **76**, 3649 (1954).
- (4) A. C. Cope and A. S. Mehta, *ibid.*, **85**, 1949 (1963).
- (5) A. C. Cope, E. Ciganek, and N. A. LeBel, *ibid.*, **81**, 2799 (1959).
- (6) H. C. Brown, W. R. Heydkamp, E. Breuer, and W. S. Murphy, *ibid.*, **86**, 3565 (1964); H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, p 130. The fact that we find total loss of deuterium on Hofmann elimination precludes the possibility of scrambling at the chloramine reaction stage.
- (7) For the method used see A. S. Mehta, Ph.D. Thesis, Massachusetts Institute of Technology, 1963.
- (8) A. C. Cope, N. A. LeBel, P. T. Moore, and W. R. Moore, *J. Am. Chem. Soc.*, **83**, 3861 (1961).

spectrometry. Integration of the nmr spectrum (using the C-7-methylene protons as an internal standard) indicated the norbornene (2) contained no deuterium, and the mass spectrum confirmed this. All compounds up through the hydroxide 1 were shown to contain one deuterium/molecule by mass spectrometry and nmr spectroscopy.

The fact that the trimethylamine formed from the initial stages of Hofmann elimination of 1 contains 6% trimethylamine- d_3 indicates this reaction proceeds to the extent of not more than 6% by an ylide mechanism. The remaining 94% of the reaction proceeds by some other reaction path, and this can be determined by the following arguments. An E1cb mechanism in this case is unlikely.³ Equilibration of 1 to give the corresponding *endo* isomer followed by *trans* elimination is also ruled out since it has been shown that the *endo* isomer gives only a trace of norbornene.⁵ The only remaining possible mechanism is thus a *cis*-E2 elimination, and this mechanism accounts for 94% of the reaction product. This is analogous to dehydrohalogenations of 2,3-dihalonorbornanes.⁹

The factors affecting this reaction, its occurrence in aliphatic and other alicyclic systems, and the effect of solvents on the mechanism of the reaction will be examined in a full paper.

(9) N. A. LeBel, P. D. Beirne, E. R. Karger, J. C. Powers, and P. M. Subramanian, *J. Am. Chem. Soc.*, **85**, 3199 (1963).

(10) Koppers Fellow, 1966; Shell Fellow, 1966-1967.

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Received February 13, 1967

Polar Additions to Olefins and Acetylenes.

IV. Evidence for Synchronous C-H and C-Cl Bond Formation in the *trans* Addition of Hydrogen Chloride to 3-Hexyne¹

Sir:

A somewhat confusing picture has developed regarding the stereochemistry of acid additions to acetylenes. These additions were once thought to be stereospecific *trans* processes based on studies of acetylenecarboxylic acid derivatives,² but recent studies have shown that 3-hexyne adds trifluoroacetic acid nonstereospecifically³ and that the hydrochlorination of 1-phenylpropyne in acetic acid yields a mixture of *cis* and *trans* adducts.⁴ Nonstereospecific addition is readily understood if vinyl cations 1 are formed as intermediates in these additions, and for additions in polar media there is substantial evidence⁵ to support this hypothesis. The factors leading to stereospecific *trans* addition are less clear. One possibility is that a slow protonation leads to a bridged cation (or π complex) 2 which then collapses rapidly to *trans* adduct. Another explanation, analogous to that pro-

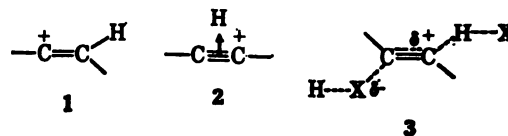
(1) Acknowledgment is made to the U. S. Army Research Office (Durham) and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) R. Friedrich, *Ann.*, **219**, 320, 368 (1883); A. Michael, *J. Prakt. Chem.*, [2] **46**, 209, 289 (1895); A. Michael and G. H. Scadinger, *J. Org. Chem.*, **4**, 128 (1939); G. Drefahl and C. Zimmer, *Ber.*, **93**, 505 (1960).

(3) P. E. Peterson and J. E. Dudley, *J. Am. Chem. Soc.*, **88**, 4990 (1966).

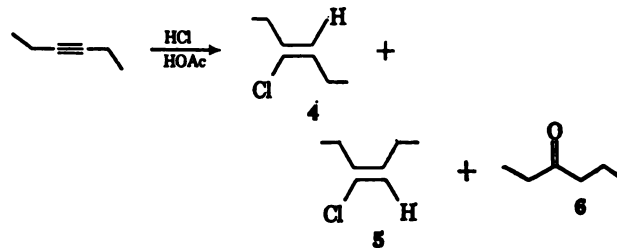
(4) R. C. Fahey and D. J. Lee, *ibid.*, **88**, 5555 (1966).

(5) See D. S. Noyce, M. A. Matesich, M. D. Schiavelli, and P. E. Peterson, *ibid.*, **87**, 2295 (1965), and references therein.



posed by Hammond⁶ for olefins, is that *trans* addition occurs *via* transition state 3 in which the C-H and C-X bonds are simultaneously formed. We report here studies of the hydrochlorination of 3-hexyne in acetic acid which show that *trans* addition can occur *via* the latter process.

The hydrochlorination of 3-hexyne in acetic acid yields 3-chloro-*trans*-3-hexene⁷ (4), 3-chloro-*cis*-3-hexene (5), and 3-hexanone (6), the latter undoubtedly formed *via* the intermediate vinyl acetate.^{4,8} The reaction was



followed by quenching samples of the reaction mixture in water, extracting three times with pentane, and analyzing the pentane fraction by vpc. Control experiments showed that 4, 5, and 6 are stable under the reaction conditions, that no fractionation occurs in the work-up, and that 4, 5, and 6 comprise >95% of the total product. The reaction was studied in the presence and absence of tetramethylammonium chloride (TMAC), and initial rates, *R*, for total product formation and product compositions were determined at less than 10% conversion. The results are presented in Table I. To these may be added the observations that, in the absence of both TMAC and HCl or in the presence of TMAC and absence of HCl, no reaction occurs.

Table I. The Hydrochlorination of 3-Hexyne in Acetic Acid at 25.0°^a

[HCl], <i>M</i>	[TMAC], <i>M</i>	10 ³ <i>R</i> , <i>M sec</i> ⁻¹	Product composition, %		
			4	5	6
0.49	...	0.30	42	≤1	58
0.78	...	0.81	48	≤1	52
1.14	...	2.0	58	≤1	42
0.60	0.054	3.0	91	≤0.2	9
0.60	0.11	5.8	94	≤0.2	6
0.60	0.21	11	96	≤0.2	4
0.78	0.21	16	97	≤0.2	3
0.38	0.21	5.7	96	≤0.2	4
0.19	0.21	2.3	97	≤0.2	3

^a 3-Hexyne concentration 0.81 *M*.

Under identical reaction conditions the steric course of addition to 1-phenylpropyne and to 3-hexyne is strikingly different: 1-phenylpropyne yields a mixture of adducts with the *cis* hydrochloride predominating, while 3-hexyne gives nearly equal amounts of ketone and *trans* hydrochloride but only a trace of *cis* hydrochloride. It is found that 3-hexyne reacts about three-

(6) G. S. Hammond and T. D. Nevitt, *ibid.*, **76**, 4121 (1954); G. S. Hammond and C. H. Collins, *ibid.*, **82**, 4323 (1960).

(7) Authentic samples were prepared as described previously: M. C. Hoff, K. W. Greenlee, and C. E. Boord, *ibid.*, **73**, 3329 (1951).

(8) E. A. Jefferey and D. P. N. Satchell, *J. Chem. Soc.*, 1876 (1962).

more slowly than 1-phenylpropyne.⁴ The ratio of chloride to ketone is found to increase substantially with the HCl concentration for 3-hexyne but was shown to undergo no significant change for 1-phenylpropyne.⁴ These observations indicate that a different mechanism operates for addition to 3-hexyne than for 1-phenylpropyne.

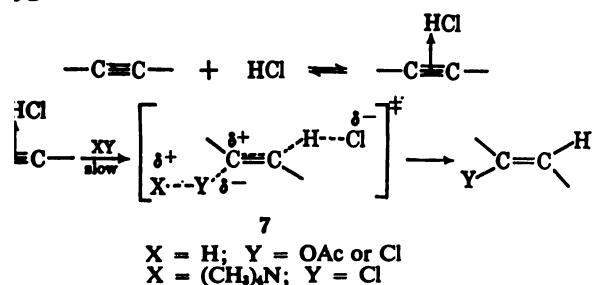
The results in Table I show, TMAC greatly enhances the rate of formation of *trans* chloride but has little effect on the rate of formation of ketone. At 25°C the rates for product formation can be expressed approximately as

$$d[4]/dt = kA[HCl]^2 + k'A[TMAC][HCl]^2$$

$$d[6]/dt = k''A[HCl]^2$$

where A is the concentration of 3-hexyne. The numerical values of the rate constants for these expressions are probably not meaningful since it is not yet clear whether fractional orders in HCl should be associated with changes in the solvent character at the high concentrations employed here or with rate expressions involving second-, and third-order terms in HCl. In either case it is clear that chloride formation in the absence of TMAC is associated with a rate equation approximately an order higher in HCl than that for ketone formation in the TMAC-catalyzed reaction. These results are unexpected for a mechanism involving the formation of a cationic intermediate but are in accord with a mechanism involving synchronous formation of the C-X and C-C bonds.

This mechanism can be formulated as shown in Scheme 1. Since acetylenes⁹ and other unsaturated carbons¹⁰ are known to form weak complexes with HCl, the first step in the reaction is postulated as a reversible complex formation. Competing at this step is



on the complex by HCl, TMAC, and HOAc leads to transition state 7, to *trans* adduct. The vinyl cation is then rapidly converted to ketone. The fractional order in HCl may result from solvation of the charge-separated transition state 7 or from competing reactions in which hydrogen dichloride ion, rather than chloride ion, is produced in the rate-limiting step.

The results show that, in the apparent rate equation, k' is over 100 times larger than k , which is consistent with TMAC being a better nucleophile than

trifluoroacetic acid, being polar and strongly acidic but weakly nucleophilic, should favor addition via a vinyl cation intermediate. There is, in fact, evidence suggesting that a vinyl cation mechanism may be competitive with the synchronous process for the hydrochlorination in acetic acid. Thus, although chloride 5 is a negligible product for addition at 25°C, we find that at 80°C it amounts to 5% of the total reaction product under kinetically controlled conditions. The present study is being extended to lower acid concentrations and higher temperatures in order to further delineate this apparent competition between stepwise and synchronous addition mechanisms.

(11) Alfred P. Sloan Foundation Research Fellow, 1966–1968.

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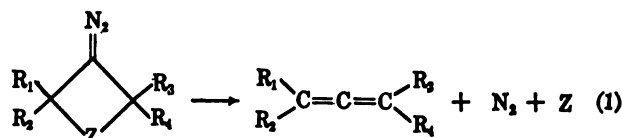
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Received February 17, 1967

Synthesis of Allenes by Means of Cycloelimination Reactions

Sir:

Although cycloeliminations of the type shown in equation 1 would be of synthetic and theoretical interest, no such reactions have been recorded in the literature. We wish to report the first examples of this type of reaction.



When an ethereal solution of 4-keto-3,3,5,5-tetramethylpyrazoline hydrazone¹ (1) was treated at room temperature, under nitrogen, with a 10–20% molar excess of nickel peroxide,² a transient yellow color was formed and vigorous nitrogen evolution ensued, ceasing after ca. 10 min. Analysis of the colorless supernatant by glpc³ indicated the presence of tetramethylallene (2) in yields of 87–91% (eq 2). Freshly prepared silver(I) oxide is less effective, allene 2 being produced in poor (2.5–3.5%) yield. The tetramethylallene thus produced was identified by comparing its glpc retention times (three different columns) and its infrared, nmr, and mass spectra with those of authentic tetramethylallene. Solutions of the intermediate diazo compound 3 are stable at 0°C for at least 30 min, 3 being detectable by its yellow color and by the presence of a strong infrared diazo absorption⁴ (2075 cm⁻¹ in *n*-decane; 2060

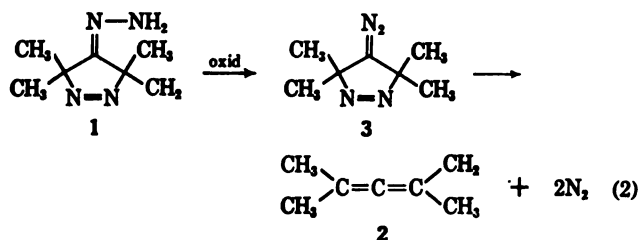
(1) W. L. Mock, Ph.D. Thesis, Harvard University, Cambridge, Mass., Sept 1964. A referee has suggested that, owing to the general inaccessibility of this thesis, the general procedures developed by Mock for the preparation of 1 and 4 be outlined. The 4-keto-3,3,5,5-tetramethylpyrazoline precursor of 1 is obtained from the hypobromite oxidation of the 2,4-diamino ketone resulting from reduction of 2,4-diazido-2,4-dimethyl-3-pentanone with hydrogen sulfide. The diazide may be prepared from the corresponding dibromo ketone [A. Favorsky and A. Umnova, *J. Prakt. Chem.*, **88**, 679 (1913)]. Compound 4 may be prepared from the corresponding ketone which is obtained from the peracetic acid oxidation of the known 2,2,4,4-tetramethyl-3-thietanone [G. Claeson, A. Thalen, and L. Schotte, *Arkiv Kemi*, **21**, 295 (1963)].

(2) (a) K. Nakagawa, H. Onoue, and K. Minami, *Chem. Commun.*, **730** (1966); (b) K. Nakagawa, R. Konaka, and T. Nakata, *J. Org. Chem.*, **27**, 1597 (1962).

(3) Glpc analysis was done on an Aerograph A 90-P3 gas chromatograph using a 5 ft × 0.25 in. column of 20% SE-30 on 60–80 mesh Chromosorb W. Both tetramethylallene and toluene, the internal standard used for the yield determinations, are stable to nickel peroxide under the reaction conditions.

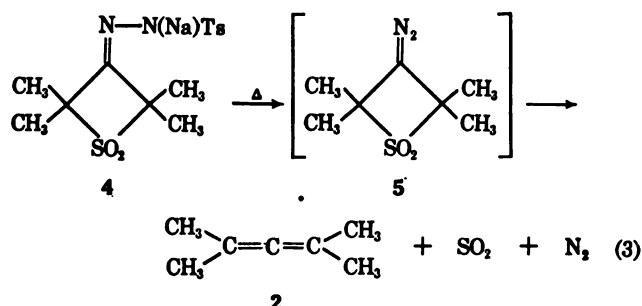
J. Cook, Y. Lupien, and W. G. Schneider, *Can. J. Chem.*, **34**, 1566.

H. C. Brown and J. D. Brady, *J. Am. Chem. Soc.*, **71**, 3573



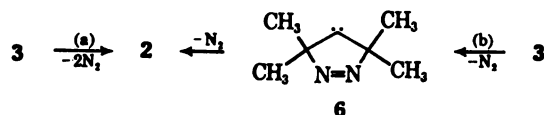
cm⁻¹ in cyclohexene) which fades rapidly if the solution is allowed to warm. Although hydrazone 1 is less soluble in hydrocarbon solvents than it is in ether, the yields of allene 2 are but little affected, averaging ca. 82% in tetramethylethylene and cyclohexene and 77% in *n*-hexane and *n*-decane.

Cycloelimination leading to the formation of tetramethylallene can also be effected when one of the leaving groups is sulfur dioxide (eq 3). When the dry sodium salt, 4, of the tosylhydrazone of 2,2,4,4-tetramethyl-3-thietanone dioxide,¹ prepared by treatment of a tetrahydrofuran solution of the tosylhydrazone with excess sodium hydride, was pyrolyzed *in vacuo* at ca. 110–160° according to the method of Shechter, *et al.*,⁵ a 54–56% yield of tetramethylallene was obtained (presumably *via* diazo compound 5) along with sulfur dioxide (identified by its glpc retention time on two different columns and by its infrared spectrum) and sodium *p*-toluenesulfonate (identified by its infrared spectrum).



Preliminary attempts to extend this cycloelimination reaction to the sodium salt of 2,2,4,4-tetramethylcyclobutanedione monotosylhydrazone (elimination of carbon monoxide) have not yielded sufficient tetramethylallene to be detectable by glpc.⁶

Since the two cycloelimination reactions would appear to be mechanistically similar, only the first will be discussed. It is clear that diazo compound 3 is a precursor of allene 2. Whether the two nitrogen molecules are lost simultaneously (pathway a) or stepwise (pathway b) is yet unknown.^{7,8} Preliminary attempts



(4) P. Yates, B. L. Shapiro, N. Yoda, and J. Fugger, *J. Am. Chem. Soc.*, **79**, 5756 (1957).

(5) G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *ibid.*, **87**, 936 (1965).

(6) The products of this reaction are under investigation. See G. Maier and M. Strasser, *Tetrahedron Letters*, 6453 (1966), and references cited therein, for the pyrolysis of similar systems in which cycloelimination does not occur.

(7) For possibly related reactions involving the formation of olefins, see (a) E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Am. Chem. Soc.*, **87**, 934 (1965); (b) D. M. Lemal and E. H. Banitt, *Tetrahedron Letters*, 245 (1964).

(8) Allenes and other cumulenes have been synthesized by means of carbenic rearrangements. See (a) W. Kirmse, "Carbene Chemistry,"

to trap carbene 6 with cyclohexene or with tetramethylene have been unsuccessful; high yields of methylallene are obtained in these solvents and trace amounts (<2%) of additional reaction products are detectable by glpc.⁹ While failure to trap carbene 6 cannot be used as evidence against its existence, the absence of intramolecular C–H insertion product expected for a dialkylcarbene with available β-hydrogen atoms,^{11,12} suggests that carbene 6, if formed, is extremely short-lived, cycloelimination of nitrogen being faster than intramolecular C–H insertion or intermolecular addition to olefins. Possibly pathways a and b may be operative.¹³

Experiments designed to test the generality and the chemical course of this type of cycloelimination reaction are in progress.

Acknowledgment. This research was partially supported by a grant from the Research Corp.

Academic Press Inc., New York, N. Y., 1964, pp 61–64, and references therein; (b) L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963); (c) L. Skattebøl, *J. Org. Chem.*, **31**, 2789 (1966); (d) K. G. D. J. Martin, and N. T. Castellucci, *ibid.*, **30**, 3572 (1965). For synthesis of optically active allenenes, see (e) W. M. Jones, J. W. Jr., and F. B. Tutwiler, *J. Am. Chem. Soc.*, **85**, 3309 (1963); (f) Jones and J. W. Wilson, Jr., *Tetrahedron Letters*, 1587 (1965). For synthesis of strained cyclic allenenes, see (g) E. T. Marquis and Gardner, *ibid.*, 2793 (1966). For the synthesis of higher cumulenes, see (h) F. T. Bond and D. E. Bradway, *J. Am. Chem. Soc.*, **87**, 4977 (1965); (i) G. Maier, *Tetrahedron Letters*, 3603 (1965); (j) L. Skattebøl, *ibid.*, 2175 (1965).

(9) In some reactions small (ca. 4–5%) amounts of 4-keto-tetramethylpyrazoline were detected, presumably formed by hydrolysis of hydrazone 1 by the hydrated nickel peroxide.

(10) The 2,2-diphenylcyclopropylidene has been trapped by see W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *J. Am. Chem. Soc.*, **85**, 2754 (1963).

(11) See ref 8a, pp 52–57.

(12) Treatment of 1,1-dibromotetramethylcyclopropane with lithium gives no tetramethylallene, instead yielding 1-methylpropenylcyclopropane (95%) whose formation is attributed to molecular C–H insertion by initially formed tetramethylcyclopropylidene.¹⁰ For another viewpoint, see M. J. Goldstein and Dolbier, Jr., *J. Am. Chem. Soc.*, **87**, 2293 (1965).

(13) W. M. Jones and M. H. Grasley, *Tetrahedron Letters* (1962).

(14) National Science Foundation Teaching Assistant, summer 1966; National Science Foundation Predoctoral Fellow, 1966–1968.

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The Rearrangement of Phosphorane Boranes

Sir:

The numerous examples of substituent rearrangement from negatively charged boron,¹ and the previously observed² reduction of triphenylphosphine oxide by organoboranes, suggested that phosphoranes might undergo similar reactions. Although these 1,3-dipolar adducts are in general sufficiently stable to allow isolation under normal conditions, rearrangement does in fact occur at higher temperatures.

When triphenylphosphinemethyleneborane³ (refluxed in chlorobenzene (bp 131°) for 40 min, a

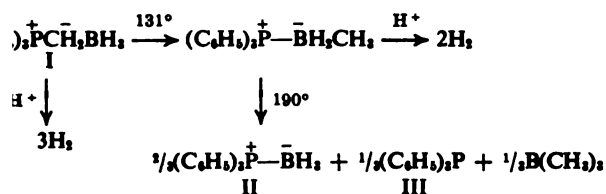
(1) For an analogous rearrangement involving a sulfur ylide, see J. J. Tufariello and L. T. C. Lee, *J. Am. Chem. Soc.*, **88**, 4757 (1966).

(2) R. Köster and Y. Morita, *Angew. Chem. Intern. Ed. Engl.*, **4**, 593 (1965).

(3) M. F. Hawthorne, *J. Am. Chem. Soc.*, **80**, 3480 (1958); *ibid.*, **81**, 1961 (1961).

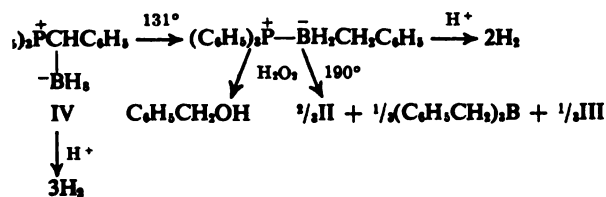
(4) D. Seyferth and S. O. Grim, *ibid.*, **83**, 1613 (1961).

ion results which evolves 2 moles of hydrogen mole of I) on treatment with acid.

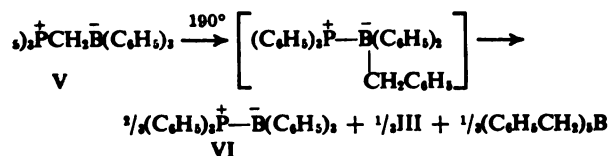


On refluxing in decalin (bp 185–190°) for 20 min, rearrangement of I is followed by alkyl redistribution of boron component. Triphenylphosphineborane (II), which crystallizes from this solvent on cooling, was obtained in 85% yield. Trimethylborane, swept from reaction vessel by a slow stream of argon, was condensed (in high yield) and identified as the pyridinate. Elemental analysis of the residual decalin solution indicated that it contained essentially only triphenylphosphine (III).

Triphenylphosphinebenzylideneborane³ (IV) is similarly rearranged by heating for a short time in chlorobenzene or diglyme, as shown by the formation of benzyl alcohol on oxidation with basic peroxide.⁶ In a slurry of IV in decalin is refluxed for 15 min, resulting clear solution on cooling deposits crystals, which again could be isolated in good yield.



The generality of the rearrangement was extended by finding that both aryl and alkyl groups will migrate in analogous phosphorane boranes. Triphenylphosphinemethylenetriphenylborane⁴ (V), heated without solvent to 205°, or in decalin for 15 min, gives crystalline triphenylphosphinetriphenylborane^{6,7} (VI), indicating



migration of the phenyl group followed by phenyl-alkyl redistribution. The formation of a benzylidene species was again demonstrated by alkaline hydrolysis formation of benzyl alcohol.⁵ Evidence has been presented⁴ that, unlike borane and triphenylborane, trialkylboranes do not form stable complexes with triphenylmethylenephosphorane. Consequently, the question of possible rearrangement of a trialkylborane adduct (viewed as an especially unstable intermediate) was of particular interest.

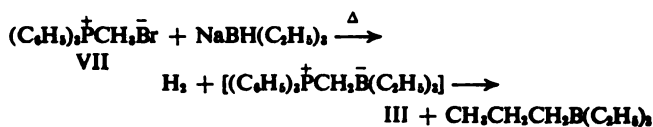
The starting material is inert under these conditions; no benzyl alcohol is formed, and the phosphorane borane is recovered in high yield.

Lack of reaction may be due to low solubility, as typical phosphonium salts would be expected to react rapidly under these conditions.

G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).

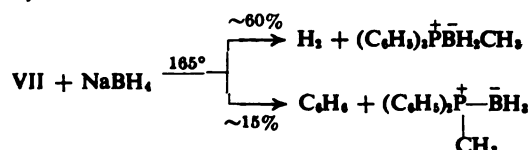
In the absence of solvent, this material (impure) sublimes to the bottom of the reaction vessel. In a separate experiment, VI, prepared by the method of Wittig and Haag,⁴ was partially sublimed to give material of depressed melting point. Presumably sublimation occurs via dissociation of this complex, and consequently the sublimed VI is contaminated with free triphenylborane and/or triphenylphosphine.

When methyltriphenylphosphonium bromide (VII) is heated in refluxing triethylborane (bp 94°) or diglyme (bp 165°) with sodium triethylborohydride,⁸ hydrogen is evolved with concurrent development of a deep red color. The color disappears after a few minutes of refluxing in either solvent. The formation of *n*-propyl-

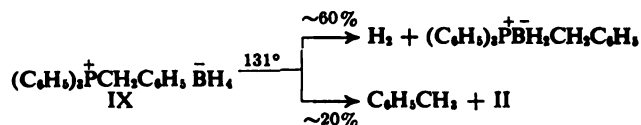


diethylborane was demonstrated by vpc.⁹

The reaction of phosphonium salts with sodium borohydride has also been investigated. A mixture of VII and sodium borohydride in diglyme on heating evolves hydrogen (60%), again with development and subsequent disappearance of a deep red color. Benzene is formed directly in a side reaction, along with methyl-diphenylphosphine (VIII)¹⁰ (presumably as the borane adduct).



Benzyltriphenylphosphonium borohydride (IX) (mp 150–154° dec), which is obtained in nearly quantitative yield on mixing aqueous solutions of the phosphonium chloride and sodium borohydride, decomposes in boiling chlorobenzene in an analogous manner.



The mechanism of thermal decomposition of IX is to be contrasted with that of the reaction between the corresponding phosphonium halide and lithium aluminum hydride. The latter proceeds rapidly at room temperature (in diglyme) with negligible gas evolution. Toluene is again formed directly, along with a high yield (>80%) of triphenylphosphine (isolated subsequent to hydrolysis).¹¹

The toluene obtained from the triphenylbenzylphosphonium salt (in both the borohydride reaction and the lithium aluminum hydride reduction), as well as the benzene obtained in the reaction of VII, presumably arise *via* hydride attack on positive phosphorus to give intermediate (or transition state) pentavalent phosphorus compounds. Evidence for the formation of a related intermediate pentavalent phosphorus hydride (isolable at low temperature) has recently been presented.¹² Formation of toluene by nucleophilic displacement on carbon would seem to be ruled out by

(8) H. C. Brown, H. I. Schlesinger, I. Sheft, and D. M. Ritter, *J. Am. Chem. Soc.*, **75**, 192 (1953).

(9) G. Schomburg, R. Köster, and D. Henneberg, *Z. Anal. Chem.*, **170**, 285 (1959); as anticipated, in the higher boiling solvent (diglyme) some isomerization to isopropyl-diethylborane occurred.

(10) The formation of III and VIII was demonstrated by mass spectral analysis; borane complexes, it was shown, display strong free phosphine parent peaks.

(11) (a) W. J. Bailey and S. A. Buckler, *J. Am. Chem. Soc.*, **79**, 3567 (1957); (b) W. J. Bailey, S. A. Buckler, and F. Marktscheffel, *J. Org. Chem.*, **25**, 1966 (1960); (c) S. T. D. Gough and S. Trippett, *J. Chem. Soc.*, 4263 (1961).

(12) D. Hellwinkel, *Angew. Chem. Intern. Ed. Engl.*, **5**, 968 (1966).

the fact that no methane is obtained in the reaction of VII.

It is also significant that only trace amounts (<1%) of benzene were formed in the thermal decomposition of IX. The ylide triphenylbenzylidenephosphorane, presumably an intermediate in the borohydride reaction, has been reported^{11c} to give benzyldiphenylphosphine on reduction with lithium aluminum hydride. It appears that complex formation between the ylide and generated borane, with subsequent rearrangement, competes more successfully with an alternate cleavage process in the borohydride than in the lithium aluminum hydride reaction.

(13) National Science Foundation Senior Postdoctoral Fellow, 1966-1967.

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Received March 3, 1967

The Stereochemistry of the Free-Radical Addition of Thiolacetic Acid to 2-Chloro-4-*t*-butylcyclohexene

Sir:

Contemporary studies of radical-chain additions to cyclohexenes¹ have been directed toward determination of both the *trans/cis* addition stereoselectivity and the conformational preference imparted to both the addition and the displacement steps by use of "conformationally fixed" cyclohexenes.²⁻⁵ Although the additions of thiols are not stereospecific in contrast to those of hydrogen bromide,^{2,6} *trans* stereoselectivity with a predominance of *trans*-diaxial addition has been observed.²⁻⁴ In at least one case, the results have been attributed to the intervention of an unsymmetrically bridged thiyl radical which was said to account for ~88% of the reaction pathway.³ The reported dependence of isomeric adduct (*trans/cis*) composition from 1-halocyclohexenes⁷ on the ratio of thiol addenda to olefin was not verified with the 4-substituted cyclohexenes.²⁻⁵

We wish to report a study of the AIBN-initiated addition of thiolacetic acid to 2-chloro-4-*t*-butylcyclohexene (1). The four possible diastereomeric products were detected and characterized, and reproducible temperature and concentration effects were observed.⁸ The results provide significant new data for a more detailed description of the stereochemical course of free-radical additions to cyclohexenes.

Typical runs afforded the following product distributions: 53.2% 2, 5.7% 3, 28.3% 4, and 12.8% 5 in hexane at 63°; 78.7% 2, 1.6% 3, 12.8% 4, and 6.9%

(1) The stereochemistry of free-radical additions to olefins has been reviewed: B. A. Bohm and P. I. Abell, *Chem. Rev.*, **62**, 599 (1962).

(2) N. A. LeBel, R. F. Czaja, and A. DeBoer, to be published.

(3) P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966).

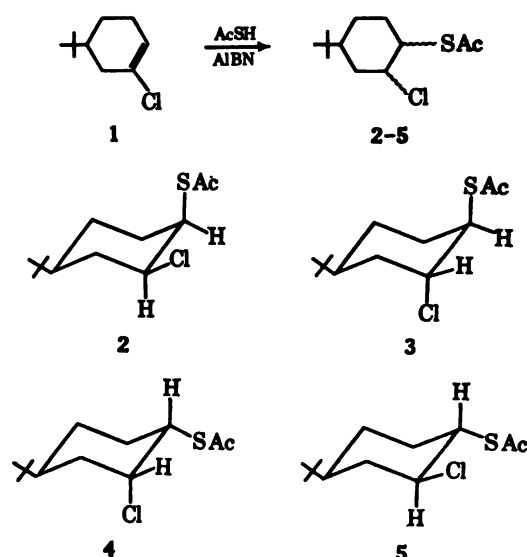
(4) F. G. Bordwell and G. S. Whitney, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1962, p 64Q; F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.*, **30**, 3764 (1965).

(5) Cf. also E. S. Huyser and J. R. Jeffrey, *Tetrahedron*, **21**, 3083 (1965); E. S. Huyser, H. Benson, and H. J. Sinnige, *J. Org. Chem.*, **32**, 622 (1967).

(6) See P. D. Readio and P. S. Skell, *ibid.*, **31**, 753 (1966).

(7) H. L. Goering, D. I. Relyea, and D. W. Larsen, *J. Am. Chem. Soc.*, **78**, 348 (1956).

(8) The synthesis of 1 and the results of other additions to 1 will be reported in the full article. Satisfactory elemental analyses have been obtained for most new compounds reported herein.



5 in hexane at -78°. A summary of pertinent stereochemical data is given in Table I. The products were separated by gas chromatography and characterized independently; in addition, 2 and 3 were compared with authentic samples. Proton nmr and infrared spectra completely supported the structural assignments.

Table I

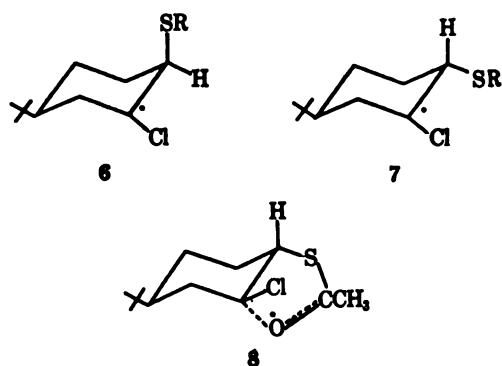
Run	Molar ratio ^a	Solvent (temp, °C) ^b	(2 + 3)/(4 + 5)	2/3	4/5
1	1:10	Hexane (63)	1.2	6.3	1.9
2	1:1	Hexane (-78) ^c	4.1	49.2	1.8
3		Pentane (37)	2.2	12.4	2.4
4		Hexane (63)	1.4	9.3	2.2
5		Heptane (86)	1.2	7.5	2.5
6		Heptane (106)	1.2	6.6	2.6
7		Methanol (64)	1.3	6.9	1.8
8	10:1	None (67)	2.4	11.4	2.0
9		Pentane (40)	3.1	15.5	2.4
10		Hexane (63)	2.5	10.0	2.2
11		Heptane (86)	1.8	8.2	2.2
12		Methanol (63)	1.9	7.7	1.8
13	30:1	None (63)	3.0	10.5	2.1
14		Methanol (66)	2.2	8.2	2.0

^a AcSH:olefin. Most solutions were made by adding AcSH to 3 ml of a 1 M solution of 1 in the solvent. ^b Reactions were generally run for 1 hr to 40-60% completion with 5 mole % AIBN. Analyses were by gc; deviations in normalized percentages were $\pm 1.0\%$ for 2 and 4, and $\pm 0.5\%$ for 3 and 5. ^c Ultraviolet initiated.

The results unequivocally demonstrate that the relative proportions of adducts vary significantly with changes in the molar ratio of starting materials and with temperature. These variations persisted in solvents of widely different polarity. The ratio of adducts resulting from axial relative to equatorial attachment of the thiyl group in the addition step [(2 + 3)/(4 + 5)] increases with lower reaction temperatures (runs 2-6, 8-11) and with higher molar ratios of thiol (runs 1, 4, 10; 5, 11; 7, 12, 14; 8, 13).

It is reasonable to attribute these *primary* concentration and temperature effects to reversibility of the addition step. Stereoelectronic control leads to preferential axial attack by the thiyl radical, affording intermediate 6, whereas 7 would result from less-favored "equatorial attack."⁹ This initial preference is at least 4:1 (run 2) and is probably much higher. Elevated temperatures and low thiol concentration favor reversal and

ulation of products from the more stable⁹ intermediate 7. On the other hand, low temperature and high thiol concentration promote rapid displacement which is kinetically favored 6. Radical-chain additions of thiol species to 4-*t*-butylcyclohexenes, examined under various reaction conditions, lead to decreasing amounts of products with axial-X groups in the following order: RSH > ArSH > AcSH > HSH. Reversibility is important for the former three addenda, as a consequence of the lower stability of alkanethiyl radicals and the high transfer rate with ArSH, and especially with Br.



displacement reactions with intermediates 6 and 7 lead to over-all *trans* stereoselectivity, but that from intermediate 6 is considerably higher and is enhanced at low temperature and high thiol concentrations. One tempting explanation for preferential *trans*-displacement (to give 2) involves an *unsymmetrically* bridged thiol radical as previously utilized.⁸ However, if a bridged intermediate is dominant in promoting the high 2/3 *trans* ratio, a significant variation in the magnitude of the *trans* ratio would be anticipated as the thiol addendum varied. Although additional accurate data are required, it appears that the proportions of adducts 2 to 3 are very similar for most thiols under identical conditions. Furthermore, even *symmetrically* bridged radicals, if such are intermediates, cannot maintain configurational integrity in additions to acyclic dienes.¹

On the other hand, preferential axial chain transfer has been established for the 4-*t*-butyl-¹⁰ and 1-thiolacyclopentyl-4-*t*-butylcyclohexyl⁴ radicals. The vicinal, axial-thiyl substituent of 6 should direct displacement 2 even more toward the axial position, and a bridged thiol radical is not required.

A surprising observation is that the ratio 4/5 is relatively insensitive to reaction conditions. The "open" intermediate 7 appears to control product distribution; however, it is intriguing to note that *trans* addition is favored over *cis* addition (4/5 ~ 1.8-2.6). Additions of other thiols to 1- or 2-*t*-butylcyclohexenes have indicated that thiol-acid seems to be unique in providing a 4/5 > 1.^{2,3} A possible rationale for this reversal involves the five-membered, bridged intermediate in equilibrium with 7, since this pathway is unavailable to alkyl- and arylthiols. However, a dipolar factor is contributory, particularly in light of the results

reported for 1-methyl-4-*t*-butylcyclohexene and thiolacetic acid.⁴

In the present case, the observed concentration effect does not involve chair-chair interconversions,⁷ but rather comes mainly from reversibility of the addition step complemented by a secondary effect of variable chain-transfer preference with the axial thiyl radical 6.

In the full article we shall elaborate a general scheme to accommodate all available data on the stereochemistry of radical additions of thiols to cyclohexenes. The present report serves to clarify certain existing ambiguities and also emphasizes the need for complete product identification.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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Received February 6, 1967

Coordination-Catalyzed Skeletal Rearrangement of 1,4-Dienes

Sir:

Our forthcoming publication¹ describes the addition of α -olefins to conjugated dienes, to produce high yields of 1,4-dienes. A homogeneous catalyst, prepared *in situ* from the reaction of a bis(tertiary phosphine)nickel(II) salt and an alkylaluminum compound, is employed. In an extension of this work we have investigated the behavior of the 1,4-diene products in the presence of the catalyst species.

3-Methyl-1,4-pentadiene (I, 0.012 mole), bis(tri-*n*-butylphosphine)nickel dichloride (0.001 mole), and diisobutylaluminum chloride (0.004 mole) were mixed in 100 ml of dry deoxygenated toluene. During 90 min at 24°, ca. 53% of I was converted to a mixture of products which included components with vpc retention times corresponding to a 35% yield of 1,4-hexadiene (*trans*:*cis* ratio = 11), a 4% yield of *trans*-2-methyl-1,3-pentadiene, 8% *cis*-3-methyl-1,3-pentadiene, a 15% combined yield of *trans*-3-methyl-1,3-pentadiene and *trans,trans*-2,4-hexadiene, and 3% *trans,trans*-2,4-hexadiene. Two components, ca. 9 and 7%, have not been resolved and identified. The remainder was non-volatile material, presumably oligomers of conjugated C-6 products.

It is apparent that the 3-methyl-1,3-pentadienes are derived from the double bond positional isomerization of I. However, the remaining products arise from skeletal rearrangements. A strong indication that the remaining C-6 conjugated products are derived from 1,4-hexadiene, as the primary rearrangement product, was found when *trans*-² and *cis*-1,4-hexadienes³ were treated separately with the catalyst under the above conditions. During 120 min, 34% of the *trans* isomer was converted to *trans,trans*- and *trans,cis*-2,4-hexadiene (*trans,trans*:*trans,cis* ratio = 2.7) in 87% yield.

(1) R. G. Miller, T. J. Kealy, and A. L. Barney, submitted for publication.

(2) T. Alderson, E. L. Jenner, and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **87**, 5638 (1965).

(3) G. Hata, *ibid.*, **86**, 3903 (1964).

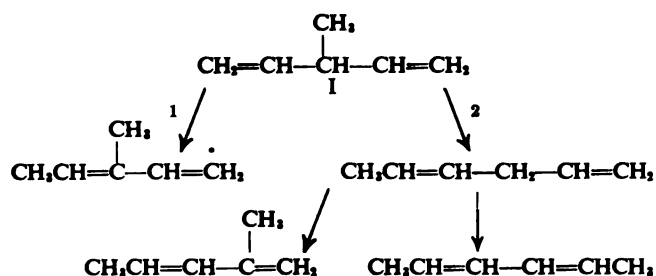
It has been suggested that intermediates of type 7 arise by rapid reversible conformational reorganization of an initial twist-boat.^{4,5}

F. D. Greene, C. Chu, and J. Walia, *J. Am. Chem. Soc.*, **84**, 2463 *J. Org. Chem.*, **29**, 1285 (1964).

The major product from the *cis*-1,4-hexadiene was derived from a skeletal rearrangement. In addition to the *trans*,*cis*- and *cis*,*cis*-2,4-hexadienes (*trans*,*cis*:*cis*,*cis* ratio = 4.0) afforded in 22% yield, a 75% yield of *trans*-2-methyl-1,3-pentadiene was obtained, the conversion of the 1,4-hexadiene to products being ca. 70%.⁴

The products from all of these reactions were isolated and characterized in experiments in which the concentration of diene precursor was increased by a factor of 9–10 over those described above in order to provide sufficient material with which to work. In general, this led to lower yields of rearranged products. The compounds, after isolation by preparative vpc, were identified by their nmr and/or infrared spectra and by comparison of vpc retention times with those of authentic samples.⁵ Proof that the reactions were indeed catalyzed by a species derived from the interaction of diisobutylaluminum chloride with bis(tri-*n*-butylphosphine)nickel dichloride in the presence of the dienes was obtained from a series of experiments in which I and the 1,4-hexadienes were mixed independently with the aluminum and the nickel catalyst precursors. In all cases, the 1,4-diene was recovered unchanged.

It appears that all of the characterized C-6 products from the interaction of I with the catalyst arise from two primary reaction paths: (1) the double bond positional isomerization of I, and (2) a skeletal rearrangement of I to afford the 1,4-hexadienes.



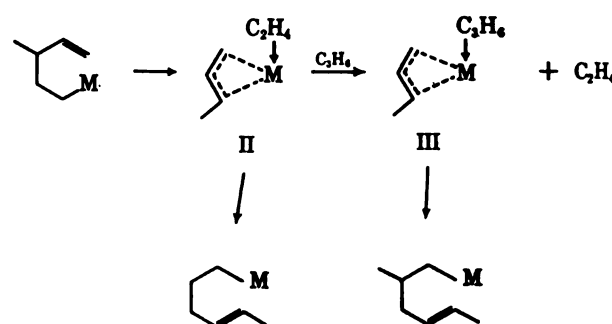
Information suggesting the nature of path 2 was obtained from experiments in which I was mixed with the catalyst in the presence of an excess of propylene. Admixture of 41 g (0.52 mole) of I with 81 g (1.9 moles) of propylene and the catalyst precursors (Al:Ni = 6:1, mmols) in 400 ml of toluene for 19 min in the 86–90° range (same conditions as utilized for the codimerization of propylene and butadiene to give 2-methyl-1,4-hexadiene¹) afforded a 9% yield of *trans*-2-methyl-1,4-hexadiene. Other products included 1,4-hexadiene (*trans*:*cis* ratio = 4) in 4.5% yield, *cis*-3-methyl-1,3-pentadiene in 5% yield, and *trans*-3-methyl-1,3-pentadiene in 5% yield based on 52% recovery of I. These compounds accounted for ca. 98% of the products in the 64–94° boiling point range.

The isolation of appreciable quantities of 2-methyl-1,4-hexadiene in these experiments suggests that interaction of the catalyst with I can lead to a species which

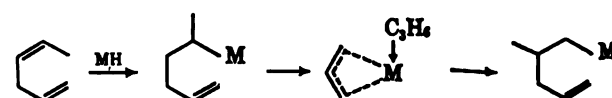
(4) No evidence was found that 2-methyl-1,3-pentadiene was produced from *trans*-1,4-hexadiene. The combined amount of *cis*-1,4-hexadiene and 2-methyl-1,3-pentadiene in the product mixture from the *trans* isomer was slightly less than the level of *cis*-1,4-hexadiene (3%) present in the starting material. This also eliminated the possibility that appreciable isomerization of *trans*- to *cis*-1,4-hexadiene took place under these conditions.

(5) Standard mixtures of most products described herein were analyzed by vpc to determine the relationship between mole ratio and relative signal intensity. Product ratios of 2-methyl-1,3-pentadiene were based on signal intensity alone.

possesses a C-4 fragment and ethylene bonded to nickel, such as II. Displacement of the ethylene by propylene could lead to a species like III from which 2-methyl-1,4-hexadiene results. The double bond positional isomerization of the 1,4-dienes and the rearrangement of I to 1,4-hexadiene could arise through the two possible modes of addition of a nickel hydride to a terminal double bond.⁶ A 2,1 addition of NiH affords products that, on NiH elimination, could give either the 1,4-diene precursor or its conjugated isomers. However, the 1,2-addition products, possessing terminal C–Ni bonds, could give the 1,4-diene precursor or possibly generate ethylene and a C-4 fragment *via* a Ni–C β elimination.⁷ The latter mode of reaction appears, at present, to offer the best rationalization of the formation of a C-7 diene from a C-6 precursor in these experiments. The possible participation of “fragmentation” products such as II or isomeric σ -methylallyl species is being investigated.



Although the rearrangement of I to 1,4-hexadiene can be explained by the intervention of elimination products such as II, other pathways cannot be excluded. The rearrangements of 1-methyl-1-pent-4-enyl derivatives of sodium, lithium, and magnesium⁸ provide a close analogy to the gross rearrangement of I. The formation of 2-methyl-1,3-pentadiene from *cis*-1,4-hexadiene can be rationalized by a C–M elimination–addition route analogous to that suggested above. However, the expected diene product here is 2-methyl-



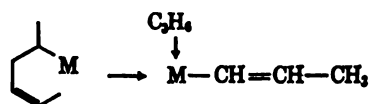
1,4-pentadiene. Our observation that the rate of rearrangement of *cis*-1,4-hexadiene exceeds the rate of double bond isomerization of 2-methyl-1,4-pentadiene and our failure to detect the latter diene in the rearrangement product mixtures indicate that if this process is operating here, the primary 1,4-diene product is isomerized before it becomes free of the metal.⁹ Other

(6) We have no evidence that would demonstrate the participation of an actual nickel hydride complex in these reactions. The results described here and elsewhere¹ are consistent with the capability of the catalyst to effect a gross addition of a nickel hydride to an olefinic bond.

(7) An accurate determination of the amount of ethylene present in product mixtures from the reaction of I, propylene, and the catalyst was not achieved. Vpc analyses of the recovered propylene indicated the presence of a component with the retention time of ethylene in amounts ca. 20–30 times that present in the propylene reagent. Butadiene was not detected in the reagents or in the product mixtures.

(8) (a) E. A. Hill, H. G. Richey, Jr., and T. C. Rees, *J. Org. Chem.*, **28**, 2161 (1963); (b) E. A. Hill and J. A. Davidson, *J. Am. Chem. Soc.*, **86**, 4663 (1964).

(9) An alternative elimination–addition route involving a propenyl-nickel intermediate could give the conjugated diene directly.



pathways seem equally plausible, particularly one involving the participation of a cyclopropylcarbinylnickel derivative.¹⁰

Carbon-metal β -elimination products have been reported in the pyrolyses of neopentyl derivatives of sodium,¹¹ potassium,¹² and aluminum,¹³ systems in which a β elimination of M-H is precluded. The rearrangements of cyclobutylcarbinyl¹⁴ and cyclopropylcarbinyl¹⁰ Grignard reagents can be pictured as formally involving intramolecular C-M eliminations.

Further study of the 1,4-diene rearrangements and the extension of the investigation to other transition metal systems are in progress.

(10) M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 2646 (1960).

(11) R. A. Finnegan, *Chem. Ind. (London)*, 895 (1962).

(12) R. A. Finnegan, *Tetrahedron Letters*, 1303 (1962).

(13) K. Ziegler, K. Nagel, and W. Pfohl, *Ann.*, **629**, 210 (1960).

(14) Chemistry Department, University of North Dakota, Grand Forks, N. D.

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Contribution No. 159

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Conformational Rigidity^{1,2} in Aliphatic Paraffins.

Synthesis and Determination of Absolute

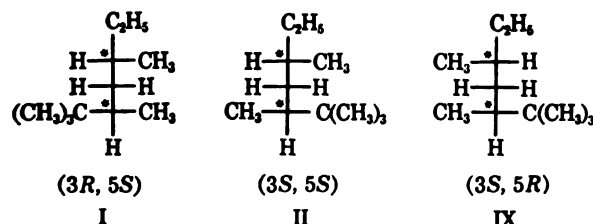
Configuration of (3*S*,5*S*)- and (3*R*,5*S*)-2,2,3,5-Tetramethylheptane

Sir:

The high optical activity in solution of some stereoregular polymers obtained from optically active α olefins³ has been attributed^{2,4} substantially to the fact that few conformations having high optical rotation of the same sign are allowed for the monomeric unit of such polymers in solution.

As no low molecular weight paraffins were known having $[M]$ of the same order of magnitude of the one found for the monomeric unit of these polymers, we have synthesized (3*R*,5*S*)- and (3*S*,5*S*)-2,2,3,5-tetramethylheptane (I and II, respectively); for I the existence of two conformations having $[M] +180$ and $+60^\circ$, and for II the existence of one conformation having $[M] -180^\circ$ can be foreseen by the Brewster method⁵ (Chart I).

Chart I



A mixture of the two diastereoisomers I and II has been prepared starting with (−)(*S*)-3-methylpentanal,

(1) A. Abe and M. Goodman, *J. Polymer Sci.*, **A1**, 2193 (1963).

(2) P. Pino, *Advan. Polymer Sci.*, **4**, 443 (1965).

(3) P. Pino and G. P. Lorenzi, *J. Am. Chem. Soc.*, **82**, 4745 (1960).

(4) P. Pino, F. Ciardelli, G. P. Lorenzi, and G. Montagnoli, *Makromol. Chem.*, **61**, 207 (1963).

(5) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959).

bp 120–121° (760 mm), n_D^{25} 1.4002, $[\alpha]_D^{25} -7$, 10°, having an optical purity of 97%,⁶ and allowing it to react with *t*-butylmagnesium chloride.

The (−)(*S*)-2,2,5-trimethylheptan-3-ol (III) thus obtained, bp 85° (20 mm), n_D^{25} 1.4350, d_4^{25} 0.8305, $[\alpha]_D^{25} -2.17^\circ$ (neat) (*Anal.* Calcd for $C_{10}H_{20}O$: C, 75.88; H, 14.01. Found: C, 75.91; H, 13.80), was oxidized according to Brown⁷ to (+)(*S*)-2,2,5-trimethylheptan-3-one (IV), bp 75° (22 mm), n_D^{25} 1.4193, d_4^{25} 0.8183, $[\alpha]_D^{25} +19.16^\circ$ (neat) (*Anal.* Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.64; H, 12.96), which was allowed to react with methylmagnesium bromide, yielding (+)(*S*)-2,2,3,5-tetramethylheptan-3-ol (V), bp 90° (20 mm), n_D^{25} 1.4390, d_4^{25} 0.8387, $[\alpha]_D^{25} +10.13^\circ$ (neat) (*Anal.* Calcd for $C_{11}H_{24}O$: C, 76.67; H, 14.04. Found: C, 76.21; H, 14.06).

V was dehydrated by distillation in the presence of I_2 and the mixture of olefins thus obtained was finally hydrogenated at 120° by H_2 in the presence of Raney nickel, yielding a mixture of I and II, bp 61–62° (18 mm), n_D^{25} 1.4202, d_4^{25} 0.7465, $[\alpha]_D^{25} -0.69^\circ$ (neat), $[\alpha]_D^{25} -0.83^\circ$ (c 15, *n*-pentane). *Anal.* Calcd for $C_{11}H_{24}$: C, 84.52; H, 15.48. Found: C, 84.73; H, 15.59.

The mixture was analyzed by vpc (50-m squalane capillary column); only two components were present, the one with the higher retention time prevailing ($60 \pm 3\%$).

By fractional crystallization from propane at -80° , mixtures of I and II having different compositions have been obtained; a sample having a diastereoisomeric purity of 95% showed bp 54–55° (14 mm), n_D^{25} 1.4208, $[M]_D^{25} -87.47 \pm 0.1^\circ$ (neat), $[M]_D^{25} -87.52 \pm 1^\circ$ (c 20.47, *n*-pentane). *Anal.* Calcd for $C_{11}H_{24}$: C, 84.52; H, 15.48. Found: C, 84.81; H, 15.22.

By plotting the composition of such mixtures *vs.* their optical rotation and extrapolating at 100% of diastereoisomeric purity, the optical rotation has been calculated for both diastereoisomers.

Taking in account the optical purity of the starting material we have assigned $[M]_D^{25} +137.8 \pm 3^\circ$ (c 20.47, *n*-pentane)⁸ to the lower retention time diastereoisomer, $[M]_D^{25} -97.5 \pm 4^\circ$ to the higher retention time diastereoisomer.

In order to establish the relationship between the sign of the optical rotatory power and the absolute configuration of the two asymmetric carbon atoms of the diastereoisomers we have prepared a mixture of (3*S*,5*S*)- and (3*S*,5*R*)-2,2,3,5-tetramethylheptane (II and IX, respectively), starting with (−)(*R*)-2,3,3-trimethylbutan-1-ol, $[\alpha]_D^{25} -15.5^\circ$ (c 3.41, ethanol), optical purity 37.4%.⁹ (−)(*R*)-1-chloro-2,3,3-trimethylbutane (VI), bp 89–91° (158 mm), n_D^{25} 1.4313, d_4^{25} 0.8872, $[\alpha]_D^{25} -19.93^\circ$ (neat) (*Anal.* Calcd for $C_7H_{15}Cl$: C, 62.44; H, 11.23; Cl, 26.33. Found: C, 62.39; H, 11.15; Cl, 26.44), was obtained from the alcohol by reaction with $SOCl_2$ in pyridine, and its Grignard reagent was allowed to react with propanal.

(6) L. Lardicci, F. Navari, and R. Rossi, *Tetrahedron*, **22**, 1991 (1966).

(7) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(8) Standard deviation calculated by the least-squares method.

(9) The optical purity has been calculated on the basis of the pure (−)(*R*)-2,3,3-trimethylbutan-1-ol, $[\alpha]_D^{25} -41.4^\circ$: M. Farina and E. M. Peronaci, *Chim. Ind. (Milan)*, **48**, 602 (1966); *Chem. Abstr.*, **65**, 12091a (1966).

(5*S*)-5,6,6-Trimethylheptan-3-ol thus obtained was not isolated and was oxidized according to Brown⁷ to the (–)(*S*)-5,6,6-trimethylheptan-3-one (VII), bp 128–130° (126 mm), n_D^{25} 1.4277, α_D^{25} –7.00° (neat, $l = 1$) (Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 75.97; H, 12.44), which was purified through its semicarbazone, mp 159–160°.

VII was allowed to react with methylmagnesium bromide, and (–)(*S*)-3,5,6,6-tetramethylheptan-3-ol (VIII), bp 89–92° (18 mm), n_D^{25} 1.4435, α_D^{25} –7.00° (neat, $l = 1$) (Anal. Calcd for $C_{11}H_{24}O$: C, 76.67; H, 14.04. Found: C, 76.28; H, 13.89), was obtained.

VIII was dehydrated by distillation in the presence of I_2 , and the olefins thus obtained were hydrogenated by H_2 at 120° in the presence of Raney nickel, yielding a mixture of (3*S*,5*R*)- and (3*S*,5*S*)-2,2,3,5-tetramethylheptane (IX and II, respectively), n_D^{25} 1.4202, $[\alpha]_D^{25}$ –26.19° (c 20.58, *n*-pentane). Anal. Calcd for $C_{11}H_{24}$: C, 84.52; H, 15.48. Found: C, 84.24; H, 15.43.

Acid-catalyzed rearrangements in the dehydration and acid oxidation steps have to be considered improbable on the basis of published data^{10,11} on similar compounds.

As I and II have optical activity of opposite sign, IX must have optical activity of the same sign as II; therefore II must have optical rotation of the same sign as the mixture of II and IX and possess therefore negative optical rotation. Consequently the diastereoisomer I, (3*R*,5*S*), has positive optical rotation.

The mixture of II and IX was analyzed by vpc, as in the case of the mixture of I and II; it contained $55 \pm 3\%$ II which has negative optical rotation and higher retention time; taking into account the optical purity of VI, a value of $[M]_D^{25}$ $-108.28 \pm 1.30^\circ$ (c 20.58, *n*-pentane) can be calculated for the molar rotation of the mixture of IX and II. Comparing such a value with the one calculated for the same composition on the basis of the absolute value of the molar rotations of I and II ($[M]_D^{25}$ $115.6 \pm 4^\circ$), a satisfactory agreement is obtained. This agreement can be taken as an indication that both in the synthesis of the mixtures of I and II and of II and IX no extensive racemization occurs at the two asymmetric centers.

Comparing the values found with the value calculated by the Brewster method,⁵ a substantial agreement has been found both concerning the sign and the order of magnitude of the optical rotation of I and II, the discrepancy between the values calculated and found being larger in the case in which a single conformation is allowed (see Table I).

Table I

Compd	Max $[M]_D^{25}$ found (c 20.47, <i>n</i> -pentane) ^a	$[M]_D$ calcd by Brewster method ^a
I	$+137.8 \pm 3$	+120
II	-97.5 ± 4	–180

^a In degrees.

Our data confirm the previous hypothesis⁴ that, in aliphatic hydrocarbons containing a hydrogen atom

(10) P. Pino, S. Pucci, E. Benedetti, and P. Bucci, *J. Am. Chem. Soc.*, **87**, 3263 (1965).

(11) L. Lardicci and R. Rossi, *Atti Soc. Toscana Sci. Nat. Pisa Proc. Verbal Mem.*, **B69**, 22 (1962); *Chem. Abstr.*, **63**, 9795a (1965).

attached to the asymmetric carbon atoms,¹² when the presence of a few conformations having high optical rotation of the same sign can be foreseen by conformational analysis⁵ a relatively high optical rotation can be found. This shows the substantial soundness but also the limits of conformational analysis in investigating the conformation of both low and high molecular weight hydrocarbons.

Acknowledgment. We thank Dr. V. Malaguzzi of the Institute of Pharmaceutical Chemistry of the University of Pisa for aid and collaboration in performing the chromatographic analysis.

(12) We thank one of the referees for calling our attention to the paper by H. Wynberg, G. L. Hekkert, J. P. M. Houbiers, and H. W. Bosch, *J. Am. Chem. Soc.*, **87**, 2635 (1965).

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The Configuration of Vinyl Radicals. The Generation and Trapping of Each Member of a Configurationally Isomeric Pair of Vinyl Radicals

Sir:

We wish to report evidence that vinyl radicals derived from symmetrically disubstituted alkenes exist in a nonlinear configuration capable of facile isomeric interconversion. In addition we are pleased to communicate the results of the first successful attempt to trap the *cis* and *trans* isomers of a vinyl radical prior to their complete equilibration.

Several investigations bearing on the structure of vinyl radicals have been reported recently.^{1–7} Under conditions of kinetic control, free-radical additions to terminal acetylenes yield predominantly the product of *trans* addition.^{1–3} Skell and Allen¹ attribute this stereoselectivity to the configurational stability of the intermediate vinyl radical. Others^{2,3} have suggested that the intermediate radical undergoes rapid *cis*–*trans* equilibration, but that the product-forming abstraction reaction involves stereoselective capture of one isomer of this pair.

Elegant electron spin resonance investigations have shown that at low temperatures in liquid ethylene-ethane⁴ or in an argon matrix⁵ the unsubstituted vinyl radical possesses a nonlinear configuration which undergoes facile inversion. The minimum activation energy for inversion is estimated to be approximately 2 kcal/mole.⁴ The 1-methylvinyl radical generated by irradiation of allene in ethane at –172° is also nonlinear.⁴ The inversion rate of the 1-methylvinyl radical is less than that for the unsubstituted vinyl radical. Since inversion of the vinyl radical presumably involves

(1) P. S. Skell and R. G. Allen, *J. Am. Chem. Soc.*, **80**, 5997 (1958); **86**, 1559 (1964).

(2) A. A. Oswald, K. Griesbaum, B. B. Hudson, Jr., and J. M. Bregman, *ibid.*, **86**, 2877 (1964).

(3) J. A. Kampmeier and G. Chen, *ibid.*, **87**, 2608 (1965).

(4) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

(5) E. L. Cochran, F. J. Adrian, and V. A. Bowers, *ibid.*, **40**, 213 (1964).

(6) R. M. Fantazier and J. A. Kampmeier, *J. Am. Chem. Soc.*, **88**, 5219 (1966).

(7) L. A. Singer and N. P. Kong, *ibid.*, **88**, 5213 (1966); *Tetrahedron Letters*, 2089 (1966).

Yield of Isomeric 3-Hexenes from Reaction of Sodium Naphthalenide with *cis*- and *trans*-3-Chloro-3-hexene^a

Run	Temp, °C	Product, % yield ^{b,c}			
		With <i>cis</i> -3-chloro-3-hexene ^d	<i>trans</i> -Hexene	With <i>trans</i> -3-chloro-3-hexene ^e	<i>cis</i> -Hexene
F	0	69	31	85	15
F	27	74	26	85	15
IE	0	56	44	82	18
IE	27	59	41	81	19

^a *cis*- and *trans*-3-chlorohexenes were prepared from isopure *trans*- and *cis*-3-hexene, respectively, in the manner described by M. C. Hoff, K. W. Greenlee, and C. E. Boord, *J. Am. Soc.*, **73**, 3329 (1951). ^b Reactions were carried out in the manner previously described.¹⁰ Analysis was by vapor phase chromatography on an 8-ft column packed with a 30% AgNO₃-silicic acid solution coated 20% by weight on Chromosorb P. Relative data were obtained by comparison of peak areas to that of an internal standard (pentane) of known concentration. Each datum represents the average of at least three independent experiments. In general, yields were reproducible to $\pm 6\%$ of the reported. Both 3-hexenes were shown to be configurationally stable under the reaction conditions. ^c Bp 119.5°; n_D^{20} 1.4341. ^d Bp 114.6°; n_D^{20} 1.4341. ^e THF = tetrahydrofuran; = 1,2-dimethoxyethane.

inversion process,^{4,5} whereas inversion of the 1-vinyl radical does not,⁴ no reliable estimate of relative activation energies for inversion of these species is possible. Thus one cannot employ results of the esr studies to determine whether substitution at the 1 position stabilizes or destabilizes the linear configuration relative to the non-linear configuration for the vinyl radical.

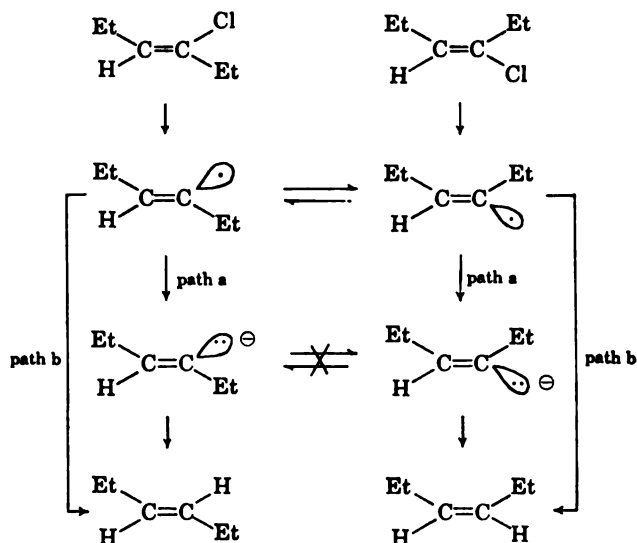
h Fantazier and Kampmeier⁶ and Singer and ⁷ have studied the vinyl radical generating decomposition of *t*-butyl peresters of *cis-trans* pairs of unsaturated acids. Decompositions carried out in hydrogen-donating solvents led to mixtures of olefins whose relative concentration was independent of the duration of the perester employed. Although both can interpret these results in terms of rapid equilibration of the intermediate vinyl radicals, these data are very well explained by postulating the intervention of a single, linear⁸ vinyl radical as the intermediate in the decomposition of both the *cis* and *trans* peresters.⁹ Previous work has shown that the naphthalene radical undergoes an electron-transfer reaction with halides to yield halide ion and alkyl free radicals.¹² In an effort to generate isomeric vinyl free radicals, we have examined the reaction of sodium naphthalenide with *cis*- and *trans*-3-chloro-3-hexene.

For substituted vinyl radicals, the linear (sp) configuration would have at least three inherent advantages relative to the nonlinear form: (1) decreased torsional strain, (2) decreased nonbonded and (3) increased bond strengths resulting from sp hybridization at the radical site. The imprecision with which the relative stability of linear and nonlinear configurations of the unsubstituted vinyl radical is known renders impossible an *a priori* estimate of the relative stabilities of the two forms for a substituted vinyl radical. Singer and Kong⁷ were able to show that the temperature dependence of the ratio of *cis*- to *trans*-propenylbenzene derived from α -methylpercinnaamate could be interpreted logically in terms of rapidly equilibrating nonlinear vinyl radical intermediates. To these results on the basis of a single linear vinyl radical intermediate would require the seemingly unreasonable postulate that the reactivity of hydrogen atom abstraction increases with tempera-

The sole detectable product derived from both chlorohexenes was a mixture of *cis*- and *trans*-3-hexene formed in at least 98% yield. The product analyses for several runs at two temperatures and in two solvent systems are presented in Table I.

In all instances, *trans*-3-hexene predominates in the product mixture, but the ratio of *cis*- to *trans*-3-hexene is decidedly a function of the configuration of the 3-chloro-3-hexene employed. This observation immediately excludes the possible intermediacy of either a single linear (sp) vinyl radical or two isomeric, configurationally stable, nonlinear (sp²) vinyl free radicals. Use of sodium naphthalenide as the reducing agent precludes the possibility that a vinyl carbanion is generated directly by a two-electron reduction of 3-chloro-3-hexene.

We conclude that the initial charge-transfer reaction generates a nonlinear vinyl radical which is capable of facile inversion at the radical site, but that the radical is trapped before complete equilibration with its configurational isomer is achieved.¹³



The interconverting vinyl radicals might be trapped either by reduction to a configurationally stable carbanion^{14,16} (path a) or by hydrogen abstraction from

(13) Inherent in the interpretation here presented is the assumption that initial electron transfer does not yield a hexenyl chloride radical anion as a discrete intermediate. Several lines of evidence point to the validity of this assumption. Perhaps the most compelling lies in the observation that the reaction cross section for the vapor-phase reaction of sodium atoms with vinyl chloride is on the order of 0.1 to 1.0 Å². If vinyl chloride radical anions were viable species, one would expect this reaction to occur by a "stripping" mechanism. Such a mechanism, however, is known to lead to reaction cross sections on the order of 10³ to 10⁴ Å². Low reaction cross sections are characteristic of the "rebound" mechanism, a path known to be followed in the vapor-phase reaction of alkali metal atoms with molecules, such as methyl iodide, which cannot form radical anions possessing even transient stability. For details, see: D. R. Herschbach, *Advan. Chem. Phys.*, **10**, 319 (1966); K. R. Wilson and D. R. Herschbach, *Nature*, **208**, 183 (1965).

(14) For a summary of the evidence which indicates considerable configurational stability for vinyl carbanions, see D. J. Cram, "Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 133-135.

(15) Reduction of both *cis*- and *trans*-3-chloro-3-hexene with sodium in liquid ammonia, a reaction which presumably proceeds *via* the vinyl carbanion,^{14,17} yields alkene with at least 96% retention of configuration. We have yet to establish conclusively that vinyl carbanion isomerization does not occur under the conditions of our investigation. Such isomerization, if it does occur, would not invalidate the present results as evidence for the nonlinearity of the 3-hex-3-enyl radical.

(16) See Hoff, *et al.*, footnote a, Table I.

(17) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 71.

G. D. Sargent, J. N. Cron, and S. Bank, *J. Am. Chem. Soc.*, **88**, 966.

J. F. Garst, W. Ayers, and R. C. Lamb, *ibid.*, **88**, 4260 (1966).
S. J. Cristol and R. V. Barbour, *ibid.*, **88**, 4261 (1966).

solvent (path b). The fact that *trans*-3-hexene, the thermodynamically more stable isomer,¹⁸ always predominates in the reaction mixture suggests that the former alternative (path a) is adopted. Vinyl free radicals generated by perester decomposition and trapped by reaction with hydrogen atom donors (e.g., cumene) invariably lead to products which, relative to the equilibrium mixture, are markedly enriched in the thermodynamically less stable olefin.^{6,7} This is readily explained in terms of increased steric interaction between the donor and acceptor molecules in the transition state for hydrogen atom donation to the *trans* radical as compared with the *cis* radical.⁷ The transition state for electron transfer from radical anion to the vinyl radical presumably need not be so highly oriented or so intimate as that for hydrogen atom donation. Thus transfer should take place with equal ease to either the *cis*- or *trans*-vinyl radical.

Acknowledgment. We are pleased to thank the Mobil Oil Corporation for an unrestricted grant-in-aid employed in support of this research.

(18) $\Delta G^\circ_{298^\circ\text{K}}(\text{trans-3-hexene(g)}) = 18.86 \text{ kcal/mole}$; $\Delta G^\circ_{298^\circ\text{K}}(\text{cis-3-hexene(g)}) = 19.66 \text{ kcal/mole}$; F. D. Rossini, *et al.*, "Selected Values of the Properties of Hydrocarbons," National Bureau of Standards Circular C461, U. S. Government Printing Office, Washington, D. C., 1947.

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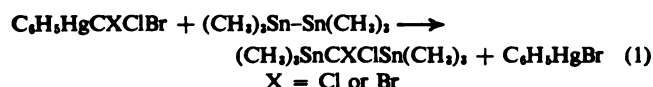
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Received February 4, 1967

The Reaction of Phenyl(trihalomethyl)mercurials with Hexamethylditin. The First Case of Dihalocarbene Insertion into a Metal-Metal Bond to Give a Stable MCX₂M System

Sir:

In a recent communication¹ we described the reaction of phenyl(bromodichloromethyl)mercury with bis(trimethylsilyl)mercury and bis(trimethylgermyl)mercury. We proposed that an intermediate formed in these reactions was the product of dichlorocarbene insertion into the Si-Hg and Ge-Hg bonds, Me₃MCCL₂-HgMMe₃ (M = Si and Ge), and that further reactions of this intermediate led to the observed products. This explanation in terms of dihalocarbene insertion into metal-metalloid bonds suggested to us that other such insertions into covalent metal-metal bonds should be possible and that in favorable cases the initial M-CX₂-M systems could be both thermally stable and kinetically stable with respect to further attack by CX₂ and thus capable of isolation. We have found this to be the case with hexamethylditin in its reaction with phenyl(bromodichloromethyl)mercury and phenyl(dibromochloromethyl)mercury (eq 1).



As an example, we describe the reaction between PhHgCCl₂Br and hexamethylditin. A mixture of 0.10

(1) D. Seyferth, R. J. Cross, and B. Prokai, *J. Organometal. Chem.* (Amsterdam), **7**, P20 (1967).

mole each of the mercurial² and hexamethylditin in 250 ml of dry benzene was stirred and heated at reflux under nitrogen for 3.5 hr. The reaction mixture was filtered to remove 30.6 g of gray solid, mp 276-286° (phenylmercuric bromide contaminated with some metallic mercury). Concentration of the orange filtrate at 10 mm resulted in crystallization of 3.64 g of diphenylmercury. Trap-to-trap distillation at 0.8 mm (pot temperature to 100°) removed the remaining solvent and minor amounts of trimethyltin halides; further distillation at 2×10^{-4} mm at room temperature gave small amounts of trimethyltin halides and phenyltrimethyltin,³ leaving a liquid identified as bis(trimethyltin)dichloromethane, (CH₃)₃SnCCl₂Sn(CH₃)₃, bp 48-50° (2×10^{-4} mm), n^{25}_D 1.5326, analysis for all elements satisfactory, in 53% yield. Its nmr spectrum (CS₂) showed a sharp singlet at 0.3 ppm downfield from internal tetramethylsilane, with the expected tin satellites ($J_{\text{Sn}^{119}\text{-H}^1} = 53.5 \text{ cps}$; $J_{\text{Sn}^{117}\text{-H}^1} = 51.5 \text{ cps}$), and the infrared spectrum (pure liquid) showed bands at 2980 (s), 2915 (s), 1191 (s), 770 (vs), 725 (s), 667 (m), 632 (s), 527 (s), and 507 (sh) cm⁻¹. The mass spectroscopically determined molecular weight was 410 (calculated 410); the major fragment was Me₃Sn⁺.

A similar reaction using phenyl(dibromochloromethyl)mercury gave bis(trimethyltin)bromochloromethane, (CH₃)₃SnCBrClSn(CH₃)₃, bp 61° (2×10^{-4} mm), n^{25}_D 1.5502, in 39% yield. A satisfactory analysis and mass spectroscopic molecular weight were obtained. The trimethyltin resonance occurred at 0.3 ppm, and the infrared spectrum showed absorption at 2970 (m), 2900 (m), 1190 (m), 768 (vs), 720 (s), 674 (sh), 659 (s), 580 (s), and 526 (vs) cm⁻¹. It is of interest to note that the reaction of phenyl(bromodichloromethyl)mercury with hexamethylditin in benzene for 6 days at room temperature gave bis(trimethyltin)dichloromethane in 52% yield.

Attempts to utilize these bis(trimethyltin)dihalomethanes as sources of the carbene (CH₂)₃SnCCl₂ have thus far been unsuccessful, mostly because of the thermal stability of these compounds. Bis(trimethyltin)dichloromethane was not decomposed on being heated in a sealed tube at 145° for 40 hr. Attempted reaction with tetramethylethylene at 180° for 4 days gave trimethyltin chloride as the only identifiable organotin product. Similarly, bis(trimethyltin)bromochloromethane survived 20 hr of heating at 130° in the presence of tetramethylethylene without decomposition, but at 190-200° (24 hr) both trimethyltin bromide and chloride were formed.

We have found that nucleophilic attack by iodide ion at the metal in a trihalomethylmercury or -tin compound provides another procedure for the release of CX₂ from such reagents.⁵ In the case of bis(trimethyl-

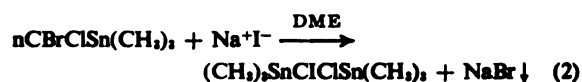
(2) D. Seyferth and J. M. Burlitch, *ibid.*, **4**, 127 (1965).

(3) By-product formation can be rationalized in terms of a reaction between phenylmercuric bromide and hexamethylditin to give trimethyltin bromide and PhHgSnMe₃. Decomposition of the latter then gives PhSnMe₃ and metallic mercury in one mode, diphenylmercury, metallic mercury, and hexamethylditin in another. This point is being examined.

(4) Note analogous release of CCl₂ from Me₃SnCCl₂ and Me₃SnCCl₂Br in this connection: D. Seyferth, F. M. Armbrrecht, Jr., B. Prokai, and R. J. Cross, *J. Organometal. Chem.* (Amsterdam), **6**, 573 (1966).

(5) (a) D. Seyferth, J. Y.-P. Mui, M. E. Gordon, and J. M. Burlitch, *J. Am. Chem. Soc.*, **87**, 681 (1965); (b) D. Seyferth, M. E. Gordon, J. Y.-P. Mui, and J. M. Burlitch, *ibid.*, **89**, 959 (1967); (c) D. Seyferth, H. Dertouzos, R. Suzuki, and J. Y.-P. Mui, *J. Org. Chem.*, in press.

monochloromethane, however, attack of iodide at carbon (eq 2). The product, obtained in



yield, was unstable in air, turning bright orange on exposed surfaces. Its combustion analysis, spectroscopic molecular weight, and infrared spectrum were in agreement with the structure shown. We recognize that our discovery of the first case of carbene insertion into a metal-metal bond to give the $-\text{M}-\text{CX}_2-\text{M}-$ system opens up a broad new field of research in the organometallic aspects of carbene chemistry. The study of compounds containing metal-metal bonds has received much attention in the past few years, as the many papers on this subject show.⁶ We currently are investigating reactions of phenyl(trihalomethyl)mercurials with compounds containing main group metal-main group bonds, main group metal-transition metal bonds, transition metal-transition metal bonds with the view of preparing and studying new $\text{M}-\text{CX}_2-\text{M}$ systems.

Acknowledgments. The authors are grateful to the Directorate of Chemical Sciences, Air Force Office of Scientific Research, for generous support of this research and to M&T Chemicals, Inc. for gifts of chemicals. This investigation was supported in part by a Health Service Fellowship 5-F1-GM-23,742 (to A.).

D. Seyferth and R. B. King, "Annual Surveys of Organometallic Chemistry," Vol. 1 and 2, Elsevier Publishing Co., Amsterdam, 1966, for recent references.

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Presence of Dehydroalanine in the Antibiotic Nisin: Its Relationship to Activity

The peptide antibiotic nisin^{1,2} was treated with hydrogen bromide³ (0.1 N HCl, 37°, 24 hr) in order to cleave the methionyl peptide bonds, a product of low molecular weight (fractions 91-110; 22 ml) was isolated by gel chromatography on a Sephadex G-25 column (6 × 120 cm; 0.2 N CH₃COOH).

The same product was isolated from control experiments in the absence of the reagent, indicating a bond is labile under mildly acidic conditions. Aliquots were pooled and lyophilized fractions from both experiments were analyzed directly using the accelerated method⁴ of an amino acid analyzer.⁵ A single substance was eluted from the 0.9 × 60 cm column at an effluent volume of 172-182 ml. Lysine was the only amino

acid found in the total hydrolysate. The hydrolysate of the dinitrophenylated product contained only N^ε-dinitrophenyllysine, thus indicating the presence of an N^ε-substituted derivative of lysine.

The product of the reaction of this lysine derivative with ninhydrin showed optical densities at 570 and 440 mμ which were reminiscent of those of free lysine. We therefore concluded that the N^ε substituent is labile under the conditions of the ninhydrin reaction.

Similar observations had been made earlier with pyruvylamino acids formed during cleavage of the aminoacyl bond of N-aminoacyl-S-alkylcysteine peptides.⁶

The isolated product was treated with *o*-phenylenediamine.⁷ Lysine was liberated in a yield of 50% after 4 hr of reaction at 37°. The fragment thus appeared to be pyruvyllysine. Since dehydroalanine peptides are cleaved with the formation of pyruvyl peptides it is implied that the COOH-terminal sequence⁸ of nisin is *dehydroalaninyllysine*. The release of pyruvyllysine in dilute acid is, however, slow (2%/24 hr; cf. below, conditions for the quantitative cleavage).

The molecular weight of nisin was determined by the method of partial substitution.⁹ Monodinitrophenyl-nisin was isolated and purified¹⁰ by countercurrent distribution in the system butan-1-ol-acetic acid-water, 4:3:1.

A molecular weight value of 3510 was calculated for this derivative, which is one-half that reported earlier.³ It is, however, in agreement with the minimum molecular weight determined from the amino acid analyses of nisin (micromoles/0.5 mg; 92% recovery without dry weight correction) and *monodinitrophenyl-nisin* (micromoles/0.5 mg; quantitative recovery after desiccation): lysine (0.382; 0.267), histidine (0.255; 0.265), ammonia (0.425; 0.459), aspartic acid (0.139; 0.144), serine (0.119; 0.113), lanthionine + β-methylanthionine (0.740; 0.760), proline (0.130; 0.129), glycine (0.400; 0.421), alanine (0.260; 0.270), valine (0.134; 0.138), methionine (0.253; 0.261), isoleucine (0.376; 0.393), leucine (0.257; 0.268); mol wt (nisin), 3290; mol wt (mono-DNP-nisin), 3460.

These data indicate clearly that only one residue of lysine has been dinitrophenylated. Dinitrophenylation did not take place at the COOH-terminal lysine, since pyruvyllysine is still released from mono-DNP-nisin.

The above partial structure of the antibiotic is supported by: (a) the addition of mercaptoacetamide to the double bond of dehydroalanine at pH 4.5 and room temperature (with 1.6 mM nisin solution, the following values were determined for carboxymethylcysteine in the addition product: 0.24 residue, 24 hr, 1.6 mM mercaptan; 1.2 residues, 24 hr, 28 mM mercaptan; 1.2 residues, 72 hr, 56 mM mercaptan; the test for free sulhydryl groups with maleimide was negative and the hydrolysate was free of cystine); (b) a comparison

from Apin & Barrett Ltd., Yeovil, England. The purification of the antibiotic by gel chromatography and countercurrent distribution was published separately by E. Gross, J. L. Morell, and P. Q. Lee.

C. Cheeseman and N. J. Berridge, *Biochem. J.*, **71**, 185 (1959).
E. Gross and B. Witkop, *J. Biol. Chem.*, **237**, 1856 (1962).

H. Spackman, "Serum Proteins and the Dysproteinemias," Underman and F. W. Sunderman Jr., Eds., J. B. Lippincott Co., Philadelphia, Pa., 1964, pp 166-173.

H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 58.

(6) E. Gross, C. H. Plato, J. L. Morell, and B. Witkop, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., 1965, Abstract 125, p 60C.

(7) H. B. T. Dixon and V. Moret, *Biochem. J.*, **94**, 463 (1965).

(8) Contrary to earlier reports (cf. ref 2) on the absence of free end groups, nisin also contains a free terminal amino group, namely, that of isoleucine.

(9) A. R. Battersby and L. C. Craig, *J. Am. Chem. Soc.*, **74**, 4023 (1952).

(10) E. Gross, J. L. Morrell, and P. Q. Lee, unpublished data.

of the isolated nisin fragment with an authentic sample of pyruvyllysine which was synthesized according to the procedure of Bergmann and Grafe.¹¹ Pyruvic acid and acetamide were combined to give α,α -diacetaminopropionic acid which was converted to the azlactone by treatment with acetic anhydride on a steam bath and coupled with N^ε-carbobenzoxyllysine benzyl ester. The protecting groups were removed by catalytic hydrogenation. α,α -Diacetaminopropionyllysine, mp 145° (uncor) (*Anal.* Calcd for $C_{13}H_{24}O_5N_4 \cdot H_2O$: C, 46.49; H, 7.84; N, 16.76. Found: C, 47.15; H, 7.96; N, 16.59), was treated with HCl in glacial acetic acid (110°, 10 min) to form pyruvyllysine. The synthetic product was eluted from the 60-cm column of the amino acid analyzer^{4,5} at the same position as the nisin fragment. The conversion of α,α -diacetaminopropionyllysine to pyruvyllysine is quantitative, as judged by the disappearance of the peak of α,α -diacetaminopropionyllysine (effluent volume: 111–123 ml) and the appearance of only the peak corresponding to pyruvyllysine. Free lysine was absent. The ratio of the calibration value of lysine to that of pyruvyllysine is 1.56. Treatment of 1 μ mole of nisin with HCl in glacial acetic acid (110°, 10 min) released 0.9 μ mole of pyruvyllysine.

The antibiotic activity of nisin and its derivatives was tested against *Staphylococcus aureus* (ATCC-10537). Nisin strongly inhibits the growth of the bacterium. Monodinitrophenylisin was also a growth inhibitor.

The addition product of nisin and mercaptoacetamide showed a very weak growth inhibitory effect, which is perhaps due to partial reactivation of the originally inactive carboxamidomethylthiolisin. Enzyme systems capable of catalyzing this type of elimination have been described.¹²

The reaction products of the acid-catalyzed cleavage of the C α -N bond of dehydroalanine in nisin, namely des-(dehydroalanyllysine)-nisin and pyruvyllysine, are both inactive against *Staphylococcus aureus*. However, when pyruvyllysine was combined with des-(dehydroalanyllysine)-nisin in a ratio of 2:3 and kept in a moist state for 48 hr at room temperature, a recombination product was obtained which again displayed antibiotic activity against *Staphylococcus aureus*. A quantitative determination showed a decrease of 70% in the original amount of pyruvyllysine. This reaction may represent a step in the biosynthesis of the antibiotic. It will undoubtedly be of importance in the contemplated synthesis of biologically active analogs of nisin.

It has thus been clearly shown for the first time that dehydroalanine is present in a naturally occurring peptide antibiotic. The biological activity of nisin is directly related to the presence of dehydroalanine in the molecule. We believe that the addition of mercaptans is the *in vitro* model reaction for the biological action of nisin. Metabolically important compounds, such as sulfhydryl-containing enzymes, glutathione, or coenzyme A, may be intercepted by nisin.

This supposition is being tested, as far as coenzyme A is concerned, on malarial parasites. These are known to be sensitive to deficiency in coenzyme A, whether

this is caused by dietary host deprivation¹³ or the presence of antipantothenes.¹⁴

Two groups of five mice each received four consecutive daily doses of (a) 500 mg/kg of nisin orally; (b) 250 mg/kg of nisin intraperitoneally. On day 4, parasite growth in the mice of group b was reduced by 98% of that on control animals. On day 7, the reduction in parasite growth was 80% for group a.

It remains to be seen whether these effects can be reversed by infusion of acetyl coenzyme A.

Acknowledgment. We gratefully record that the support of Dr. B. Witkop has decisively furthered this work. It is a pleasure to acknowledge the skillful assistance of Miss Patricia Q. Lee. We also wish to express our thanks to Dr. R. Schmitt for the bacterial activity tests and to Dr. G. M. Jeffery and his associates, who tested the antimalarial properties of nisin.

(13) S. Brackett, E. Woletzky, and M. Baker, *J. Parasitol.*, **32**, 435 (1945).

(14) W. Trager, *Trans. N. Y. Acad. Sci.*, **28**, 1094 (1966).

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Received March 18, 1967

The Tricyclo[2.1.0.0^{2,5}]pentane System

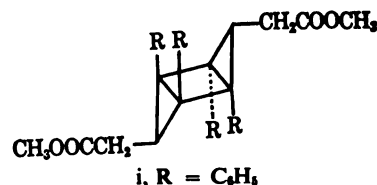
Sir:

Recently it was reported that the photolysis of diazo-ketones **1a** and **b** in tetrahydrofuran provided ketones **2a** and **b**, respectively, and the tricyclo[2.1.0.0^{2,5}]pentane skeleton was assigned to these compounds mainly on the basis of spectral evidence.^{1–3} Doering and Pomerantz, interpreting the spectral data of **2a** in a different manner, suggested an alternative structure (**3**).⁴ Although the evidence then available to us and subsequent works⁵ have convinced us that the tricyclic structure is the correct representation of **2a** and **b**, we have undertaken an X-ray crystal analysis of a derivative of **2a**. The result now confirms the correctness of our structure and, further, provides the precise geometry of the ring system, which is essential for understanding its unusual properties.

(1) S. Masamune, *J. Am. Chem. Soc.*, **86**, 735 (1964).

(2) Our original nomenclature is corrected: J. D. Connolly and K. H. Overton, *Ann. Rept. Progr. Chem.* (Chem. Soc. London), **348** (1964); J. Meinwald and J. K. Crandall, *J. Am. Chem. Soc.*, **88**, 1292 (1966).

(3) Irradiation of a methanolic solution of **1** gave in addition to **2** (10–15%) the methyl ester of the homologated acid (20%) and a dimeric compound (20–30%), mp 236–237°, for which structure **i** accommodates all experimental data: H. H. Stechl, *Ber.*, **97**, 2681



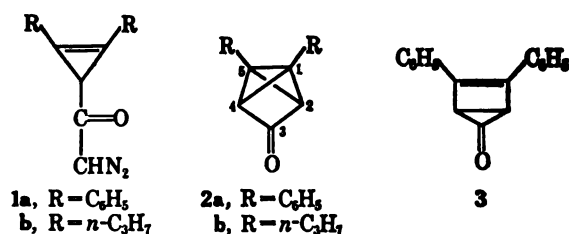
(1964); N. Obata and I. Moritani, *Bull. Chem. Soc. Japan*, **39**, 2250 (1966). Somewhat to our surprise, a highly purified sample of **1** evolved nitrogen very slowly upon irradiation and provided no ketone **2**. Addition of a sensitizer reproduced the products mentioned above. Copper-catalyzed reaction of **1** in refluxing benzene afforded a trace amount of **2** (at most 1%) (see ref 4).

(4) W. von E. Doering and M. Pomerantz, *Tetrahedron Letters*, 961 (1964).

(5) (a) S. Masamune, *ibid.*, 945 (1965); (b) S. Masamune, K. Fukumoto, Y. Yasunari, and D. Darwish, *ibid.*, 193 (1966).

(11) M. Bergmann and K. Grafe, *Z. Physiol. Chem.*, **187**, 187 (1930).

(12) M. Flavin and C. Slaughter, *Biochemistry*, **3**, 885 (1964).



Crystals of 1,5-diphenyltricyclo[2.1.0.0^{2,5}]pent-3-yl *p*-bromobenzoate, mp 138.5–139°, are triclinic: $a = 5.92$, $b = 8.98$, $c = 17.85$ Å, $\alpha = 89^\circ 17'$, $\beta = 82^\circ 46'$, $\gamma = 89^\circ 50'$, $Z = 2$, space group $P\bar{1}$. The structure was determined with visual Cu K α data from three-dimensional Patterson and electron-density distributions and refined by ten cycles of block-diagonal least-squares, the final R value being 0.16 for 1228 reflections. Sections of the electron-density distribution, and a corresponding diagram of the ring system, are shown in Figure 1, and the dimensions of the tricyclopentane ring system are given in Table I.

Table I. Bond Distances (Angstroms) and Valency Angles (Degrees) in the Tricyclopentane System^a

C(2)–C(3)	1.50	C(2)–C(3)–C(4)	81.7
C(3)–C(4)	1.54	C(3)–C(4)–C(5)	89.3
C(2)–C(5)	1.53	C(3)–C(4)–C(1)	92.2
C(1)–C(2)	1.54	C(3)–C(2)–C(5)	90.8
C(4)–C(5)	1.53	C(3)–C(2)–C(1)	92.9
C(1)–C(4)	1.52	C(4)–C(5)–C(2)	81.3
Mean	1.53	C(4)–C(1)–C(2)	81.4
		C(5)–C(4)–C(1)	56.3
C(1)–C(5)	1.44	C(5)–C(2)–C(1)	56.1
		C(4)–C(5)–C(1)	61.4
C(2)···C(4)	1.99	C(4)–C(1)–C(5)	62.3
		C(2)–C(5)–C(1)	62.3
		C(2)–C(1)–C(5)	61.6
External angles at C(1) and C(5) = 134.4–142.1 (six angles), mean 138		C(2)–C(3)–O	115.6
		C(4)–C(3)–O	109.5

^a Standard deviations are 0.05 Å and 3°.

The crystal analysis has confirmed the formulation of the compound as a derivative of tricyclo[2.1.0.0^{2,5}]pentane. The great strain in the ring system is indicated by the valency angles given in Table I, there being six C–C–C angles of about 60°, three of about 80°, and four of about 90°. The C(2)···C(4) nonbonded distance is only 1.99 Å. The bond distances, however, do not appear to be greatly influenced by the strain. Six of the C–C distances are in the range 1.50–1.54 Å, mean value 1.53 Å (standard deviation of the mean = 0.02 Å), close to the normal single bond length. The bond which is common to the two three-membered rings, C(1)–C(5), measures 1.44 ± 0.05 Å, so that this bond does seem to be shortened slightly, although the difference from the other bonds (0.09 Å = 1.8σ) cannot be claimed to be definitely statistically significant.

All the dimensions of the substituent groups are normal. The orientations of the two phenyl groups with respect to the tricyclopentane ring system are similar, but not quite identical, and are probably influenced by intermolecular interactions.

The geometry of a derivative of 2 now being known, we understand better the unusual spectral behavior of this strained system. It is interesting to note that mass

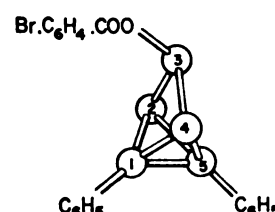
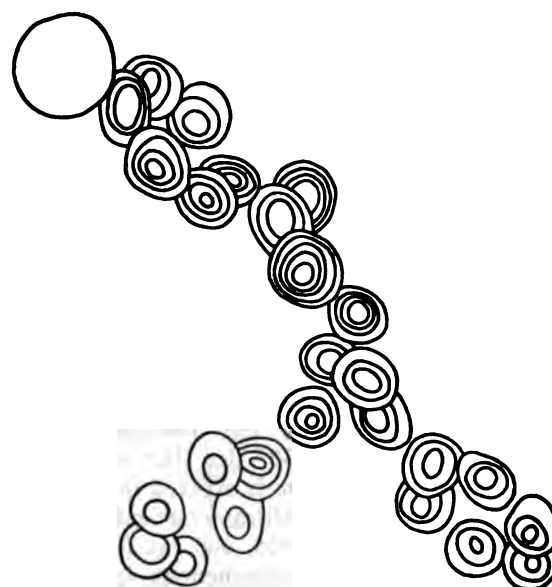


Figure 1.

spectra of 2 and the corresponding hydroxy compound exhibited, in addition to their parent peaks, pronounced peaks at $M - \text{CO}^+$ and $M - \text{CHO}$, respectively. The interpretation of these peaks, of course, must await further studies.⁶

(6) We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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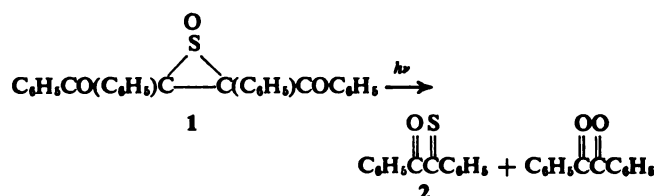
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Received March 20, 1967

Photolysis of Dibenzoylstilbene Episulfoxide. Formation of Monothiobenzil¹

Sir:

Irradiation of dibenzoylstilbene episulfoxide² (1) in benzene at 7–11° gives deep blue monothiobenzil³



(1) This work was supported in part by Grant GP-5513 of the National Science Foundation.

(2) D. C. Dittmer and G. C. Levy, *J. Org. Chem.*, **30**, 636 (1965). Its stereochemistry is unknown.

(3) No previous characterization of monothiobenzil has been reported, although it has been suggested as a decomposition product of

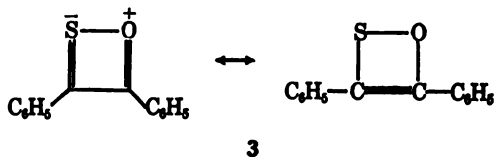
(2; 55%) and benzil (56%). This photochemical decomposition of dibenzoylstilbene episulfoxide is the first such decomposition of an episulfoxide, a relatively new class of compounds.⁴

Solutions of about 0.3 g of episulfoxide in 500 ml of benzene were irradiated with a water-cooled, internal mercury arc lamp (Hanovia Type L, 450 w) with or without a Pyrex filter. Purified nitrogen was passed through the solution and reaction vessel for at least 30 min before irradiation, and a positive pressure of nitrogen was maintained during the reaction.

Monothiobenzil was obtained as a blue oil after column chromatography on silicic acid which separated it from the benzil. Monothiobenzil forms the same 2,4-dinitrophenylhydrazone, mp 188–190° (lit.⁵ mp 189°), and dioxime, mp 238° dec (lit.⁶ mp 238° dec) as benzil. Hydrogen sulfide is evolved in the preparation of these derivatives. Ultraviolet and visible spectra in chloroform [λ 247, 325, 606 m μ ($\epsilon \sim 30$)] were similar to those of thiobenzophenone in chloroform [λ 248, 329, 598 m μ ($\epsilon' \sim 167$)]. Monothiobenzil exhibits in the mass spectrum a molecular ion at m/e 226 and ions at m/e 198, 178, 121, and 105 formed by the loss of CO, SO, C₆H₅CO, and C₆H₅CS radicals, respectively. The thioketone is a labile compound, and a satisfactory analysis has not been obtained.

The infrared and ultraviolet spectra, melting point and mixture melting point (95°), and 2,4-dinitrophenylhydrazone (mp 185–189°) of the benzil produced in the irradiation are identical with those of authentic benzil.

Monothiobenzil is of interest because of the possibility of interaction between sulfur as an electron acceptor and oxygen as an electron donor as indicated in 3. The interaction of two sulfur atoms on adjacent



carbon atoms in the dianion *cis*-dimercaptomaleonitrile has been considered.⁸ No definite evidence for or against interaction between sulfur and oxygen has been obtained, but the mass spectrum of monothiobenzil indicates no ion is formed by loss of sulfur alone, whereas in the mass spectrum of thiobenzophenone an important fragment corresponds to the parent ion minus sulfur.⁹

A possible mechanism for the photochemical de-

didesyl sulfide and of a dibenzyl thioketal: A. Schönberg and O. Schütz, *Ann.*, **454**, 53 (1927); A. Schönberg and Y. Iskander, *J. Chem. Soc.*, 90 (1942).

(4) In addition to dibenzoylstilbene episulfoxide, several other episulfoxides have been prepared recently and thermochemical loss of sulfur monoxide from them has been observed: G. E. Hartzell and J. N. Paige, *J. Am. Chem. Soc.*, **88**, 2616 (1966); G. E. Hartzell and J. N. Paige, *J. Org. Chem.*, **32**, 459 (1967). Thermochemical decomposition of dibenzoylstilbene episulfoxide, observed by us, gives a complex mixture of products, among which are benzil, benzoic acid, and *trans*-dibenzoylstilbene.

(5) N. R. Campbell, *Analyst*, **61**, 391 (1936).

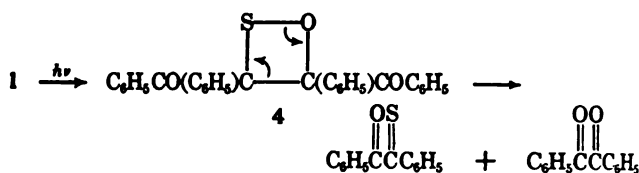
(6) G. Ponzio and L. Avogadro, *Gazz. Chim. Ital.*, **53**, 317 (1923); J. Meisenheimer and W. Lamparter, *Ber.*, **57**, 276 (1924).

(7) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *J. Am. Chem. Soc.*, **79**, 712 (1957).

(8) H. E. Simmons, D. C. Blomstrom, and R. D. Vest, *Ibid.*, **84**, 4756 (1962).

(9) Determination of whether monothiobenzil has an *s-cis* or *s-trans* structure would be pertinent to the question of the importance of 3.

composition of 1 involves rearrangement to the oxathietane, 4.



Work is in progress on the mechanism of photochemical and thermochemical rearrangements of episulfoxides.

(10) National Science Foundation Undergraduate Research Scholar.

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Received March 28, 1967

A Novel Method for the Reduction of α,β -Unsaturated Ketones

Sir:

We wish to report a novel method for the selective reduction of only those double bonds which are conjugated with the carbonyl group as in an α,β -unsaturated ketone under the nonreducing conditions. This method involves the condensation of a ketone with benzylamine to give the corresponding Schiff base (I), which on treatment with a base (0.1–1 mole) such as potassium *t*-butoxide undergoes rearrangement to II (cf. the isomerization of β,γ -unsaturated ketones \rightarrow α,β -unsaturated ketone analogs). The rearrangement can be carried out with or without any solvent. Various solvents used are benzene, monoglyme, diglyme, dimethyl sulfoxide, hexamethylphosphoramide, *t*-butyl alcohol, and other protic and aprotic solvents. Hydrolysis of II with dilute acetic acid furnishes the corresponding saturated aldehyde or a ketone with the concomitant formation of benzaldehyde. Rearrangement can also be effected with an acid catalyst such as *p*-toluenesulfonic acid, but the yields are unsatisfactory in this case.

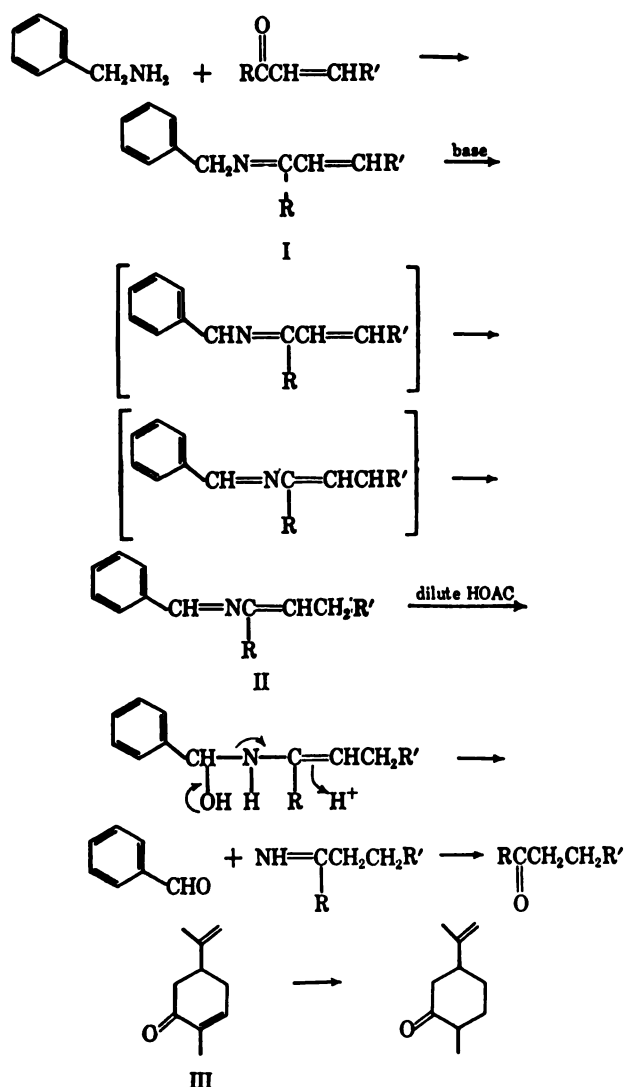
The method may be illustrated by the reduction of a typical α,β -unsaturated ketone such as *d*-carvone (III), as described below.

A mixture of 20 g (0.084 mole) of the benzylamine Schiff base of *d*-carvone (bp 113° (0.02 mm); *Anal.* Found: C, 85.67; H, 8.60) and 0.93 g (0.0084 mole) of potassium *t*-butoxide in 75 ml of anhydrous diglyme was stirred at room temperature and under nitrogen for 20 min. To the resulting solution 30 ml of 50% acetic acid was added and stirring was continued for another 20 min. After the usual work-up, the product, dihydrocarvone, bp 90–92° (15 mm) (oxime mp 88°; lit.¹ mp 88–89°) was obtained in 75% yield.

Other monocyclic ketones reduced by this method are 3-methyl- Δ^2 -cyclohexenone, 3,5-dimethyl- Δ^2 -cyclohexenone, 3,4-dimethyl- Δ^2 -cyclohexenone, 2,4-dimethyl- Δ^2 -cyclohexenone, and isophorone, the overall yields being 40–70%.

The I–II rearrangement was found to be slower for the ketones with alkyl groups at the β position than for those lacking such substitution. For instance, the

(1) J. L. Simonson, "The Terpenes," Vol. I, 2nd ed, The University Press, Cambridge, England, 1953, p 352.

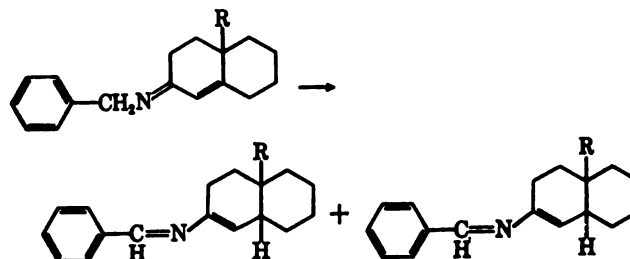


room temperature rearrangement of the Schiff base of 3,5-dimethyl- Δ^2 -cyclohexenone with 0.1 mole of potassium *t*-butoxide in hexamethylphosphoramide solution proceeded to the extent of only 56.7% in 1 hr.² On the other hand, under similar conditions the rearrangement of the Schiff bases of 2,4-dimethyl- Δ^2 -cyclohexenone and *d*-carvone was complete within 5 min. The slowness is most likely due to (a) the intermediacy of a tertiary carbanion in contrast to the secondary carbanion arising from the Schiff's bases of ketones lacking substitution at the β position, and (b) hyperconjugative and inductive effects of the alkyl groups enhancing the ground-state stability of the Schiff bases of the β -substituted ketones. The rate of the rearrangement could, however, be accelerated by increasing the amount of base and the reaction temperature. For instance, the rearrangement of the Schiff base of 3,5-dimethyl- Δ^2 -cyclohexenone with 1 equiv of KO-*t*-Bu was complete within 40 min at 100°.

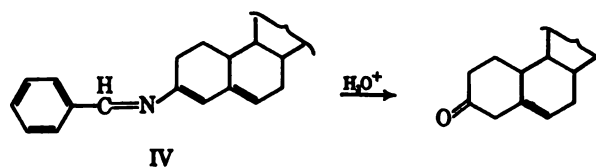
Reduction of bicyclic ketones, *e.g.*, $\Delta^{1(9)}$ -2-octalone and 10-methyl- $\Delta^{1(9)}$ -2-octalone, when the rearrangement of their Schiff bases was stopped after 30–40% completion, led to the corresponding *trans*-decalones. These results indicate that, in this mode of reduction,

(2) The extent of the rearrangement of the Schiff base was followed by the disappearance of bands due to benzylic protons in the nmr spectrum and by the determination of saturated and unsaturated ketones in the hydrolyzed product by glpc.

the transition state for the kinetic protonation at the β -carbon atom is analogous to that involved in the metal-ammonia reduction of these ketones.³ It is, however, obvious that under equilibrating conditions the rearrangement of these Schiff bases would lead to a thermodynamic mixture of the *cis* and *trans* isomers and thus provide a direct method for the determination of the thermodynamic stabilities of various substituted Δ^1 -octalins.⁴ Further work along these lines is in progress.



Reduction of steroidal Δ^4 -3-ketones, *e.g.*, testosterone and cholestenone, proceeded in relatively poor yields in our hands, due to the formation of side products. Pregna- $\Delta^{5,16}$ -dien-3 β -ol-20-one was reduced to pregnenolone in 40% yield. Reduction of cholest- $\Delta^{4,6}$ -dien-3-one led to a mixture of cholest- Δ^4 - and Δ^6 -en-3-ones in 50% yields.⁵



(3) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964); M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

(4) The Schiff base of $\Delta^{(9)}$ -2-octalone on heating with 0.1 mole of potassium *t*-butoxide at 130° for 19 hr gave a 1:4 mixture of *cis*- and *trans*-decalones.

(5) The formation of Δ^4 -3-one is due to the protonation of IV at C-4 which is analogous to the protonation of $\Delta^{1,6}$ -enolate. Also see S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **87**, 3228 (1965), and references cited therein.

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Received April 1, 1967

Chlorine(III) Oxide, a New Chlorine Oxide

Sir:

There are four known stable oxides of chlorine: Cl_2O , ClO_2 , Cl_2O_6 (which dissociates to ClO_3 in the vapor), and Cl_2O_7 . These compounds have been known and characterized for a long time and they are discussed in inorganic textbooks. In the course of a study of the decomposition of chlorine dioxide¹ we have discovered a new oxide of empirical formula $\text{ClO}_{1.5}$. We believe this chlorine(III) oxide to be Cl_2O_3 , and we wish to report its synthesis and behavior in this communication.

When gaseous ClO_2 is admitted from a Pyrex storage vessel at room temperature to another Pyrex vessel at a temperature above about 50°, it explodes after an induction period. We found that the induction period

(1) E. T. McHale and G. von Elbe, to be published.

is reduced or even eliminated by exposure of the storage vessel to light, and the effect of such illumination persists for many hours. Obviously, a photochemical reaction occurs which produces a fairly stable compound that acts as a promoter of the explosive decomposition of ClO_2 . The existence of such promoter has already been noted in an earlier study of the chain mechanism of ClO_2 decomposition,² but the substance has hitherto not been identified.

Several workers have reported the photolysis of ClO_2 ,^{3,4} where the lowest temperature was 15° . The identified products comprise Cl_2 , O_2 , and Cl_2O_6 . The last is described⁵ as a red liquid at room temperature, which freezes at $+3.5^\circ$ to an orange solid. The vapor pressure as a function of temperature has been carefully measured from -30 to $+15^\circ$, it being 0.31 torr at 0° . In the vapor phase this oxide is almost completely dissociated into ClO_2 .^{6,6} Prolonged irradiation of Cl_2O_6 produces the heptoxide, Cl_2O_7 .⁷ We have prepared both Cl_2O_6 and Cl_2O_7 by the procedures described in the literature and have tested the effect of these and other compounds on the ClO_2 induction period. The results were substantially negative for Cl_2O_7 , Cl_2 , and O_2 ; this also applies to Cl_2O ,² whereas Cl_2O_6 (or ClO_3) was found to be an inhibitor rather than a promoter. The promoting agent is thus another, hitherto unknown photolysis product.

We used the following method for isolating this product. One millimole of ClO_2 (see ref 1 for preparation and purification) was admitted to a 500-cc spherical Pyrex flask. A U-tube manometer was connected directly to the top of the vessel, the mercury being protected with a layer of Kel-F oil. The lower half of the reactor was immersed in a -45° bath, and ultraviolet light from a 100-w lamp was directed at the upper half. Under these conditions ClO_2 remains a gas (vapor pressure, 37 torr at -45°); no detectable Cl_2O_7 is formed, and the condensable products, Cl_2O_6 and the unknown agent, collect at the vessel bottom as a dark brown crystalline solid. Within 20–30 min the ClO_2 is completely consumed. The Cl_2 and O_2 products are pumped away and the bulb evacuated to <0.1 torr with no indication of loss of any of the dark brown solid.

At -45° the solid decomposes very slowly, an estimated 10% in 20 min. At -78° it is stable indefinitely. When the -45° bath is replaced with a 0° bath, the pressure rises from zero to some constant value of the order of 15 torr depending on the amount of brown solid originally formed, and no further increase takes place. A solid orange residue remains after the pressure rise which has a vapor pressure of ca. 0.3 torr at 0° and a melting point of $+3^\circ$, in near-perfect agreement with the data reported for Cl_2O_6 . If the warm-up from -45 to 0° is conducted in darkness, one observes a series of flashes of orange light throughout the vessel, indicating that the brown material explodes as it gasifies. The flashes continue until all the brown solid is gone, leaving the orange Cl_2O_6 residue plus the gaseous explosion products of the other photolysis product.

(2) H.-J. Schumacher and G. Steiger, *Z. Physik. Chem.*, B7, 363 (1930).

(3) H. Booth and E. J. Bowen, *J. Chem. Soc.*, 127, 510 (1925).

(4) J. W. T. Spinks and J. M. Porter, *J. Am. Chem. Soc.*, 56, 264 (1934).

(5) C. F. Goodeve and F. D. Richardson, *J. Chem. Soc.*, 294 (1937).

(6) C. F. Goodeve and F. A. Todd, *Nature*, 132, 514 (1933).

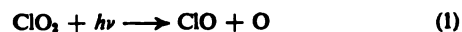
The brown solid then is a mixture of Cl_2O_6 and the unidentified photolysis product. We have determined the composition of this unknown product by measuring the O_2/Cl_2 ratio of the decomposition products. The results of duplicate measurements on three separate preparations were: 1.42, 1.43; 1.59, 1.59; 1.50, 1.48. The average of these measurements is 1.50 ± 0.1 .

The analytical technique consisted of measuring the total pressure of the explosion products, O_2 and Cl_2 , in the reactor of 0° , allowing for a vapor pressure of 0.3 torr of Cl_2O_6 , and then measuring the O_2 pressure after Cl_2 had been condensed on a cold spot at the bottom of the bulb at -196° . Numerous tests on synthetic mixtures of known O_2/Cl_2 ratios confirmed the validity of the technique. The temperature of -196° ensured that only O_2 remained in the gas phase, and no O_2 itself condensed since the vapor pressure is ca. 160 torr at -196° , and in all experiments the O_2 pressure in the 500-cc reactor after cooling ranged from 6.0 to 8.5 torr. Furthermore, we took care to satisfy ourselves that only O_2 and Cl_2 were formed in the explosive decomposition.

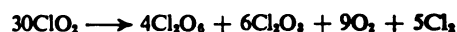
Parenthetically it should be noted that this new oxide was probably previously prepared in small quantities by Goodeve and Richardson.⁵ They report that the color of Cl_2O_6 , prepared photolytically, can be taken as an indication of purity, and that at low temperature an "impurity" colored the hexoxide dark brown.

To summarize, this new chlorine oxide is a dark brown solid at -45° and below when condensed with Cl_2O_6 . It has a vapor pressure <0.1 torr and decomposes slowly at -45° , but not at all at -78° . Since its vapor explodes at approximately 1–2 torr pressure and temperatures well below 0° , it does not lend itself to a determination of physical properties such as boiling point, melting point, and vapor pressure. The empirical formula is $\text{ClO}_{1.5}$, and we believe it to be the unknown chlorine sesquioxide, Cl_2O_3 . This last formula is the most reasonable, but it would be desirable to determine the molecular weight since theoretically the molecular formula could be $(\text{ClO}_{1.5})_n$ with n any even integer. Again, however, such measurements as vapor density or freezing point depression are not feasible with this compound.

The new oxide is very likely formed in the reactions



These are just two of many reactions in the mechanism, since we find Cl_2O_6 , O_2 , and Cl_2 as primary products. The actual over-all stoichiometry at -45° which we have measured by mass balance is



but this equation is probably unique to our reaction conditions.

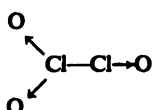
Assuming that $n = 2$, it is possible to infer the structure of Cl_2O_3 from this study and what is known of the other chlorine oxides. The most stable of the chlorine oxides are Cl_2O^7 and Cl_2O_7 ,⁸ which decompose homogeneously and must be heated to 100° or above to decompose at measurable rates. These both contain the

(7) C. N. Hinshelwood and C. R. Prichard, *J. Chem. Soc.*, 123, 2730 (1928).

(8) R. V. Figini, E. Colocchia, and H.-J. Schumacher, *Z. Physik. Chem. (Frankfurt)*, 14, 32 (1958).

Cl-O-Cl linkage in their structures. ClO_2 is much less stable and decomposes heterogeneously at $40\text{--}50^\circ$,² while Cl_2O_8 is even less stable and decomposes heterogeneously at room temperature.⁵ If Cl_2O_8 had a stability-imparting Cl-O-Cl linkage, one would expect to find it a considerably less labile molecule than it is.

A consideration of the relative volatilities of the oxides likewise indicates the structure. Cl_2O_7 is a relatively volatile material with a vapor pressure of 80 torr at 0° ,⁹ and an estimated 1 torr at -45° . Cl_2O_8 is an oil at 20° , with a vapor pressure of approximately 1 torr, and 0.31 torr at 0° .⁵ Since Cl_2O_8 is less volatile than Cl_2O_7 , its structure can hardly be of the same type as Cl_2O_7 , whereas a structure similar to Cl_2O_8 accounts for its behavior very satisfactorily. Cl_2O_8 is bound in the condensed phase by a Cl-Cl bond which is only 1.7 kcal;¹⁰ it exists almost entirely as ClO_2 in the vapor phase.^{5,6} Accordingly, we believe the structure of Cl_2O_8 to be



with a weak Cl-Cl bond of a few kilocalories. The extreme instability is then due to dissociation to yield the reactive ClO radical. The heat of formation of Cl_2O_8 should then be of the order of $+45$ kcal/mole, since the heats of formation of ClO and ClO_2 are $+24$ and $+25$ kcal/mole, respectively.¹¹

Acknowledgment. This work was supported by the Air Force Office of Scientific Research, Propulsion Division, under Contract No. AF 49(638)-1645.

(9) C. F. Goodeve and J. Powney, *J. Chem. Soc.*, 2078 (1932).

(10) J. Farquharson, C. F. Goodeve, and F. D. Richardson, *Trans. Faraday Soc.*, 32, 790 (1936).

(11) "JANAF Thermochemical Tables," The Dow Chemical Co., Midland, Mich., 1964.

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Received August 8, 1966

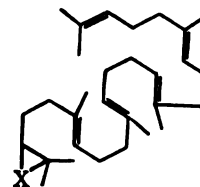
2,3-Iminosqualene, a Potent Inhibitor of the Enzymic Cyclization of 2,3-Oxidosqualene to Sterols

Sir:

Recent studies have demonstrated that the squalene analog 10,11-dihydrosqualene is not readily cyclized under the influence of the sterol-producing enzymes of rat liver homogenate, but instead is converted to a mixture of mono- and dioxido derivatives by addition of oxygen to either or both of the terminal olefinic groupings,¹ a fact which suggested that 2,3-oxidosqualene (**1a**) might be an intermediate in the biosynthesis of sterols from squalene. This possibility has been fully verified by an appropriate series of experiments.^{2,3} More recently, the enzyme which effects anaerobically the conversion of 2,3-oxidosqualene has

been separated from hog liver microsomes in water-soluble form and has been partially purified.⁴ This note describes the results of an investigation aimed at the development of an effective inhibitor for this enzyme, 2,3-oxidosqualene cyclase.

Experiments to determine inhibition were performed anaerobically with solutions of partially purified 2,3-oxidosqualene cyclase in amounts sufficient to effect ca. 30% conversion of $25\text{ }\mu\text{M}$ ^{14}C -labeled 2,3-oxidosqualene to lanosterol in 30 min. Parallel, duplicate runs were made with and without the substance under test. Table I records some of the data which have been obtained from the study of (\pm)-2,3-iminosqualene (**1b**), (\pm)-2,3-sulfidosqualene (**1c**), and decahydro-(\pm)-2,3-iminosqualene as potential inhibitors. The results summarized in the table show strikingly that 2,3-iminosqualene (**1b**) is a powerful inhibitor of 2,3-



1a, X=O
b, X=NH
c, X=S

oxidosqualene cyclase, as might be expected from the greater basicity of **1b** as compared with **1a** and the supposition that the enzyme operates on the oxygen of **1a** as a proton-transfer reagent. Decahydro-**1b**, although a weaker inhibitor than **1b**, is still effective; evidently the high basicity of the imino grouping largely offsets the geometric perturbations in the enzyme-inhibitor complex due to the saturated carbon chain. Relative to these aziranes, 2,3-sulfidosqualene (**1c**) is a weak inhibitor. It is also inert to 2,3-oxidosqualene cyclase, as could be shown by experiments with ^{14}C -labeled **1c** in which essentially all the radioactivity was accounted for in the recovered substrate **1c** after incubation with the cyclizing enzyme. Little, if any, inhibition of lanosterol synthesis from the oxide **1a** and 2,3-oxidosqualene cyclase was observed with 3β -amino-

Table I. Inhibition of 2,3-Oxidosqualene Cyclase*

Inhibitor	Inhibitor concn, μM	% conversion of 1a to lanosterol
None	30
1b	1.4	3
1c	1.4	26
Decahydro- 1b	1.4	25
1b	4.4	0 ^b
1c	4.4	26
Decahydro- 1b	4.4	18
1c	Ca. 1000	15
Decahydro- 1b	Ca. 100	15

* Substrate concentration $25\text{ }\mu\text{M}$; anaerobic incubation at 37° for 30 min. ^b In addition, no conversion of **1a** to lanosterol occurs after 3 hr of incubation.

(4) P. D. G. Dean, P. R. O. de Montellano, K. Bloch, and E. J. Corey, *J. Biol. Chem.*, in press.

(1) E. J. Corey and W. E. Russey, *J. Am. Chem. Soc.*, 88, 4751 (1966).

(2) E. J. Corey, W. E. Russey, and P. R. O. de Montellano, *ibid.*, 88, 4750 (1966).

(3) E. E. van Tamelen, J. D. Willet, R. B. Clayton, and K. E. Lord, *ibid.*, 88, 4752 (1966).

lanosta-8,25-diene, 3 β -aminolanost-8-ene, or squalane at concentrations approximating those of substrate 1a.

The inhibitory effect of 2,3-iminosqualene on the enzymic conversion of 1a to lanosterol has been utilized to permit the accumulation of 2,3-oxidosqualene using squalene as substrate with rat liver homogenate.² Equilibration of 0.12 μ mole of (\pm)-2,3-iminosqualene with 2 ml of rat liver homogenate for 5 min at 37° followed by addition of ¹⁴C-labeled squalene (0.075 μ mole) and ca. 5 mg of reduced triphosphopyridine nucleotide and aerobic incubation for 3 hr led after chromatographic isolation to 2,3-oxidosqualene in 25–30% yield.⁵ The isolated labeled oxide 1a was further identified by its transformation to labeled lanosterol by anaerobic incubation with 2,3-oxidosqualene cyclase for 1 hr (80% conversion).

The synthesis of (\pm)-2,3-iminosqualene was accomplished by the sequence: all-*trans*-(\pm)-2,3-oxidosqualene (1a)² \rightarrow 2-azido-3-hydroxysqualene (HN₃) \rightarrow 2-azido-3-*p*-toluenesulfonoxysqualene (*p*-toluenesulfonyl chloride-pyridine) \rightarrow (\pm)-2,3-iminosqualene (1b) (LiAlH₄).⁶ The structure of 1b was confirmed chemically by its conversion using N-nitroso-4-nitrocarbazole to squalene and nitrous oxide.⁷ Decahydro-2,3-iminosqualene was synthesized by hydrogenation of 1b with palladium-on-charcoal catalyst in ethanol; the mass spectrum showed a peak due to the molecular ion at *m/e* 435, as expected for a decahydro derivative of 1b, and no peak at *m/e* 425, indicating the absence of unreduced 1b. (\pm)-2,3-Sulfidosqualene was obtained from the reaction of (\pm)-1a with potassium thiocyanate in ethanol;⁸ independent chemical evidence for the formulation of this product as 1c was obtained from the reaction with *n*-butyllithium which produced squalene cleanly.^{9,10}

Work on various aspects of the enzymic cyclization of 2,3-oxidosqualene and its analogs is continuing.

Acknowledgments. We are indebted to Professor Konrad Bloch for numerous helpful discussions during the course of this investigation. Financial support from the National Science Foundation (Grant GP-221) and the National Institutes of Health (Grant HE-02477; Predoctoral Fellowships to P. O. de M. 1965–1967) is also gratefully acknowledged.

(5) 2,3,22,23-Dioxidosqualene was also isolated in 3–10% yield. The absence of sterol formation in this experiment was indicated by the lack of radioactivity in the sterol fraction obtained after precipitation with digitonin.

(6) New substances were characterized by infrared, nuclear magnetic resonance, and mass spectroscopy. Homogeneity was indicated by thin-layer chromatographic techniques.

(7) C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.*, **83**, 4417 (1961).

(8) C. C. J. Culvenor, W. Davis, and N. S. Heath, *J. Chem. Soc.*, **282** (1949).

(9) F. G. Bordwell, H. M. Anderson, and B. M. Pitt, *J. Am. Chem. Soc.*, **76**, 1082 (1954).

(10) The racemic compounds 1a–c are all liquid at room temperature. The nmr spectra of the oxide 1a and the imine 1b each show two sharp peaks due to the geminal methyl substituents on the three-membered ring (for 1a at 1.25 and 1.30 ppm and for 1b at 1.09 and 1.17 ppm, downfield from tetramethylsilane), whereas on the spectrum of the sulfide 1c all the peaks due to methyl groups fall together at ca. 1.61 ppm.

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Received March 28, 1967

Synthesis of a Medium Ring Containing Bridge Biphenyl by Photochemically Induced Intramolecular Arylation

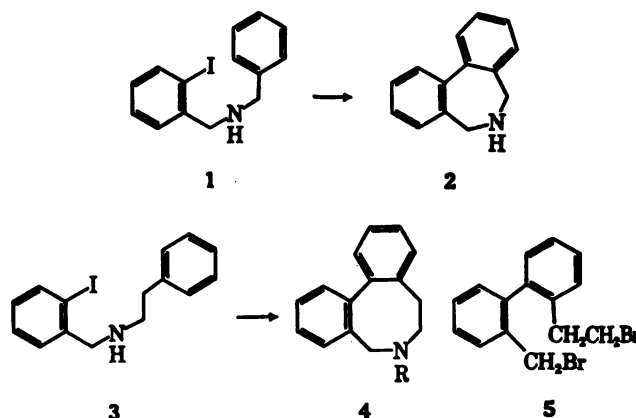
Sir:

Recent interest in intramolecular radical cyclization reactions,¹ particularly those involving aryl radicals,² prompts us to present details of a photochemical route to a bridged biphenyl containing a medium ring.

Photolysis of aryl iodides in benzene provides a useful method for the synthesis of substituted biphenyls.³ An extension of this reaction has been employed for effecting intramolecular arylations leading to phenanthrenes,⁴ and more recently to the synthesis of aporphines.⁵

The results presented in this communication demonstrate that photochemically induced intramolecular arylation may be employed not only in the formation of six-membered rings but also for constructing seven- and eight-membered cycles.

Irradiation⁶ of a dilute aqueous solution of the iodoaromatic compound I, as the hydrochloride, gave after 200 hr the photocyclized product, 6,7-dihydro-5H-dibenz[*c,e*]azepine (2),⁷ mp 74–76°, in 57% yield, together with 13% of starting material. Similarly, irradiation of N-(β -phenethyl)-2-iodobenzylamine (3) as the hydrochloride in water for 113 hr, under the same conditions as described above, afforded the photocyclized product 4 (R = H) in 25% yield, mp 119–120°⁸ [hydrochloride mp 321–322° dec], λ_{\max} 276



m μ (log ϵ 2.89), λ_{sh} 231 *m* μ (log ϵ 4.15), pmr: eight-proton multiplet, δ 7.38–6.95 (aromatic hydrogens), one-proton broad doublets, 3.83 (J = 15 Hz), 3.10 (J = 15 Hz) (C₆H₅CH₂N),⁹ five-proton multiplet, 3.20–2.10 (–HNCH₂CH₂), mol wt (mass spectrum), 209, together with N-(β -phenethyl)benzylamine (10%). The

(1) C. Walling, J. H. Cooley, A. A. Ponnaras, and E. J. Racah, *J. Am. Chem. Soc.*, **88**, 5361 (1966); N. C. Yang, A. Shani, and G. R. Lenz, *ibid.*, **88**, 5369 (1966).

(2) M. Tiecco, *Chem. Commun.*, 555 (1965); M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Letters*, 2937 (1966); N. C. Yang, G. R. Lenz, and A. Shani, *ibid.*, 2941 (1966).

(3) W. Wolf and N. Kharasch, *J. Org. Chem.*, **30**, 2493 (1965).

(4) S. M. Kupchan and H. C. Wormser, *Tetrahedron Letters*, 359 (1965); *J. Org. Chem.*, **30**, 3792 (1965).

(5) S. M. Kupchan and R. M. Kanojia, *Tetrahedron Letters*, 5353 (1966).

(6) Photolyses were carried out using a 450-w Hanovia high-pressure lamp fitted with a Pyrex sleeve.

(7) W. Wenner, *J. Org. Chem.*, **16**, 1475 (1951). We are indebted to Dr. W. E. Scott, Hoffmann-LaRoche, Nutley, N. J., for providing an authentic sample for comparison.

(8) All new compounds gave satisfactory analyses.

(9) The nonequivalence of the benzylic hydrogens indicates the eight-membered ring exists predominantly in one conformation at room temperature. Studies on the temperature dependence of the spectrum of this compound are under investigation.

of the bridged biphenyl 4 ($R = H$) was established by an independent synthesis *via* its N-benzyl derivative 4 ($R = CH_2C_6H_5$) (hydriodide, mp 235–238°) in benzylamine and the dibromide 5.¹⁰ Extension of the reaction to other bridged biphenyls containing medium-size rings is under investigation.

(11) N.A.S.A. Trainee, 1964–1967.

P. W. Jeffs, J. F. Hansen¹¹

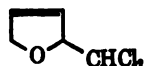
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Durham, North Carolina 27709

Received March 2, 1967

Additions and Corrections

thyl-Metal Compounds. II. The Preparation of Dihalocyclopropanes by the Reaction of Phenylmethylmercury Compounds with Olefins [*J. Chem. Soc.*, 87, 4259 (1965)]. By DIETMAR SEYDOW, JAMES M. BURLITCH, RICHARD J. MINASZ, YICK-PUI MUI, HARRY D. SIMMONS, JR., I. H. TREIBER, and SUSAN R. DOWD. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.

On page 4265, formula IV should be



Magnetic Resonance Spectroscopy. The Conformational Stability of Primary Grignard Reagents. Steric and Medium Effects [*J. Am. Chem. Soc.*, 87, 965]. By GEORGE M. WHITESIDES and JOHN D. HANSEN. The Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California.

On page 985, the radical name 2,3-dimethylbutyl mentioned in the paragraph on page 4884 and in the first column of Table I should actually be 3-methyl-2-butyl.

Isotopic Effects. VII. The ¹⁹F Nuclear Magnetic Resonance Spectra of Substituted 1- and 2-Fluorobenzenes [*J. Am. Chem. Soc.*, 89, 379 (1967)]. By J. COCK and M. J. S. DEWAR. Department of Chemistry, The University of Texas, Austin, Texas

On page 381, in the Experimental Section, line 3, should read 20%. In Table XIII, third column, entry, +1.14 should read -1.14.

Crystal and Molecular Structure of 2,4-Dithiouracil [*J. Am. Chem. Soc.*, 89, 1249 (1967)]. By ELI SHEFTER and HENRY G. MAUTNER. Department of Pharmacy, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York, and the Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut.

On page 1250 in line 6 of the Experimental Section the molar absorption coefficient μ should be 67 cm^{-1} at 6.7 cm^{-1} . The statement "the low absorption is not significant" should be deleted from the last sentence of the third paragraph of the Experimental Section.

Amigamicidin S [*J. Am. Chem. Soc.*, 89, 1278 (1967)]. By MICHINORI WAKI and NOBUO IZUMIYA. Department of Biochemistry, Faculty of Science, University of Fukuoka, Japan.

In Table I, the values in the second and third columns for the fourth row of entries (-Gly-Pro-OH) should be 0 and 100, respectively; those for the fifth row of entries (-D-Ala-) should be 25 and 75, respectively.

Total Synthesis of dl-Atisine [*J. Am. Chem. Soc.*, 89, 1483 (1967)]. By WATARU NAGATA, TSUTOMU SUGASAWA, MASAYUKI NARISADA, TOSHIO WAKABAYASHI, and YOSHIO HAYASE. Shionogi Research Laboratory, Fukushima-ku, Osaka, Japan.

On page 1485, in the first column, line 5, 4a should read 4a. On page 1486, in the first column, line 4, mp 110–130° should read mp 110–112°. On page 1491, in the second column, line 6, 2, bp 140–160° should read 3, bp 140–160°. On page 1492, in the first sentence in the second column under the heading (\pm)-4a α -Cyano-1 α -formyl-7-methoxy-1,2,3,4,4a,9,10,10a,8 β -octahydrophenanthrene (9), 30.4 g should read 30.4 mg. On page 1494, in the second column, line 12, in a by a mix- should read in a by a mix-. On page 1497, in the first column, nine lines up from the bottom, C₂₂H₂₂O₂N should read C₂₂H₂₂O₂N₂. On page 1498, in the first column, lines 42 and 52, acetoxy ketone 39a and hydroxy ketone 34a should read acetoxy ketone 39b and hydroxy ketone 39a, respectively. On page 1499, in the second column, line 21, C₂₂H₂₁N₂O should read C₂₂H₂₁NO₂.

The Stereochemistry of the Pentacyclic Oxindole Alkaloids [*J. Am. Chem. Soc.*, 89, 1739 (1967)]. By MAURICE SHAMMA and ROBERT J. SHINE, Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania; IVAN KOMPIŠ and T. STICZAY, Slovak Academy of Sciences, Institute of Chemistry, Bratislava, Czechoslovakia, F. MORSINGH, Department of Chemistry, University of Malaya, Kuala Lumpur, Malaya; and J. POISSON and J.-L. POUSET, Faculté de Pharmacie de Paris, Laboratoire de Pharmacie Galénique, Paris 6, France.

In Table I, the correct heading for the last column is $[\alpha]_D$, deg (CHCl₃).

Anodic Oxidations of Medium Ring Cycloalkanecarboxylic Acids [*J. Am. Chem. Soc.*, 89, 2139 (1967)]. By JAMES G. TRAYNHAM and JOHN S. DEHN. Coates Chemical Laboratories, Louisiana State University, Baton Rouge, Louisiana.

The formula for bicyclo[7.1.0]nonane in the illustration should be replaced by one for bicyclo[6.1.0]octane.

Book Reviews

The Molecular Orbital Theory of Conjugated Systems. By LIONEL SALEM, Maître de Recherche in the French National Research Center (C.N.R.S.), Laboratoire de Chimie Physique, Faculté des Sciences, Orsay. W. A. Benjamin, Inc., 1 Park Ave., New York, N. Y. 1966. xvi + 576 pp. 16 × 23 cm. \$19.75.

The molecular orbital theory of large organic molecules has represented a curious gap in scientific publishing; the available books in this area have been of an elementary nature, intended to introduce chemists to the simple Hückel (HMO) treatment and consequently paying little attention to more sophisticated recent developments. Dr. Salem's book represents an attempt to fill a major part of this gap, by covering the application of MO theory to the π electrons of conjugated molecules.

Successive chapters in the book discuss the HMO method and its application to various systems; the SCF MO method and various pseudo-self-consistent treatments such as the Wheland-Mann method; ground-state properties of molecules including bond lengths, resonance energies, charge distributions, dipole moments, etc.; the magnetic properties of closed-shell molecules and nmr spectroscopy, including the theory of ring currents, chemical shifts, and coupling constants; esr; chemical reactivity; light absorption; and the theory of molecular distortions, including bond alternation and the Jahn-Teller effect.

The trouble with this book is that it seems to have been written at least ten years ago, and recently updated by a hasty inclusion of references to recent work. Far too much emphasis is laid on early investigations based on the HMO method; for example, in the chapter on light absorption, 84 pages are devoted to work published before 1956 and using the simple HMO method or variants of it, while the coverage of recent developments is wholly inadequate. Ruedenberg's work is not even mentioned. The chapter on reactivity could have been written in 1954, while the section on esr spectroscopy omits all reference to recent open-shell calculations, using annihilation operator techniques. Much of the material in the first and third chapters also seems out of place, dealing in great detail with problems that were highly topical in the early fifties.

The introductions to SCF MO theory in Chapter 2, and to the theory of magnetic effects in Chapter 4, are very inadequate; hardly anyone who was already unfamiliar with this material would have the background to understand them. One gets the impression from odd phrases throughout the book that the author regards SCF MO theory as far too complicated and difficult for general use and therefore not worth discussing in detail; thus no indications are given of its use in practice or the choice of parameters in it. This attitude would again be understandable if the book was originally written ten years ago and inadequately revised. Again, the author

seems to suggest that computers are rare and exotic devices, to be used only in cases of extreme emergency (p 428: "A drawback however (*i.e.*, in SCF MO theory) is the labor involved in calculating self-consistent field orbitals;" p 432: "The numerical expressions derived from (7.103) become quite complicated and the calculations tedious. One solution is to use a computer.").

In spite of these shortcomings, this is a useful book. It contains a great deal of information and is a good source of references to the literature. If the price were more reasonable, it could be generally recommended, if only as a stop-gap until something better appears.

Michael J. S. Dewar

Department of Chemistry, The University of Texas
Austin, Texas 78712

Solid State Chemistry, Whence, Where and Whither. By J. ARVID HEDVALL, D.Ph., D.Ph.(H.C.), D.Eng.(H.C.), D.Tech.(H.C.), Emeritus Professor at the Chalmers University of Technology, Gothenburg, Sweden. American Elsevier Publishing Co., Inc., 52 Vanderbilt Ave., New York, N. Y. 1966. v + 100 pp. 14 × 21.5 cm. \$6.50.

This is a very short book (87 pages of text) which is intended as a brief survey of the development of solid-state chemistry from the first experiments more than 50 years ago to the present. Heavy emphasis is placed upon the author's own work and interests. The presentation is frequently in narrative form and deals primarily with the qualitative exploratory period of work with heterogeneous solid-state reactions.

There are 14 chapters in which are presented discussions of such diverse topics as exchange reactions, corrosion, absorption, photoactivity, catalysis, and changes in magnetic state. The author presents, in a very abbreviated and qualitative form, the factors which affect the reactivity of solids and indicates routes for further research and industrial development. Little or no mention is made of the extensive contributions made to our understanding of solids from the vast amount of research done with metals and semiconductors in recent years.

This book may be of interest to those who would like to gain the flavor of the historic development of several areas of solid-state chemistry. In this reviewer's opinion, the book is somewhat overpriced at \$6.50.

M. B. Panish

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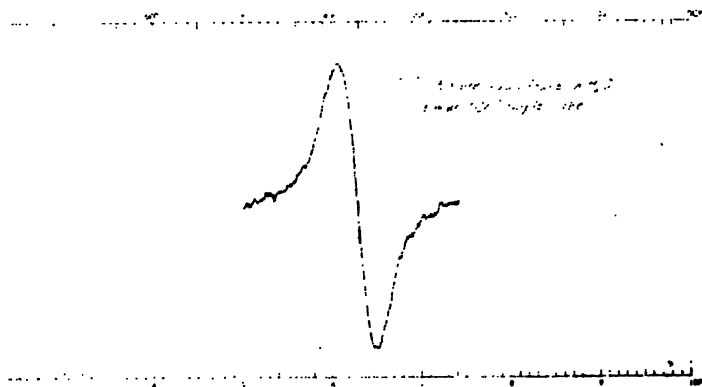
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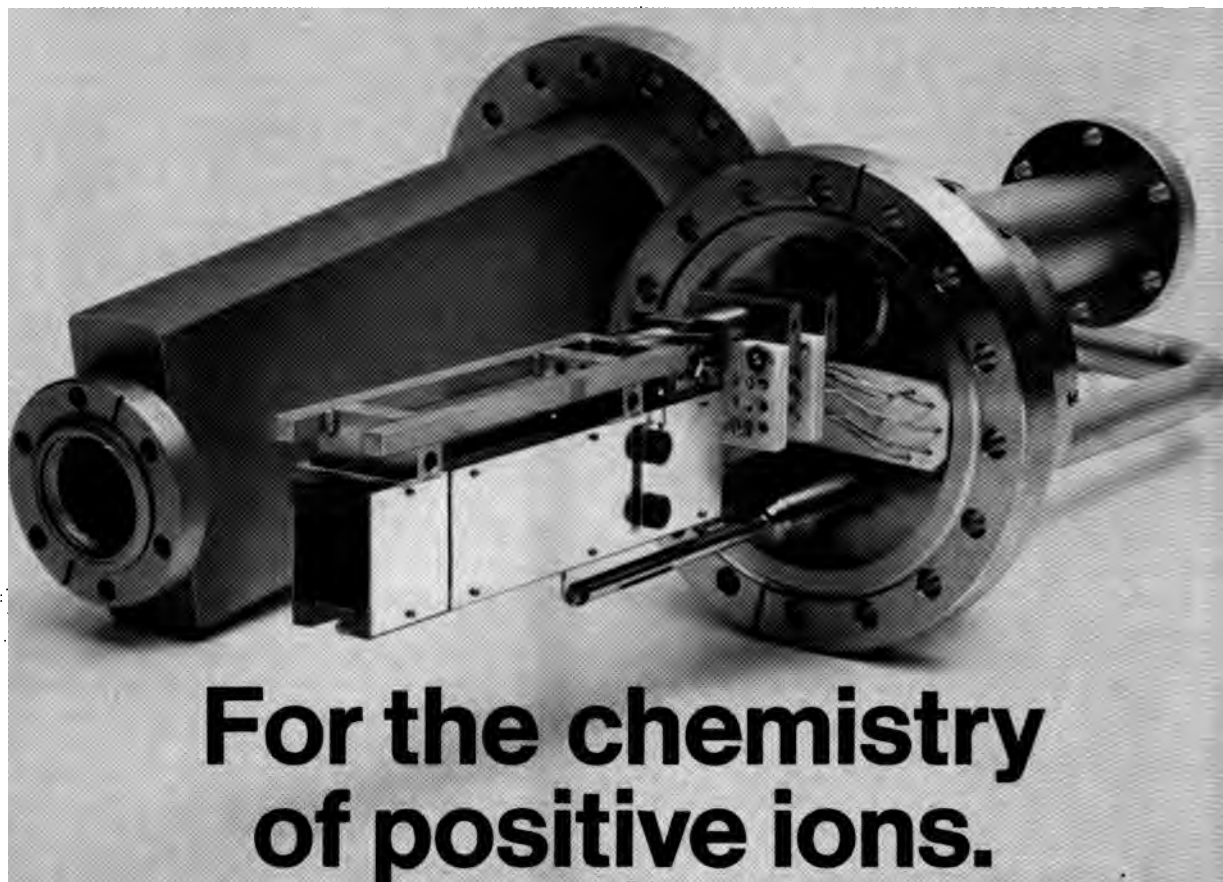
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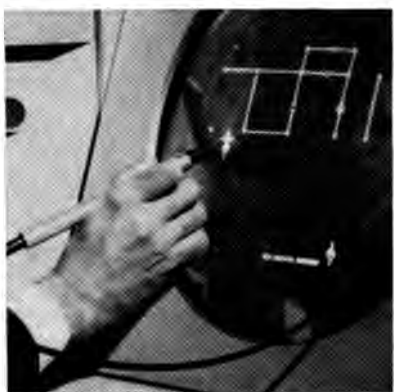
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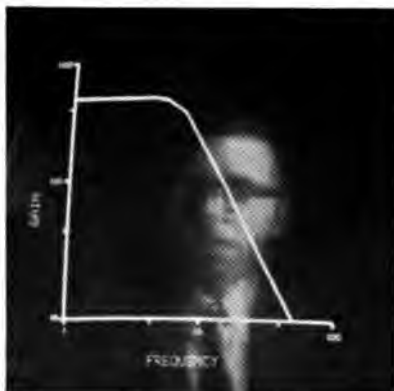
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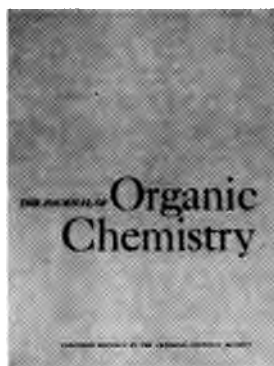
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JUNE 7, 1967

Physical and Inorganic Chemistry

Covalent and Ionic Character in Ground and Excited States of Benzene

Mary Craig^{1a} and R. Stephen Berry^{1b}

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut, and the Department of Chemistry and Institute for the Study of Metals, University of Chicago, Chicago, Illinois 60637. Received January 16, 1967

Abstract: Various wave functions for the ground (${}^1A_{1g}$) and low-lying excited states of benzene were examined by projecting onto them the valence-bond functions corresponding to Kekulé, Dewar, and Coulomb-stabilized ionic structures. The results show large (75%) contributions from singly ionic structures, 40–50% Kekulé structure for the ground state, and 30–40% covalent character to the ${}^1B_{2u}$ state. The molecular wave functions are also examined for benzene distorted to a “cyclohexatriene” structure, particularly to determine the relative contributions of the two (now nonequivalent) Kekulé structures. The more favored or short double-bond structure increases its contribution about 25%, and the less favored structure decreases by about the same fraction. The relative change in Kekulé contributions and in corresponding pairs of ionic functions are the most significant changes associated with the distortion.

The quest for usefully accurate molecular wave functions has clearly reached a fruitful plateau. Wave functions now available for diatomic and small polyatomic molecules are sufficiently accurate to permit the calculation of a large variety of the ground-state properties of interest in traditional chemistry. These functions are not only numerically accurate; through the medium of contour maps,² they provide us with clear intuitive physical understanding of the variation of wave functions from state to state and from molecule to molecule. The collection of results, taken together, offers a happy rejoinder to the pessimistic reservations that were heard during the earliest years of the computer era.

To add to the information obtainable from orbital total wave-function contours, we felt that we could gain further insight into molecular behavior from another type of analysis. This analysis, with origins in traditional interpretations of electronic structure, is nevertheless still part of the chemist's vocabulary and perhaps a meaningful contributor to his chemical

intuition. Specifically, we refer to the determination of covalent and ionic character, as represented by valence-bond functions.

The basic idea is this: each valence-bond function represents a kind of physical behavior which we “understand” or can use for the interpretation of chemical behavior. The true molecular wave function Ω or a reasonable approximation of it can be represented by a sum of contributions from a set of valence-bond (VB) functions, or from any complete basis set of functions, according to the principle of superposition. If the set happens to be a set of VB functions, we conventionally call the phenomenon of superposition “resonance.” If each function in the basis set is normalized to unity, then the coefficient or amplitude of a function is a measure of its contribution to the exact or approximate function Ω under consideration; specifically, the absolute square of the coefficient of the basis function Ψ_j is the fraction of Ω which is composed of Ψ_j .

We should explain and review just a little more of what the approach does and does not imply. First, it is very important to recognize that valence-bond

(a) Yale University; (b) University of Chicago.
(c) A. C. Wahl, *Science*, 151, 961 (1966); K. Ruedenberg, private communication.

wave functions are very highly correlated functions, with respect to both space and spin. A valence-bond analysis is not a population analysis in the sense that molecular orbital functions give population analyses; with valence-bond functions one can ask questions like "In a triplet state of benzene, what is the probability that, if one of the unpaired electrons is one atom 1, we will find the other on atom 4, while the remaining π electrons are in 2-3 and 5-6 bonds?" In other words, a valence-bond analysis is a very specific sort of analysis of electron correlation.

Second, we must remember that traditional valence-bond functions are not orthogonal to each other. This mathematical relationship between the functions has its parallel in physical terms; thus, the physical conditions represented by two valence-bond conditions are not in general mutually exclusive conditions. A covalent bond carries some ionic character in the traditional valence-bond representation. This nonorthogonality and the complexity of physical interpretation that accompanies it has two sources. One is the nonorthogonality of the basic atomic orbitals on different atoms; the other, much more bothersome for interpretive purposes, is due to the overcompleteness of the set of valence-bond structures. The first problem can be eliminated by generating a set of orthogonalized atomic orbitals, e.g., equivalent orbitals, and using these as basis functions. One necessarily delocalizes an orbital on one atom when one orthogonalizes it to an orbital on another atom. Consequently this orthogonality is obtained at the expense of a little intuitive understanding, at least insofar as our understanding of valence-bond structures are associated with localized orbitals. The other type of nonorthogonality has been discussed, for example, in connection with the question of resonance in butadiene.³ It comes from the fact that one can in general draw more structures for a molecule than the number of *independent* functions, just as one can draw more than two vectors on an array of point in a plane. Yet just as any vector on the array can be represented with any two independent (nonparallel) vectors, any of the possible valence-bond structures of a molecule can be expressed in terms of some small number of independent structures. Thus for benzene's π electrons there are twelve possible nonionic singlet VB structures, but only six (any six) are independent. And with this overcompleteness comes the nonorthogonality problem: although we may choose six independent functions, in general these are not orthogonal; if we make them orthogonal, only one function of the orthogonal set can be chosen to represent a single valence-bond structure. We are forced either to give up orthogonality and to make our individual functions easily interpretable, or to make the functions orthogonal and therefore mutually exclusive, but accept basis functions that do not represent single structures.

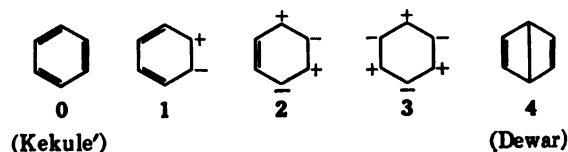
The foregoing discussion is of course simply a review of some of the ramifications of valence-bond methods that have been long recognized in the literature of wave-function calculations. However, it seemed desirable to refresh our memories of some of these ramifications because of the possible misinterpretations which might arise if they are overlooked.

(3) R. S. Berry, *J. Chem. Phys.*, **30**, 936 (1959).

We have selected several representative wave functions for the six π electrons of benzene and projected onto these functions a number of suitably symmetrized valence-bond (VB) structure functions. The squares of these projections are the numbers of interest to us here; the square of the projection of a VB structure function Ψ onto an "accurate" six-electron function Ω , namely, $|\langle \Omega | \Psi \rangle|^2$, is the fraction of Ω which is made of Ψ . An analysis of this kind could have been performed by calculating the molecular wave function with a VB basis set, but the projection procedure is far more efficient, in view of the availability of rather good wave functions.

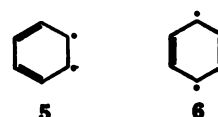
We have chosen to examine the π electrons of benzene for three reasons. First, we wished to find the relative importance of the Kekulé (or better, perhaps, Thiele) structure and of the ionic structures having the greatest Coulomb stabilization. Second, we wanted to learn how these contributions to the ground and low-lying excited states differed. Third, we were interested in the behavior of the electron pairing with molecular vibration, and particularly in the relative contributions of the two Kekulé structures when the bond lengths of the ring alternate between the values appropriate to "pure" double and single bonds.

The first reason was prompted by the results of a similar analysis of ground-state wave functions of butadiene.³ The butadiene functions were naturally composed of 70-88% of the normal covalent structure, but, surprisingly, contained over 40% of the $C^+C-C^+C^-$ structure. Such numbers raised questions in our minds of the role of multiply ionized structures in benzene. Craig⁴ had actually carried out calculations with a VB basis but had restricted his functions to the Kekulé, Dewar, and singly ionized structures, including ionic Dewar structures. In light of the butadiene results, we chose to evaluate the projections of a somewhat different set, namely, the appropriately symmetrized combinations of structures 0-4. We shall refer to a



VB function representing a single diagram like those of 0-4 as a *primitive* VB function. A linear combination of physically equivalent primitive VB functions which transforms as an irreducible representation of the molecular point group is called a *symmetrized* VB function, or for convenience, simply a VB function.

The second part of this study is a comparison of the VB composition of the $^1A_{1g}$ ground state with various VB contributions to the lower excited states. We have calculated the contributions of structures 0-3 to the $^1B_{1u}$ and $^1B_{2u}$ states, the states responsible for benzene's absorption bands in the 2400- and 2000-Å regions. We have also examined briefly the corresponding triplets, looking particularly at the roles of



(4) D. P. Craig, *Proc. Roy. Soc. (London)*, **A200**, 401 (1950).

Squares of Projections of VB Functions for Benzene in the Ground State in Equilibrium Configuration^a

VB function	Primitive Ψ_0	Symmetrized Ψ_0	Symmetrized Ψ_1	Symmetrized Ψ_2	Symmetrized Ψ_3	Primitive Ψ_4
$1A_g$ -a	0.260	0.395	0.759	0.641	0.225	...
$1A_g$ -b	0.258	0.392	0.757	0.640	0.223	...
$1A_g$ -c	0.437	0.675	0.759	0.328	0.064	0.346

^a = 1.393 Å.

es 5 and 6. Note that 6 is the triplet analog of structure 4.

Third part of the analysis was stimulated by the notion that benzene's normal vibration of b_{2u} symmetry carried the molecule into a geometry appropriate to a cyclohexatriene structure.⁶ If the C-C distances in a hypothetical "cyclohexatriene" are 1.465 and 1.335 Å,⁶ then the benzene ring is roughly 15% of its time distorted enough to pass the cyclohexatriene geometry. The rather next question was this: to what degree do the results respond to a cyclohexatriene geometry by regarding themselves according to a *single* Kekulé structure? When the C-C bonds alternate in length 1.465 and 1.335 Å, what are relative contributions of the two Kekulé structures?

Outline of the Calculations

In presenting the results of the analysis, let us first describe the "accurate" wave functions we used. The details of the method of calculation are given in Appendix 1. For the $1A_g$ ground electronic state of the undistorted (D_{6h}) benzene molecule, we used three different configurations, denoted by the letters a, b, and c: "a" is the configuration, based on *atomic* self-consistent (SCF) orbitals of carbon;⁷ "b" is a single configuration, based on Clementi's full molecular SCF function for all electrons of benzene,⁸ which is probably the best available *uncorrelated* wave function for benzene; and "c" is the 22-term configuration interaction function of Moskowitz and Barnett based on the Slater function representations of the atomic orbitals.⁹ This function does account for correlation but suffers from the limitation of a single Slater orbital representation. We shall use these three representations of the ground-state function as $1A_g$ -a, $1A_g$ -b, and $1A_g$ -c, respectively. Unfortunately no function is yet available which combines use of accurate atomic orbitals, as in b, with configuration interaction as in c.

In the excited states we examined the following functions which we denote simply by the state designation approximation: for the $1B_{2u}$ state, all three approximations, $1B_{2u}$ -a (based on atomic SCF orbitals), $1B_{2u}$ -b (based on Clementi's full molecular SCF function), and $1B_{2u}$ -c (Moskowitz' 13-term configuration interaction function for this state); and for the $1B_{1u}$ state, triplets $1B_{1u}$ and $3B_{2u}$, only the configuration interaction functions of Moskowitz, *i.e.*, the functions cor-

responding to approximation c, which have 16, 13, and 18 molecular orbital configuration basis functions, respectively.

For the distorted molecule, whose symmetry is D_{3h} , we used the $2p\pi$ atomic SCF orbital basis. With these, we carried out a variational calculation to determine a best set of molecular orbitals. Specifically, when the molecular symmetry is reduced from D_{6h} to D_{3h} , the e_g and e_u orbitals all become e'' orbitals (e'' and e''_*) and can mix, in pairs. We therefore replace the lowest configuration with a simple variational function

$$(a_{2u})^2 (e_{1g})^4 \xrightarrow{D_{6h}} (a'_{1'})^2 (e'' \cos \omega + e''_* \sin \omega)^4 \xrightarrow{D_{3h}}$$

and expand the new function in terms of simple configurations based on e'' and e''_* functions. To find the optimum mixture of the e'' and e''_* orbitals, we need only diagonalize a 2×2 one-electron Hamiltonian (see Appendix 2).

Results

A. Ground State. Table I contains the values of squares of projections onto the ground state of functions representing structures 0-4. The primitive Dewar structure 4 was done only for the configuration interaction (CI) function $1A_g$ -c; this is of little concern because it was really wanted only for comparison with the triplets. We remind the reader that the VB functions are highly nonorthogonal, so that the sums of the squares of the projections will in general be much larger than unity.

The first two rows of Table I are extremely similar, for a very simple reason. The π -molecular orbitals of D_{6h} benzene are fixed entirely by symmetry, and the composition of these orbitals in terms of VB functions is thereby determined. The only differences between the first row and the second in these two tables arise from the differences in the atomic overlap. The corresponding values for the single Slater function set without configuration interaction were also generated during the computation of the projections onto Moskowitz-Barnett functions. These are also quite similar to the first two rows, but about 10% smaller because of the smaller overlaps of the Slater basis set.

The amount of polar character in the benzene ground state is rather striking. Even after configuration interaction the $1A_g$ function retains a large portion of its singly ionic structure. The total covalent contribution increases considerably with CI, apparently at the expense of the doubly and especially the triply ionic function. We must exercise a little care in attributing an increase in one function to a decrease in another, both because of the nonorthogonality problem and because we have examined only a few structures. From

¹ Berry, *J. Chem. Phys.*, **35**, 2253 (1961).
² Costain and B. P. Stoicheff, *ibid.*, **30**, 777 (1959); H. J. Ibbett, *Trans. Faraday Soc.*, **57**, 1649 (1961).
³ Ibbett, N. R. Kestner, J. Jortner, and S. A. Rice, *J. Chem. Phys.*, **39**, 965 (1963). The $1P$ SCF AO set was used.
⁴ Clementi, private communication.
⁵ Moskowitz and M. P. Barnett, *J. Chem. Phys.*, **39**, 1557 (1963).
⁶ Vectors were very kindly supplied by Dr. Moskowitz.

the analogy of the butadiene calculation,⁸ we may expect the Slater function calculation of Moskowitz and Barnett to *underestimate* the amount of ionic character because of the inherently large estimate of the energy required to form a C^+C^- pair in this basis set.

B. Excited Singlets. Some of the VB structures are naturally excluded by symmetry considerations from contributing to particular excited states. For example, the two Kekulé structures can give only A_{1g} and B_{2u} combinations, and so are excluded from the B_{1u} ; the triply ionic structure (3) and its counterpart can give a sum and difference with A_{1g} and B_{1u} symmetry, but no B_{2u} ; the Dewar structure (4) cannot contribute B_{2u} either. These relations provided useful checks of the computational machinery.

In Table II we see both an analysis of various functions representing the ${}^1B_{2u}$, and, in the last line, the CI result alone for the ${}^1B_{1u}$. The physical situations in these two states are quite strikingly different; the lower energy B_{2u} is almost entirely covalent, while the B_{1u} has considerable doubly and triply ionic character.

Table II. Squares of Projections of VB Functions for Benzene in ${}^1B_{2u}$ and ${}^1B_{1u}$ States in Equilibrium Configuration^a

VB function	Primitive Ψ_0	Symmetrized Ψ_0	Symmetrized Ψ_1	Symmetrized Ψ_2	Symmetrized Ψ_3
${}^1B_{2u}-a$	0.149	0.439	0.844	0.520	0
${}^1B_{2u}-b$	0.147	0.432	0.840	0.512	0
${}^1B_{2u}-c$	0.320	0.907	0.525	0.116	0
${}^1B_{1u}-c$	0	0	0.562	0.611	0.215

^a Equilibrium, that is, for the ground state, with $R = 1.393$ Å.

Note that symmetry alone forces the ${}^1B_{2u}$ function to have a large amount of singly and doubly ionic character, but that CI reduces these considerably. The Moskowitz-Barnett single configuration, not shown in Table III, gives almost 0.8 for the symmetrized Ψ_1 , so the reduction is not an artifact of the orbital basis set.

C. Triplet. The triplet result can be described very briefly. Symmetry excludes the nonionic structures 5 and 6 from the next-lowest triplet, the ${}^1B_{2u}$, but not from the lowest triplet, the ${}^1B_{1u}$. The primitive function representing structure 5 contributes 26% of the total function ${}^1B_{1u}-c$, and the Dewar-like or quinoid triplet, 40% of the same function. Recall from Table I that the ground state has 35% of the primitive Dewar structure. We interpret this to mean that the lowest triplet state may have a little more quinoid character than the ground state, but not vastly more.

D. Distorted Benzene. The results in the first line of Table III exhibit an interesting contrast to the first two lines of Table I. Note that it is with the *second* lines of Tables I and II, for ${}^1A_{1g}-b$ and ${}^1B_{2u}-b$, that the

calculations of Table III should be compared, and not the third lines. No CI function is available for the distorted species, and it was our feeling that our one-parameter variation of the SCF function would give a sufficiently accurate measure of the *relative change* in the contributions of the two Kekulé structures. The total "symmetrized Ψ_0 " in column 3 of Table III is based on the projection of the sum of the functions in the first two columns and is the equivalent of a Thiele structure in the same sense as the symmetrized Ψ_0 of Table I. The value of 0.399 is essentially the same as the values of 0.395 for the symmetrized Ψ_0 function on ${}^1A_{1g}-a$ in Table I. However, the primitive Ψ_0 in D_{6h} symmetry gives a value for $|\langle \Psi_0 | {}^1A_{1g}-a \rangle|^2$ of 0.260; the two corresponding structures in our D_{3h} structure give essentially this average value, but the expected change in the relative contributions of these functions does actually occur. The contributions of the two covalent structures change, one upward and the other downward, by roughly 25%. The change is not startling, but it is very significant. By contrast to the change in the two Kekulé functions, the triply ionic contribution, Ψ_3 , does not change dramatically when the C_6 ring is distorted to D_{3h} symmetry. This lack of change is particularly evident in the ${}^1B_{2u}$ excited state, where triply ionic character is forbidden in sixfold symmetry but allowed in D_{3h} . The actual amount of triply ionic character in ${}^1B_{2u}-a$, in the D_{3h} form, is only 0.01%, so that the distortion is a very small perturbation so far as "triple-ionization" is concerned.








We shall close with a remark about a limitation of a method such as the one used here. The concept of a valence-bond structure is meaningful only in terms of a specific set of atomic orbitals. As such, it can be used to analyze only those wave functions based on a single, well-defined set of atomic orbitals. The method will not be applicable to configuration interaction wave functions based on configurations each of which has its own uniquely determined basis set, chosen for example to make each configuration satisfy self-consistent field and orthogonality relationships.

Acknowledgments. We thank Enrico Clementi and Jules Moskowitz for their kindness in supplying us with wave functions, and Paul Cade, Andrew Hazi, and Joshua Jortner for their assistance in evaluating integrals. We also thank Gerhard Closs for suggesting that we calculate the quinoid or Dewar projections. This work was supported by the National Science Foundation.

Appendix. 1. Method of Computing Projections

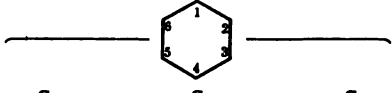

The projections were calculated in this way. Let Ψ represent the set of symmetrized VB spin eigenfunc-

Table III. Squares of Projections of VB Functions onto Distorted^a (D_{3h}) Benzene. Ground and First-Excited Singlet States

VB function ^b			"Symmetrized Ψ_0 " (Thiele) 				
${}^1A_1'$	0.337	0.204	0.399	0.573	0.342	0.481	0.351
${}^1A_1'$ from ${}^1B_2'$ ^d	0.155	0.138	0.438	0.329	0.386	0.135	0.206
							0.220
							0.0001

^a Alternating lengths of 1.335 and 1.464 Å. ^b All functions taken symmetrized to transform as A_1' in D_{3h} . ^c Determined as described in text. ^d Based on orbital parameters found in fixing ground-state function.

Sets of Atomic Overlap Integrals

							
	S_{12}	S_{13}	S_{14}	S_{23}	S_{12}	S_{13}	S_{14}
mic SCF)	0.32155	0.07992	0.04625	0.34565	0.29346	0.07847	0.04525
ment)	0.31009	0.05796	0.02674				
skowitz)	0.24850	0.03519	0.01571				

Ω represent the "accurate" wave functions, which are expressed in terms of orthonormal orbitals ψ . Then we write the transforming Ψ in terms of Ω 's as a series of matrix operations

$$\Psi = \text{VDS}^{-1}\text{C}\Omega \quad (1)$$

is the configuration interaction matrix (the except for the Moskowitz set Ω_c); S^{-1} is the matrix which is the inverse of the matrix generating functions from single MO determinants; matrix transforming single MO determinants into properly symmetrized VB functions. Neither D nor V is unitary because of the nonorthogonality of VB functions. The inversion of S^{-1} and V is straightforward. The inverse of S^{-1} and V is straightforward. The inverse of a matrix whose construction is given by Moffitt.¹⁰ The transformation from MO's ψ is given in terms of a unitary matrix diagonal matrix d (eq 2). We consider only the

$$\varphi = \text{d}u\pi = \gamma\pi \quad (2)$$

which the z component of spin is zero, so that as many electrons with spin $+\hbar/2$ as with spin $-\hbar/2$. Then, the indices 1, 2, and 3 are reserved for orbitals with $+\hbar/2$ z spin and indices 4, 5, and 6 for orbitals with $-\hbar/2$ spin. Then the matrix element of a determinant based on MO's α_i , with a determinant based on AO's β_i , ..., is written as shown in eq 3.

$$\begin{aligned} \frac{\alpha_1 \dots \alpha_{2n}}{\beta_1 \dots \beta_{2n}} &= \frac{(u_{\alpha_1 \dots \alpha_n}^{\beta_1 \dots \beta_n})(u_{\alpha_{n+1} \dots \alpha_{2n}}^{\beta_{n+1} \dots \beta_{2n}})}{d_{\alpha_1 \dots \alpha_{2n}}} \\ &= \frac{|u_{\alpha_1 \dots \alpha_n}^{\beta_1 \dots \beta_n}| |u_{\alpha_{n+1} \dots \alpha_{2n}}^{\beta_{n+1} \dots \beta_{2n}}|}{d_{\alpha_1 \dots \alpha_{2n}}} \end{aligned} \quad (3)$$

of

$$u_{\alpha_1 \dots \alpha_n}^{\beta_1 \dots \beta_n}$$

Moffitt, *Proc. Roy. Soc. (London)*, A218, 486 (1953).

denotes the determinant formed from the minor of the u matrix from the elements indicated. The quantities d_{α_i} are the α_i - α_i elements of the diagonal matrix d .

The entire transformation was set up for machine computation. For a given state and molecular geometry, the choice of functions to use for the Ω set was reflected only in the set of atomic overlap integrals one put into the input deck. For reference, the overlaps are given in Table IV.

Appendix 2. Estimation of the Distorted Ground-State Wave Function

In the D_{3h} configuration of benzene, the optimum mixture between the e'' and e''_* orbitals is found by first orthogonalizing the pair of mixed orbitals and then minimizing the energy of the mixed pair. For example in the D_{3h} representation e'' , the e_{1g} function, $\phi = C_1(\pi_1 + \pi_2 - \pi_4 - \pi_5)$, becomes nonorthogonal to the function $\phi_2 = C_2(\pi_1 + \pi_2 - 2\pi_3 + \pi_4 + \pi_5 - 2\pi_6)$; their overlap integral S_{12} is proportional to the difference between the overlap integrals $(\pi_1 | \pi_2)$ and $(\pi_2 | \pi_3)$. The secular equation was set up in terms of ϕ_1 and the function, $[\phi_2 - (\phi_1 | \phi_2)\phi_1]$, Schmidt-orthogonalized to ϕ_1 . The elements of the secular determinant are

$$H_{11}$$

$$H_{12}' = H_{12} - S_{12}H_{11}$$

$$H_{22}' = H_{22} - 2S_{12}H_{12} + S_{12}^2H_{11}$$

where

$$H_{11} = d_1^2 u_{1i} u_{1j} h_{ij} \quad h_{ij} = (\pi_i | \mathcal{H} | \pi_j)$$

$$H_{12} = d_1 d_2 u_{1i} u_{2j} h_{ij}$$

$$H_{22} = d_2^2 u_{2i} u_{2j} h_{ij}$$

using the Einstein summation convention. Elements h_{ij} were taken as $h_{ii} = 11.54 \text{ eV} =$ the valence-state ionization potential,¹¹ and h_{ij} as resonance integrals obtained by numerical integration of a Goeppert-Mayer-Sklar core potential for the different bond lengths involved.¹²

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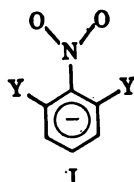
Details of the Steric Interaction in Mono-*ortho*-substituted Nitrobenzene Anion Radicals^{1a}

Ted M. McKinney and David H. Geske^{1b}

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York. Received August 25, 1966

Abstract: Previously reported electron spin resonance studies of substituted nitrobenzene anion radicals have provided substantial structural information. The present esr study of nitrobenzene anion radicals with *o*-alkyl substituents permits structural assertions based on both nitrogen and β -proton isotropic coupling constants. As an ancillary matter coupling constants (including thermal coefficients) for nitrobenzene anion radicals with *p*-alkyl substituents are presented. Data for 4- and 5-nitroindan anion radicals, where the methylene protons are essentially fixed with respect to the benzene ring, serve to substantiate the angular dependence of the β -proton coupling constants.

The study of organic free radicals by esr has provided substantial structural and conformational insights.² One such example is the work on steric hindrance in nitroaromatic anion radicals. In particular, the effect of mono- and di-*ortho* substituents with threefold symmetry [$Y = -CH_3, -C(CH_3)_3$] has already been reported.²⁻⁵



The examination of nitrobenzene anion radicals with unsymmetrical mono-*ortho* substituents [$Y = -CH_2CH_3, -CH(CH_3)_2$] is reported here. This study is directed to the question of the detailed orientation of the substituent group and of the nitro group with respect to the benzene ring. For the purposes of comparison, the *para* derivatives were also examined. Since coupling constants for the methylene and methine protons of the substituent group are the basis for conformational assertions, it was of interest to examine the temperature dependence of these coupling constants. The examination of two nitroindan anion radicals was relevant because the methylene hydrogens are essentially fixed with respect to the benzene ring.

Experimental Section

2- and 4-ethylnitrobenzenes, as obtained from Aldrich Chemical Company, Inc., were purified by preparative vapor phase chromatography, using a 10-ft column of 20% Carbowax on Chromosorb P. Refractive indices measured at 20° were 1.5353 and 1.5451 for the *ortho* and *para* isomers, respectively. The reported values are 1.5352 and 1.5459, respectively.⁶

4-Isopropylnitrobenzene was prepared by nitration of cumene (Phillips Petroleum "Pure Grade") according to the procedure of Nelson and Brown.⁷ The product boiled at 92° at a pressure of

approximately 10 mm and had a refractive index of 1.5369 at 20° which was identical with the literature value.⁶ The 2-isopropylnitrobenzene was a gift of Professor B. M. Wepster, Delft, The Netherlands.

Nitration of indan (Aldrich) using the procedure described by Newton⁸ yielded 4- and 5-nitroindan. The isomers were separated by preparative vapor phase chromatography, using the same conditions employed for the 2- and 4-ethylnitrobenzenes. The melting point of 4-nitroindan was 42.5° and that of 5-nitroindan was 40°. The literature values are 44–44.5° and 40–40.5°, respectively.^{8b}

Acetonitrile and dimethylformamide were purified by previously described procedures.⁹ Tetrapropylammonium perchlorate for use as supporting electrolyte was recrystallized three times from water.

The anion radicals were generated electrochemically using the *intra muros* technique.⁹ Variable-temperature measurements were made using the Varian V-4557 variable-temperature accessory. Esr signals were normally recorded as the first derivative of the absorption. This mode of presentation usually gave sufficient resolution for complete assignment of the spectrum. However, in some instances the proton hyperfine interactions were of such small magnitude compared to the line width that accurate measurements were impossible. Display of the second derivative greatly facilitated measurements of small splittings and of lines with overlapping components.

Reported coupling constants are averages of at least three individual measurements. For completeness, the parameters used in computed spectra are included in the appropriate figure captions. All computed spectra were simulated with a Lorentzian line shape. Details of electrochemical¹⁰ and electron spin resonance measurements¹¹ have been described previously.

Results

In order to provide a basis for direct comparison of coupling constants with data secured in the earlier study,⁵ acetonitrile (AN) was used as the solvent in this work also. Spectra were also obtained in dimethylformamide (DMF). In general, these spectra were more highly resolved and the lines were narrower than those obtained in AN. Assignment of the spectrum in DMF was often more straightforward and facilitated assignment of the spectrum obtained in AN. The nitrogen coupling constant for a particular anion radical is somewhat larger in AN than in DMF,¹² and there is a corresponding decrease in spin density at the *para* ring position. This reorganization of spin density dis-

(1) (a) Abstracted in part from the Ph.D. thesis of T. M. McKinney, Cornell University, 1965; (b) Alfred P. Sloan Research Fellow.

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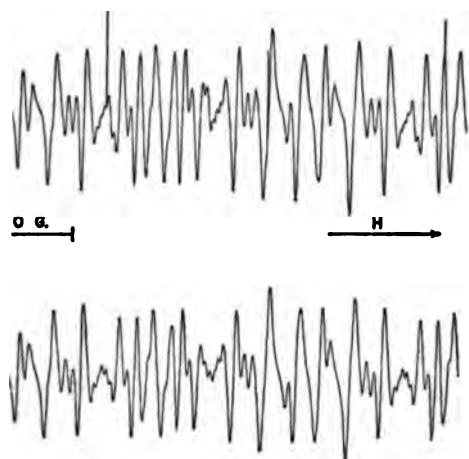
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(11) T. M. McKinney and D. H. Geske, *J. Chem. Phys.*, **44**, 2277 (1966).

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Low-field one-half of esr spectrum obtained by reduction of 0.11 mM solution of 2-ethylnitrobenzene in DMF. (b) Spectrum computed using the values (in gauss) 3.92 (1 proton), 1.125 (1 proton), 3.34 (1 proton), 1.805 (2 protons), 11.46 (1 nitrogen), a line width of 1.06, and 0.005-gauss increments.

Upon changing the solvent medium was a factor in the assignment of proton coupling to particular molecular positions.

ESR and EPR data for the compounds examined in this study are given in Table I along with data for related compounds studied earlier. The values are all close to 2.0 but they were not explicitly assigned.

All of the compounds in Table I meet the condition for reversible, one-electron reduction, namely, $E_{1/2} - E_{1/2} \approx -56$ mv. The different constants also indicate the transfer of an electron.

The nitrogen coupling is the dominant feature in the ESR spectra reported here. The proton coupling constants were assigned by analogy to the assignment of the *m*-monodeuterionitrobenzene,⁵ but in certain instances there is uncertainty as to which nucleus is responsible for a given constant. Hence, the assignments are discussed below.

4-Ethylnitrobenzene. The spectrum of the 4-ethylnitrobenzene anion radical in DMF had a line width of 0.33 gauss and was readily assigned using the coupling constants shown in Table I. By analogy to the nitrobenzene radical, the smallest splitting constant was assigned to the *meta* protons. The 3.37-gauss splitting of the equivalent nuclei with a spin of $1/2$ was compared with the coupling constants for the *ortho* protons of nitrobenzene and *p*-nitrotoluene radicals⁵ and was assigned to the *ortho* protons. This is supported by the observation of the same value in the nitrobenzene anion where there is no possibility of ambiguity in assignment of *ortho* and *para* coupling constants since the latter gives rise to a doublet.

The remaining 2.96-gauss triplet was assigned to the methylene protons of the ethyl group. The data show that the protons of the *para* substituent of ethylnitrobenzene radical do indeed have a coupling constant in DMF than in AN, and this similarity supports the assignment of coupling constants to particular positions. The coupling constants for this radical in ethanol¹³ and aqueous acetone¹⁴ are given in Table I for comparison.

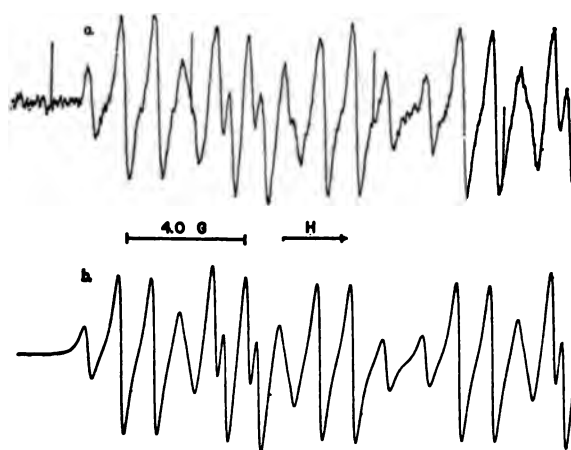


Figure 2. (a) Low-field one-half of esr spectrum obtained by reduction of 0.11 mM solution of 2-isopropyl nitrobenzene in AN. (b) Spectrum computed by using the values (in gauss) 3.565 (1 proton), 3.175 (1 proton), 1.125 (3 protons), 11.46 (1 nitrogen), a line width of 0.3, and 0.005-gauss increments.

2-Ethylnitrobenzene. Figure 1 shows the low-field half of the spectrum of the 2-ethylnitrobenzene anion radical in DMF together with a computed spectrum. This is a relatively complicated spectrum since the ring protons are not strictly equivalent in pairs. The close similarity of the experimental and computed spectra is substantial evidence for the validity of the assignment. By analogy to the nitrobenzene spectrum, the two smallest coupling constants were assigned to the positions *meta* to the nitro group. The proton coupling constants for the 3 and 5 positions were slightly different. There is no basis for distinguishing which position is associated with the larger constant, a fact indicated in Table I by bracketing the constants.

The triplet proton splitting was immediately assignable to the methylene protons of the ethyl substituent since they are the only two protons in the radical which are fully equivalent. The remaining two proton doublets were assigned to positions *ortho* and *para* to the nitro group; by analogy to the nitrobenzene radical, the larger value was assigned to the *para* ring proton. Moreover, this splitting showed the larger solvent variation.

4-Isopropyl nitrobenzene. Since the methine proton is the only nucleus in the isopropyl group which shows a resolvable splitting, the ESR spectrum for the 4-isopropyl nitrobenzene anion radical bears a formal resemblance to that for the nitrobenzene anion radical. Accordingly, the smallest coupling constant was attributed to the *meta* protons. Assignment of the 1.8-gauss constant to the methine proton is unequivocal. The line width for the ESR spectrum in DMF was 0.33 gauss. The coupling constants for this anion radical in aqueous acetone are also given in Table I.

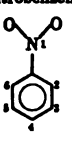

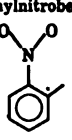
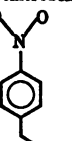
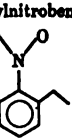
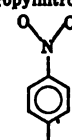
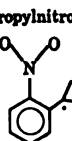
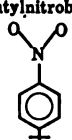
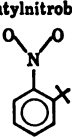
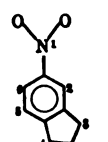
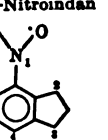
2-Isopropyl nitrobenzene. Figure 2 shows the low-field half of the experimental spectrum for the 2-isopropyl nitrobenzene anion along with a spectrum computed using the coupling constants given in the figure caption.

The outstanding features of the proton hyperfine structure are the extreme low-field lines which indi-

(13) P. B. Ayscough, F. P. Sargent, and R. Wilson, *J. Chem. Soc.*, 4518 (1963).

(14) P. L. Kolker and W. A. Waters, *ibid.*, 1136 (1964).

Table I. Polarographic and ESR Data for Nitroaromatic Anion Radicals

Compound and structure	$-E_{1/2}^a$	$-(E_{1/2} - E_{1/2}^0),$ mv	I^b	Solvent ^c	Isotropic coupling constants of anion radicals, gauss						R
					$ a_1 $ ^d	$ a_2 $	$ a_3 $	$ a_4 $	$ a_5 $	$ a_6 $	
Nitrobenzene 	1.147	56	4.1	A ^e D ^f AA ^g E ^h	10.32 9.70 13.30 13.65	3.39 3.36 3.40 3.35	1.09 1.07 0.90 1.15	3.97 4.03 3.40 3.35	1.09 1.07 0.90 1.15	3.39 3.36 3.40 3.35	
4-Methylnitrobenzene 	1.203	56	4.0	A ⁱ D AA ^g E ^h	10.70 10.40 14.10 14.05	3.39 3.40 3.50 3.40	1.11 1.10 1.10 1.15	3.98 ^j 3.94 ^j 3.80 ^j 3.75 ^j	1.11 1.10 1.10 1.15	3.39 3.40 3.50 3.40	
2-Methylnitrobenzene 	1.263	56	4.6	A ^h D	11.00 10.19	3.12 ^j 3.24 ^j	1.04 1.06	3.91 3.87	1.04 1.06	3.12 3.37	
4-Ethyl nitrobenzene 	1.199	58	4:3	A ^m D AA ^g E ^h	10.71 10.18 14.15 14.00	3.37 3.34 3.45 3.40	1.11 1.09 1.15 1.10	2.96 ^k 3.01 ^k 3.05 ^k 2.80 ^k	1.11 1.09 1.15 1.10	3.37 3.34 3.45 3.40	0.74 0.76 0.80 0.75
2-Ethyl nitrobenzene 	1.251	57	4.3	A D	11.03 10.20	1.76 ^l 1.81 ^l	[1.00 ⁿ] [0.98 ⁿ]	3.76 3.92	[1.15 ⁿ] [1.13 ⁿ]	3.29 3.34	0.56 0.56
4-Isopropyl nitrobenzene 	1.194	57	4.3	A ^m D AA ^g	10.66 10.05 14.20	3.36 3.40 3.40	1.10 1.07 1.15	1.74 ^o 1.76 ^o 1.80 ^o	1.10 1.07 1.15	3.36 3.40 3.40	0.44 0.45 0.47
2-Isopropyl nitrobenzene 	1.285	56	4.0	A D	11.47 10.41	1.13 ^o 1.13 ^o	1.13 1.13	3.66 3.75	1.13 1.13	3.20 3.18	0.36 0.35
4-t-Butyl nitrobenzene 				AA ^g E ^h	14.25 14.00	3.40 3.40	1.10 1.10	... ^p ... ^p	1.10 1.10	3.40 3.40	
2-t-Butyl nitrobenzene 	1.355	54	2.9	A ^h D	14.90 12.73	... ^p ... ^p	1.10 1.10	2.50 3.10	1.10 1.10	2.50 2.80	
5-Nitroindan 				A D	10.84 10.32	[3.30] [3.22]	1.38 ^q 1.41 ^q	5.40 ^q 5.42 ^q	1.11 1.09	[3.54] [3.52]	1.36 1.35
4-Nitroindan 				A D	10.49 9.84	4.86 ^q 4.93 ^q	1.15 ^q 1.09 ^q	3.92 3.99	1.15 1.09	3.38 3.38	1.56 1.53

I (Footnotes)

half-wave potentials are reported for acetonitrile solution with respect to the aqueous saturated calomel electrode. Data are tabulated only the least negative half-wave potential for each compound. ^b Diffusion current constant, $i_d/m^{1/2}t^{1/2}C$, where the maximum diffusion current i_d is measured in microamperes, m in milligram per second, t is seconds, and C in millimoles per liter. ^c Notation: A, acetonitrile; D, dimethylformamide; AA, 10–15% aqueous acetone; E, ethanol. ^d Nitrogen coupling constant. ^e Data from ref 9. ^f Data from P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.*, **39**, 609 (1963). ^g Data for AA from ref 14. ^h Data for E from ref 13. ⁱ Data from A. H. Maki and D. H. Geske, *J. Am. Chem. Soc.*, **83**, 1852 (1961). ^j Coupling constant for three equivalent nuclei with spin of $1/2$, from ref 5. ^k Coupling constant for two methylene protons of ethyl group at this position. ^l After completion of this work the same coupling constants were reported by E. G. Janzen and J. L. Gerlock, *J. Org. Chem.*, **32**, 820 (1967). ^m The ring protons *ortho* to the nitro group are nonequivalent, but there is no straightforward way of determining which position has the larger coupling constant. ⁿ The ring protons *ortho* to the methine proton of the isopropyl substituent at this position. ^o No splitting resolved from the *t*-butyl group. ^p Coupling constants for methylene protons.

the presence of quartet splittings with intensity ratios of approximately 1:3:3:1. Since there are not symmetrically equivalent protons in the molecule, it implies that the coupling constant for the methine proton of the isopropyl group is accidentally nearly the same as that for the two ring protons *meta* to the nitro group. The larger of the two remaining doublet splittings is assigned to the *para* ring proton by analogy to nitrobenzene case. Furthermore, this coupling constant increases when the solvent is changed from acetonitrile to DMF. The other doublet is assigned to the proton *ortho* to the nitro group.

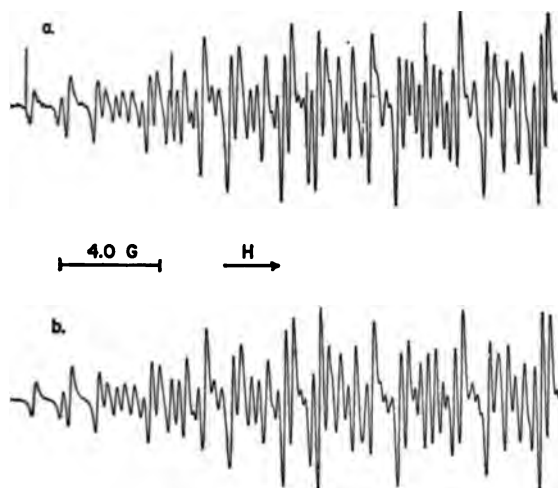


Figure 3. (a) Low-field one-half of ESR spectrum obtained by reduction of 0.96 mM solution of 5-nitroindan in DMF. (b) Spectrum computed by using the values (in gauss) 3.52 (1 proton), 3.22 (1 proton), 1.09 (1 proton), 5.42 (2 protons), 1.41 (2 protons), 10.34 (nitrogen), a line width of 0.16, and 0.005-gauss increments.

***t*-Butylnitrobenzene.** Unresolved hyperfine structure from the nine methyl protons in the *t*-butyl group contributes to the line width in this spectrum. The assignment of the spectrum of this radical in AN as reported earlier⁵ distinguished no difference in coupling constants for the *ortho* and *para* ring protons. During the present investigation the spectrum was assigned in DMF. Use of a second derivative display revealed two different doublet splittings, the larger of which was assigned to the *para* ring proton. The difference was resolved between the *meta* proton coupling constants.

Nitroindan. Experimental and computed spectra of the anion radical of 5-nitroindan are given in Figure 3. Assignment of the larger of the two methylene proton coupling constants to the protons at the 4 position (numbering defined in Table I) is based on the larger

spin density at the *para* carbon atom. The two *ortho* proton coupling constants are distinguished as different; the arbitrary nature of the assignment between positions 2 and 6 is indicated in Table I by brackets.

4-Nitroindan. The experimental ESR spectrum for the anion radical of 4-nitroindan in DMF is shown in Figure 4 along with a computed spectrum. The quartet

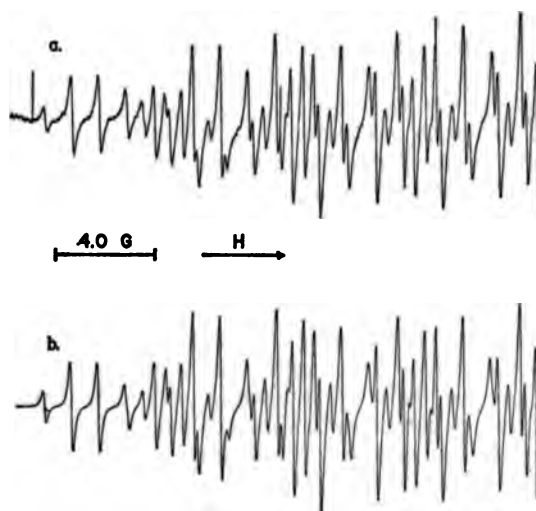


Figure 4. (a) Low-field one-half of ESR spectrum obtained by reduction of 1.1 mM solution of 4-nitroindan in DMF. (b) Spectrum computed by using the values (in gauss) 4.015 (1 proton), 3.38 (1 proton), 4.93 (2 protons), 1.09 (3 protons), 9.80 (1 nitrogen), a line width of 0.14, and 0.005-gauss increments.

structure for the smallest coupling constant was attributed to accidental coincidence of the coupling constants for the *meta* ring and methylene protons (positions 3 and 5, Table I). The triplet splitting of 4.9 gauss has been assigned to the *o*-methylene protons, and the larger of the two remaining proton coupling constants was assigned to the *para* proton.

Temperature Dependence. Data for the temperature dependence of the alkyl proton coupling constants are given in Table II. Equation 1 describes the temperature dependence of the methine proton coupling constant, a_{iso}^H , in the 4-isopropylnitrobenzene anion

$$a_{iso}^H = 1.389 + (1.23 \times 10^{-3})T \quad (1)$$

radical as a function of absolute temperature, T , with a correlation coefficient of 0.994.

Discussion

We wish to examine the above data with the intention of extracting those structural inferences which are warranted.

Table II. Temperature Dependence of Proton Coupling Constants for Alkyl Substituents^a

Radical	Temp, °K	<i>n</i> ^b	<i>a</i> _{βH} ^c
4-Isopropylnitrobenzene	233	12	1.672 ± 0.015
	263	11	1.712 ± 0.014
	283	20	1.757 ± 0.019
	333	12	1.793 ± 0.020
2-Isopropylnitrobenzene	233	12	1.120 ± 0.017
	333	16	1.128 ± 0.011
4-Methylnitrobenzene	233	6	3.965 ± 0.011
	296	6	3.942 ± 0.034
	333	6	3.949 ± 0.069
4-Ethylnitrobenzene	233		3.01
	333		3.01

^a Data for anion radicals in acetonitrile solution. ^b Number of measurements. ^c Uncertainties designated at the 95% confidence levels.

Nitrogen Coupling Constants. Attention is first of all focused on the nitrogen coupling constants. Previous work⁶ has established that introduction of bulky substituent groups *ortho* and di-*ortho* to the nitro group in nitrobenzene anion radicals results in a substantial increase in the isotropic nitrogen coupling constant, *a*_N. Thus with acetonitrile as solvent, *a*_N increases from 10.3 gauss for nitrobenzene anion radical to 23.6 gauss for one conformational isomer of the 2,3,5,6-tetraisopropylnitrobenzene anion radical.¹¹ In qualitative terms, this increase in *a*_N can be regarded as the result of the transfer of spin density from the phenyl group to the nitro group as the nitro group is twisted out of the plane of the ring by *ortho* substituents. A rationalization of nitro group nitrogen coupling constants on the basis of semiempirically calculated nitrogen and oxygen π -spin densities has been developed by Rieger and Fraenkel;⁴ twisting of the nitro group was accommodated in their molecular orbital calculations by a decrease of the carbon–nitrogen resonance integral. On the basis of examination of the anisotropic nitrogen coupling constants, Fox, Gross, and Symons^{15,16} have suggested that twisting of the nitro group along the carbon–nitrogen axis is accompanied by pyramidal distortion of the nitro group.

The nitrogen coupling constants for the nitrobenzene anion radicals (Table I), where the 2-substituent (Y) is successively –H, –CH₃, –CH₂CH₃, –CH(CH₃)₂, and –C(CH₃)₃, are 10.3, 11.0, 10.7, 11.5, and 14.9 gauss, respectively (in AN). The point of particular interest is that there is only a minimal effect on *a*_N for Y = methyl, ethyl, and isopropyl; for the symmetrical *t*-butyl group there is an abrupt increase in *a*_N.¹⁷ We interpret these data as evidence that the 2-ethyl and 2-isopropyl substituents are oriented for *minimum* interaction with the nitro group. A simplified view would state that, if the ethyl and isopropyl groups were rotating freely, the *a*_N values would be expected to be the same as for the 2-*t*-butylnitrobenzene anion radical.

(15) J. M. Gross and M. C. R. Symons, *J. Chem. Soc., Sect. A*, 451 (1966).

(16) W. M. Fox, J. M. Gross, and M. C. R. Symons, *ibid.*, 448 (1966).

(17) As in earlier studies⁶ comparison of the coupling constants for the *para*-substituted anion radicals with constants for nitrobenzene anion radical demonstrates the minor extent of the nonsteric effects of the *ortho* substituent. Although we have not secured esr data for the 4-*t*-butylnitrobenzene in AN and DMF, it is clear from the data in Table I for ethanol and aqueous acetone that the inductive effect of the *p*-*t*-butyl group is negligible.

The *a*_N of 10.5 gauss for the 4-nitroindan anion, where the methylene protons are essentially fixed in relation to the ring, is consistent with this interpretation.

Within this context it is of interest to examine *a*_N for several other *ortho*-substituted nitrobenzene anion radicals. In the *o*-nitrobiphenyl anion radical where *a*_N is 8.7 gauss in DMF,¹⁸ a compromise of twisting the nitro group out of the plane of the ring and delocalization of spin density into the *ortho*-ring substituent much be reached. Essentially the same conclusions have been reached for the anion radical of 2-nitroterphenyl.¹⁹ From the data of Carrington, Hudson, and Longuet-Higgins,²⁰ it is clear that the nitro group is hindered in the hydrogen adducts of the tetrafluoro- and pentafluoronitrobenzene anion radicals. However, *a*_N in the 2-fluoronitrobenzene anion radical²⁰ gives no evidence of steric hindrance.

Alkyl Proton Coupling Constants. Examination of the alkyl proton coupling constants in the *ortho*-substituted anion radicals for conformational implications requires a brief review of the angular dependence of transmission of spin density to β protons (β protons are defined as those protons on an sp^3 carbon which is in turn bonded to a π system). This concern was initiated by the observation of methyl proton coupling constants in methylated semiquinones by Venkataraman and Fraenkel²¹ in 1955.

Bersohn²² proposed a hyperconjugative mechanism which involved the mixing of the methyl group pseudo- π orbital with the π system on the adjacent trigonal carbon atom. Over the past 10 years an extensive literature has developed on the theory of β -proton coupling constants.^{23–32} In the main, Bersohn's proposal of hyperconjugation has been substantiated. The point of interest for derivation of conformational information is the angular dependence of the β -proton coupling constants, *a*_{βH}, as stated in eq 2 where $\rho_{C' \cdot \pi}$ is the π -electron spin density on the trigonal carbon, C', to

$$a_{\beta H} = \rho_{C' \cdot \pi}(B_0 + B \cos^2 \theta) \quad (2)$$

which the alkyl group is attached, *B*₀ and *B* are constants, and θ is the angle between the C'–C–H plane and the axis of the p_z orbital on the trigonal carbon atom. The value of *B*₀ has been variously estimated as –1.1²¹ and 4.33 gauss.³³ Estimates of *B* range from 40 to 53 gauss.^{24–36}

(18) Y. Nakai, K. Kawamura, K. Ishizu, Y. Deguchi, and H. Takaki, *Bull. Chem. Soc. Japan*, **39**, 847 (1966).

(19) R. L. Hansen, R. H. Young, and P. E. Toren, *J. Phys. Chem.*, **70**, 1657 (1966).

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(21) B. Venkataraman and G. K. Fraenkel, *J. Am. Chem. Soc.*, **77**, 2707 (1955).

(22) R. Bersohn, *J. Chem. Phys.*, **24**, 1066 (1956).

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(24) A. D. McLachlan, *Mol. Phys.*, **1**, 233 (1958).

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(26) M. C. R. Symons, *J. Chem. Soc.*, 277 (1959).

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(30) J. P. Colpa and E. de Boer, *Phys. Letters*, **5**, 255 (1963).

(31) J. P. Colpa and E. de Boer, *Mol. Phys.*, **7**, 333 (1964).

(32) D. H. Levy, *ibid.*, **10**, 233 (1966).

(33) D. H. Levy and R. J. Myers, *J. Chem. Phys.*, **43**, 3063 (1965).

(34) J. R. Morton, *Chem. Rev.*, **64**, 453 (1964).

(35) E. W. Stone and A. H. Maki, *J. Chem. Phys.*, **37**, 1326 (1962); **38**, 1254 (1963).

(36) R. W. Fessenden, *J. Chim. Phys.*, **61**, 1570 (1964).

on 2 has been widely used in the rationalization spectra of alkyl radicals in irradiated sol-

The first conformational assertions for radicals in solution were made by Stone and 1962. They interpreted the β -proton cou-
stants⁴¹ for a series of nitroalkane anion rad-
icals of a preferred orientation of the alkyl
group from a finite barrier to rotation. Since
groups in the nitroalkane anions are not
ent a_{β}^H is actually a time-averaged quantity
in eq 3, where ρ_N^{π} is the π -electron spin density
on the nitrogen atom. Evaluation of the average quan-
tity $\langle \cos^2 \theta \rangle$ in eq 3 was done quantum mechanically

$$a_{\beta}^H = \rho_N^{\pi} (B_0 + B \langle \cos^2 \theta \rangle) \quad (3)$$

and Maki⁴² under the assumption of a simple
sinusoidal barrier with a maximum barrier
 V_0 . On the basis of evaluation⁴² of this
graphic representation of $\langle \cos^2 \theta \rangle$ vs. V_0
obtained for the four different equilibrium con-
formations in Figure 5. For the 2-nitropropane
anion radical,⁴¹ V_0 was estimated as 1.1 kcal mole⁻¹
Figure 5) as the equilibrium conformation.
nitroethane anion radical,⁴¹ V_0 was estimated
as 1.1 kcal mole⁻¹ with 2a (Figure 5) as the equilib-
rium conformation. Temperature coefficients, da_{β}^H/dT ,
were calculated; however, the experimental data neces-
sitate these predictions have never become avail-
able. It has suggested that there are several rea-
sons for the calculated barriers "should not be taken
literally."⁴³ In addition to the assumption of a
sinusoidal barrier, both estimated values of V_0 are near the
limit, ~ 0.6 kcal mole⁻¹ at 298°K, a region where the
statistical method of averaging is least accurate.
In contrast to the work by Stone and Maki,⁴² a
number of workers^{36,44-50} have argued for preferred
orientations of alkyl groups in radicals in solution on the
basis of eq 3. Of particular note is the work of Fessen-
den,⁴⁴ who evaluated eq 3 for a series of radicals, $R\dot{C}H_2$,
where R is an alkyl substituent. Exact solution was
obtained because the reduced moment of inertia was
large enough to permit utilization of existing mathe-
matical tables. The experimental values⁴⁴ of a_{β}^H for the
radical over the temperature range -50 to +50°C
were in reasonable agreement with a calculated
value assuming a barrier of 295 cal mole⁻¹. The
dependence for the propyl radical using a
barrier of 412 cal mole⁻¹ was in excellent agreement

with the experimental data. The equilibrium conforma-
tions were 1b and 2b (Figure 5), respectively.

The 9-ethyl- and 9-isopropylxanthyl radicals studied
by Sevilla and Vincow⁵⁰ are distinguished by the extent
to which a_{β}^H values approach the expected limits (see
Table III) for conformations 1a and 2a (Figure 5),

Table III. R Values for Nitroalkane Anion⁴¹ and
Alkylxanthyl^{51,52} Radicals

Radical	a_N , gauss	a_{β} , gauss	R ^a
[CH ₂ NO ₂] ⁻	25.8	11.4	
[CH ₂ CH ₂ NO ₂] ⁻	25.5	9.75	0.85
[C ₂ H ₄ CH ₂ NO ₂] ⁻	24.8	9.98	0.87
[CH ₂ CHNO ₂ CH ₂] ⁻	25.2	4.60	0.40
[CH ₂ CHNO ₂ CH ₂ CH ₂] ⁻	24.7	3.19	0.28
9-Methylxanthyl		12.18	
9-Ethylxanthyl		6.22 ^b	0.51
9-Isopropylxanthyl		0.86 ^c	0.07

^a Ratio of β -proton coupling constant to methyl proton coupling
constant in parent radical. ^b Value for 110°. ^c Value for -10°.

respectively. V_0 for the ethylxanthyl radical has been
estimated as 6 kcal mole⁻¹.⁵¹ An even larger barrier
is indicated for the isopropyl radical.

In order to simplify the comparison of β -proton
coupling constants within a series of related radicals
such as the nitroalkane anions, it is convenient to
define the quantity R in eq 4. a_{β}^H is the coupling con-

$$R = \frac{a_{\beta}^H}{a_{CH_3}^H} \quad (4)$$

stant for the β protons of the alkyl substituent, and
 $a_{CH_3}^H$ is the coupling constant for the β protons of the
corresponding methyl-substituted radical. The methyl
group is usually regarded as freely rotating, i.e., V_0
 ~ 0 ;⁵² eq 5 is valid even with a barrier provided that
transitions between potential minima are rapid.⁴³

$$a_{CH_3}^H = \rho_1^{\pi} \left(B_0 + \frac{B}{2} \right) \quad (5)$$

With the definition of R in eq 4 it is not necessary to
explicitly evaluate ρ_C^{π} in eq 2 or ρ_N^{π} in eq 3 as long as

(51) M. D. Sevilla, private communication.

(52) The barrier for the methyl group in nitromethane has been esti-
mated as 6 cal mole⁻¹.

Yagawa and K. Itoh, *J. Chem. Phys.*, **36**, 2157 (1962).
Jaseja and R. S. Anderson, *ibid.*, **36**, 2727 (1962).
Piette, P. Ludwig, and R. N. Adams, *J. Am. Chem. Soc.*,
84, 4212 (1962).

the reduced moments of inertia were too large for exact
solution of the appropriate Schrodinger equation by standard methods,
the limiting solutions were used by Stone and Maki.⁴²

Stone, Ph. D. Thesis, Harvard University, 1962.
Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147

Dixon, R. O. C. Norman, and A. L. Buley, *J. Chem. Soc.*,

Chem. Commun., **1964**, 866 (1964).

Orvaja, H. Fischer, and G. Giacometti, *Z. Physik. Chem.*
45, 1 (1965).

Urrington and P. F. Todd, *Mol. Phys.*, **8**, 299 (1964).

Schumann, *Z. Physik. Chem. (Frankfurt)*, **43**, 198 (1964).

Sevilla and G. Vincow, Abstracts, 150th National Meet-
ing of the American Chemical Society, Atlantic City, N. J., Sept 13-17,

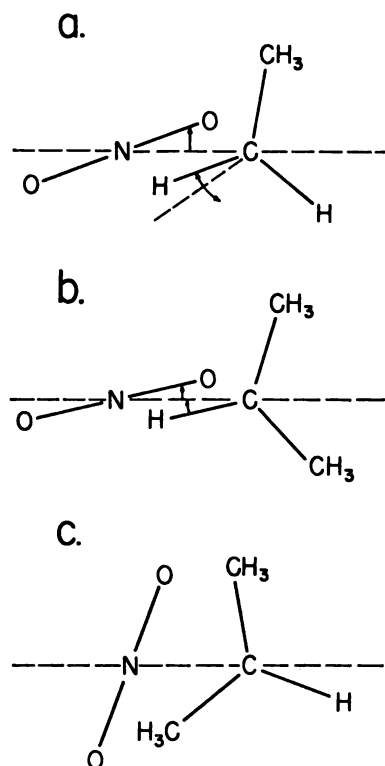


Figure 6. Representation of conformations of adjacent nitro and alkyl groups.

they remain essentially constant within the series. Furthermore, if one assumes $B_0 \ll B$, there is no need to select a value for B . Under these assumptions the values of R for conformations 1a, 1b, 2a, and 2b in Figure 5 are 0, 2, 0.5, and 1.5, respectively, under conditions of infinite barrier. The relation between R and $\langle \cos^2 \theta \rangle$ is as given in eq 6. To facilitate com-

$$R = 2\langle \cos^2 \theta \rangle \quad (6)$$

parison of R values for radicals in Table I, values of R for the nitroalkane anion radicals⁴¹ and alkyl-xanthyls^{50,51} are presented in Table III.

A substantial body of esr data for rigid radicals is available^{38,44,45,53,54} to support the validity of eq 2. Nevertheless, we felt that it was appropriate to examine several nitroaromatic anion radicals where the β protons are essentially fixed in relation to the benzene ring.

The 4- and 5-nitroindan anion radicals are in this category. The experimental R values for the methylene protons in the *para* position (position 4, Table I) in the 5-nitroindan anion radical are 1.35 and 1.36. R for the *ortho* (position 2, Table I) methylene protons of 4-nitroindan anion radicals are 1.56 and 1.53. Since conformation 2b (Figure 5) describes both of these methylene groups, the theoretical R value is 1.50. One might choose to argue that the reduced value of R for the *para*-position methylene groups, 1.36 in 4-nitroindan anion radical, is evidence for some torsional motion of the methylene group, *i.e.*, axial-equatorial inversion. In the same context the closer coincidence of experimental R values in the 5-nitroindan with 1.50 would be regarded as evidence for a more rigid structure as a consequent of the adjacent nitro group. These

(53) W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 4850 (1964).

(54) L. M. Stock and H. Suzuki, *J. Am. Chem. Soc.*, 87, 3909 (1965).

detailed assertions may not be fully warranted and should surely be viewed with caution. However, we do regard the data for the nitroindan radicals as reasonable evidence for the validity of eq 2.⁵⁵

Turning now to consideration of data for the *p*-alkylnitrobenzene anion radicals, it is important to note the comment of Carrington and Todd⁴⁸ who suggested, on the basis of the data of Ayscough, Sargent, and Wilson¹³ (Table I), that the preferred orientation of the ethyl group in 4-ethylnitrobenzene anion radical corresponds to 2a (Figure 5). Data for this anion radical in four solvent media are included in Table I. The R values (extreme right column, Table I) range from 0.74 to 0.80. If one accepts the Stone-Maki model,⁵⁶ the corresponding range of V_0 is 0.9 to 0.55 kcal mole⁻¹ with 2a (Figure 5) as the equilibrium conformation.⁵⁶

R values calculated for the *p*-isopropylnitrobenzene anion radical from the data in this work and from the data of Kolker and Waters¹⁴ (Table I) are 0.44 and 0.47, respectively. Within the Stone-Maki model this corresponds to a barrier, V_0 , of 1.0 kcal mole⁻¹ and 1a (Figure 5) as the equilibrium conformation. The observed temperature coefficient, 1.39×10^{-3} gauss deg⁻¹, may be compared with a calculated value of 3.8×10^{-3} gauss deg⁻¹. There are several possible explanations for the discrepancy between observed and calculated temperature coefficients. One possibility is that the approximate solution⁵⁶ is inadequate. A more likely alternative is that the real barrier is more complex than the simple sinusoidal barrier assumed in the calculation.⁵⁶ In fact, there could even be a shallow potential minimum at $\theta = 0^\circ$. We conclude that it is not possible to specify in detail the nature of the potential barrier.

With the strong indication at hand that the *p*-alkyl substituents undergo anisotropic averaging, it is appropriate to examine data for the *o*-alkylnitrobenzene anion radicals. It should be clear at the outset that the *ortho*-substituted radicals no longer possess twofold symmetry; thus, there is no reason to suppose that the potential barrier experienced by the β protons and the nitro group has twofold symmetry.

Observation of a coupling constant for three equivalent methyl protons in the *o*-methylnitrobenzene anion radical provides no information about the barrier to rotation. It does establish that transitions between potential minima are rapid⁵⁷ (*cf.* eq 5). Janzen and Gerlock⁵⁸ find line-width effects in the esr spectrum of 2-trifluoromethylnitrobenzene anion indicating hindered rotation of the trifluoromethyl group. While it is possible that 2-*t*-butylnitrobenzene anion is similar in a dynamic sense, the question cannot be settled on the basis of the esr spectrum.

We feel that it is significant to note that R for the *o*-ethylnitrobenzene anion, 0.56, is substantially smaller than R for the *para* substituent, 0.74–0.80, which is in turn smaller than R for the nitroethane anion radical,

(55) E. G. Janzen and J. L. Gerlock, *J. Org. Chem.*, 32, 820 (1967), find no splittings for the bridgehead protons in 2-nitrotritycene anion radicals. This observation is consistent with eq 2 since $\theta = 90^\circ$.

(56) Figure 3 in ref 35 was used for this estimate. The reduced moments of inertia for nitroaromatic and nitroaliphatic anion radicals are sufficiently comparable that this procedure is valid.

(57) We assume that eq 3 is applicable.

(58) E. G. Janzen and J. L. Gerlock, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept. 1966, Abstract 158-V.

(Table III). It should be recalled that R for **2a** (Figure 5) at the limit of large barrier is 0.50. While tempting to utilize the Stone-Maki model to estimate $V_0 \sim 4$ kcal mole⁻¹ it is also clear from the absence of symmetry (*vide infra*) that the approximation of a simple twofold barrier is *not* applicable; thus a barrier cannot be evaluated quantitatively. The schematic representation of conformation in Figure 6a is consistent with both alkyl proton and nitrogen coupling constants. By comparison with the range of R values for *p*-propylnitrobenzene anion, 0.44–0.47, the value of R for *o*-isopropylnitrobenzene anion is also considerably reduced. This value of R corresponds to $V_0 = 5$ kcal mole⁻¹ for conformation **1a** (Figure 5); since barrier is not strictly twofold, this value can only be regarded as indicative. The schematic representation in Figure 6b combines data for both nitrogen and proton coupling constants. A substantially larger nitrogen coupling constant would be expected if the two isopropyl groups were *cis* to the nitro group (Figure 6c) rather than *trans* (Figure 6b). Therefore, we can infer from the spatial requirements of the two methyl groups that the preferred orientation to be that shown in Figure 6b.

The question of the conformation of the neutral parent molecules, the 2-alkylnitrobenzenes, has been examined on the basis of spectrophotometric data.⁵⁹

The twist angles for the nitro group inferred for the various substituents were 2-methyl, 34°; 2-ethyl, 40°; 2-isopropyl, 47°; and 2-*t*-butyl, 65°. The abrupt increase in the twist angle for the *t*-butyl derivative was ascribed to the fact that all the other groups have at least one β -hydrogen atom which permits a favorable orientation such as Figure 6b.

Electrochemistry. ESR data provide an understanding of the structure of the anion radical. By contrast standard electrode potentials as approximated by half-wave potentials are dependent on the free-energy difference between the neutral molecule and the anion. The change in half-wave potential attributable to steric effects, ΔE_s ,⁶ for the *o*-alkylnitrobenzene as computed from data in Table I are 0.06, 0.05, 0.09, and 0.16 v,⁶⁰ for methyl, ethyl, isopropyl, and *t*-butyl, respectively. The abrupt effect of the *t*-butyl groups on ΔE_s parallels the change of a_N with alkyl substitution.

Acknowledgment. The authors acknowledge support from the National Science Foundation through Grants GP-1985 and GP-4906 as well as through GP-1687 for partial support for purchase of the ESR spectrometer. We are indebted to Professor B. M. Wepster for a gift of 2-isopropylnitrobenzene.

(59) B. M. Wepster, *Progr. Stereochem.*, **2**, 110 (1950).

(60) Since E_1 for 4-*t*-butylnitrobenzene is not available, a value of 1.19 v vs. sce was assumed in the calculation of ΔE_s .

Absorption and Emission Spectra of 1,2,4,5-Tetracyanobenzene-Naphthalene Complex Crystal

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Abstract: The electronic absorption and emission spectra of the charge-transfer complex of 1,2,4,5-tetracyanobenzene with naphthalene were studied by measuring them under various conditions, and by carrying out a theoretical study on the basis of configuration interaction among the ground, locally excited, and charge-transfer configurations. By combining the theoretical results with the polarized absorption measurements of the single crystal, it is concluded that the longest wavelength band at 24,600 cm⁻¹ may be ascribed to the first charge-transfer transition, and that the second charge-transfer band appears at 31,500 cm⁻¹ overlapping with local excitation bands. The fluorescence spectrum of the crystal at liquid N₂ temperature, which commences at 23,200 cm⁻¹ and shows vibrational structure, nicely satisfies the well-known mirror image relation to the first charge-transfer band. On the other hand, the fluorescence spectrum of the crystal at room temperature is structureless and is shifted to lower frequencies compared with that at liquid N₂ temperature. The phosphorescence spectrum of the complex observed at liquid He temperature shows well-resolved vibrational structure which is satisfactorily coincident with that of the phosphorescence spectrum of naphthalene itself. This means that the phosphorescent state of the complex may be regarded as the locally (within naphthalene) excited triplet state.

The electronic spectra of charge-transfer (abbreviated hereafter to CT) complexes in crystalline state are interesting research subjects in connection with the theory developed by Mulliken.¹ The experimental evidence for the existence of the CT absorption can be obtained from the directions of the transition moments of the bands determined by polarized absorption measurements of single crystals, and the study of absorption and emission spectra of CT complexes may give valuable

information about the interaction between the CT and locally excited structures and about electron- and energy-transfer phenomena in CT complex crystals. So far, however, the measurements of polarized absorption spectra have been carried out with rather few CT complex crystals, although many studies have been done with electronic spectra of solutions.^{2,3} The most

(2) G. Briegleb, "Elektronen-Donator-Acceptor-Komplexe," Springer-Verlag, Berlin, 1961.

(3) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(1) R. S. Mulliken, *J. Chim. Phys.*, **61**, 20 (1963).

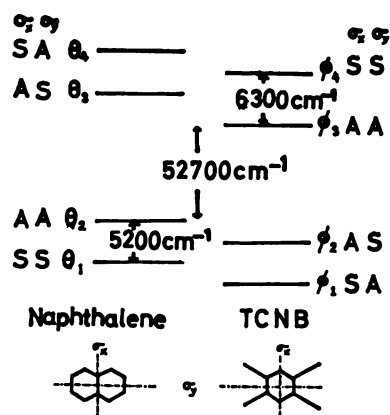


Figure 1. The orbital symmetries of the naphthalene and TCNB molecules and the differences of the orbital energies. $\epsilon(\theta_2) - \epsilon(\theta_1)$ and $\epsilon(\phi_4) - \epsilon(\phi_3)$ are estimated by the multi-CT bands. $\epsilon(\phi_2) - \epsilon(\theta_2)$ is the difference between the ionization potential (I_p) of donor and the electron affinity (A_i) of acceptor. According to the photoionization experiment (F. I. Vilisov, *Soviet Phys. Usp.* (Engl. Transl.), 6, 888 (1964); *Usp. Fiz. Nauk*, 81, 669 (1963)), I_p is 8.13 eV. A_i was estimated to be 1.60 eV by the aid of the CT band positions of some complexes in the previous paper.⁸

extensive studies on the polarized absorption and fluorescence spectra of single crystals have been done for the trinitrobenzene-anthracene complex.⁴⁻⁷ Hochstrasser and his co-workers observed the vibrational structure in the CT band at room and liquid N₂ temperatures,⁴ and they inferred the existence of localized excitons from experimental results showing that the absorption and fluorescence polarization ratios at 300°K are very different from each other.⁵ Further, they reported that the CT transition intensity in the crystal is about twice that in solution.⁶

In a previous paper⁸ we reported on the absorption spectra of the 1,2,4,5-tetracyanobenzene (TCNB)-mesitylene complex crystal and showed that the absorption band of the acceptor (TCNB) is changed in the complex as a result of the mixing of the CT structure with the TCNB locally excited electronic structure.

The present paper is concerned with the absorption, fluorescence, and phosphorescence spectra of the TCNB-naphthalene complex crystal. We measured the spectra at various temperatures and considered them theoretically by the semiempirical MO method, using the crystal structure of the complex recently determined by Kumakura, Iwasaki, and Saito.⁹

Experimental Section

TCNB was prepared by Ishitani and Maruyama of our laboratory by the method described in the previous paper.⁸ Naphthalene was purified by repeated recrystallizations in ethanol. The TCNB-naphthalene complex crystal was prepared by mixing the acceptor and the donor in methylene chloride and by evaporating the solvent at room temperature.

(4) S. K. Lower, R. M. Hochstrasser, and C. Reid, *Mol. Phys.*, 4, 161 (1961).

(5) R. M. Hochstrasser, S. K. Lower, and C. Reid, *J. Chem. Phys.*, 41, 1073 (1964).

(6) R. M. Hochstrasser, S. K. Lower, and C. Reid, *J. Mol. Spectry.*, 15, 257 (1965).

(7) J. Tanaka and K. Yoshihara, *Bull. Chem. Soc. Japan*, 38, 739 (1965).

(8) S. Iwata, J. Tanaka, and S. Nagakura, *J. Am. Chem. Soc.*, 88, 894 (1966).

(9) S. Kumakura, F. F. Iwasaki, and Y. Saito, *Bull. Chem. Soc. Japan*, in press.

The absorption spectra in solution and in thin film were measured with a Cary recording spectrophotometer, Model 14 M. A spectrophotometer attached with a microscope and a Roschen-type polarizer¹⁰ was used for the polarized ultraviolet absorption measurement of single crystals. The emission spectra at room and liquid N₂ temperatures were measured with a JASCO Model CT-50 grating monochromator with a RCA 1P28 or EMI 9529 A photomultiplier tube as detector, and those at liquid H₂ and liquid He temperatures with a Fuess prism monochromator, Kodak 103a F plates being used.

Theoretical Section

In the previous paper⁸ we calculated the electronic structures of the TCNB complexes with methyl-substituted benzenes. Consequently we could predict some possible stable geometrical structures of the complexes.¹¹ Furthermore, it was demonstrated that the mixing of the CT configuration with the acceptor locally excited configurations plays an important role in the excited states of some CT complexes. A similar theoretical consideration has been made for the TCNB-naphthalene complex on the basis of the structure determined by the X-ray crystal analysis technique.

For the sake of simplicity, only the highest two occupied (ϕ_1, ϕ_2 and θ_1, θ_2) and lowest two vacant molecular orbitals (ϕ_3, ϕ_4 and θ_3, θ_4) of TCNB and naphthalene¹² were considered. The symmetry and energy of each orbital are shown in Figure 1. The wave function of the ground configuration is given by the Slater-type determinant

$$\Phi_G = |\phi_1 \bar{\phi}_1 \phi_2 \bar{\phi}_2 \theta_1 \bar{\theta}_1 \theta_2 \bar{\theta}_2| \quad (1)$$

The lowest CT configurations are

$$\begin{aligned} \Phi_{CT_1} &= \Phi(\theta_2^{-1} \phi_3) \\ \Phi_{CT_2} &= \Phi(\theta_1^{-1} \phi_3) \\ \Phi_{CT_3} &= \Phi(\theta_2^{-1} \phi_4) \\ \Phi_{CT_4} &= \Phi(\theta_1^{-1} \phi_4) \end{aligned} \quad (2)$$

The lowest two locally excited configurations of TCNB and of naphthalene are approximately written as¹³ for TCNB

$$\begin{aligned} \Phi_{L1} &= 0.7878\Phi(\phi_1^{-1} \phi_3) + 0.6159\Phi(\phi_2^{-1} \phi_4) \\ \Phi_{L2} &= -0.5032\Phi(\phi_1^{-1} \phi_4) + 0.8642\Phi(\phi_2^{-1} \phi_3) \end{aligned} \quad (3)$$

for naphthalene

$$\begin{aligned} \Phi_{L3} &= \frac{1}{\sqrt{2}}\{\Phi(\theta_1^{-1} \theta_3) + \Phi(\theta_2^{-1} \theta_4)\} \\ \Phi_{L4} &= \Phi(\theta_2^{-1} \theta_3) \end{aligned} \quad (4)$$

where

$$\Phi(\theta_i^{-1} \phi_j) = \frac{1}{\sqrt{2}}\{|\dots \theta_i \bar{\phi}_j \dots| + |\dots \phi_j \bar{\theta}_i \dots|\}$$

(10) J. Tanaka, *ibid.*, 36, 833 (1963).

(11) Recently Niimura, Ohhashi, and Saito determined the structure of the hexamethylbenzene (HMB)-TCNB complex by the aid of the X-ray crystal analysis technique.¹² The results are in good agreement with our expectation on the stable configuration. The center of HMB molecule is located above one of the C-C bonds of the TCNB benzene ring.

(12) N. Niimura, Y. Ohhashi, and Y. Saito, General Symposium on Molecular Structure and Spectroscopy, Osaka, Japan, Oct 1966.

(13) The self-consistent field molecular orbitals of TCNB and naphthalene are determined using the Pariser-Parr-Pople approximations. The parameters used for TCNB were described in the previous paper,⁸ and Pariser's parameters¹⁴ were used for naphthalene.

(14) R. Pariser, *J. Chem. Phys.*, 24, 250 (1956).

(15) The wave functions of the locally excited configurations were determined by the configuration interaction including the one-electron excited configurations which are composed of the four orbitals considered.

the configuration interaction among the above nine ground configurations was considered. The energies of the excited configurations Φ_{L1} , Φ_{L2} , Φ_{L3} , and Φ_{L4} are taken to be equal to the corresponding transition energies observed with TCNB and naphthalene, the energy of the ground configuration Φ_G being taken to be the standard: $E_G = 0$, $E_{L1} = 3.93$, $E_{L2} = 4.66$, $E_{L3} = 4.06$, $E_{L4} = 4.43$. The energies of the CT configurations, the configuration being taken as an example, can be related as

$$\cong +\epsilon(\phi_2) - \epsilon(\theta_2) - \int \phi_2(1)\phi_2(2) \frac{e^2}{r_{12}} \theta_2(2) \times d\tau_1 d\tau_2 = I(\theta_2) - A(\phi_2) - C_{22} \quad (5)$$

where $\epsilon(\phi_2)$ and $\epsilon(\theta_2)$ are the orbital energies, and $I(\theta_2)$ and $A(\phi_2)$ are the ionization potential of the donor and electron affinity of the acceptor, respectively (see ref. 1). C_{22} is the Coulomb repulsion energy between two electrons belonging to ϕ_2 and θ_2 orbitals. In fact, it is evaluated with the aid of the point-charge approximation. In the above expressions for the configuration energies the following two approximations are adopted. (1) The electrostatic interactions between the two component molecules are equal in the ground and locally excited configurations, because both the donor and acceptor molecules have no net moment and so the electrostatic interaction is thought to be very small. (2) The overlap integrals between the donor and acceptor orbitals are neglected. Using the SCF MO of the isolated constituent molecule, we can write the off-diagonal elements of the electron Hamiltonian which represent the interaction of the ground configuration with the excited configurations as¹⁶

$$\langle \Phi_G | H | \Phi(\theta_i^{-1}\phi_{j'}) \rangle - \langle \Phi_G | \Phi(\theta_i^{-1}\phi_{j'}) \rangle E_0 = \frac{1}{2} \left[\left(i | -\frac{1}{2}\Delta + V(A) + V(D_i^+) | j' \right) - S_{ij'} \{ \epsilon_i + \sum_k S_{ik} \langle k' | V(D_i^+) | j' \rangle - \sum_k S_{kj} \langle k | V(A) | i \rangle \} \right] \quad (6)$$

where operators $V(A)$, $V(D)$, and $V(D_i^+)$ are defined

$$V(D) | \phi_i \rangle = - \sum_a \int \phi_i^*(1) \frac{Z_a}{r_{a1}} \phi_i(1) d\tau_1 + \sum_k \{ 2(\phi_i \phi_i | kk) - (\phi_i \phi_i | k \phi_i) \} \\ V(D_i^+) | \phi_i \rangle = (\phi_i | V(D) | \phi_i) - (\phi_i \phi_i | ii) + (\phi_i | i | \phi_i)$$

$$\phi_j \phi_i | \phi_k \phi_i \rangle = \int \phi_j^*(1) \phi_k^*(2) \frac{1}{r_{12}} \phi_i(1) \phi_i(2) d\tau_1 d\tau_2$$

In eq. 6, the terms higher than second order with regard to the transition dipole moment are neglected. The first and second terms of this equation contribute mainly to the value of the integral. The third and fourth terms are thought to be small compared with the first and second terms and may be

The matrix elements in the variation method including the overlap integrals are $\mathcal{K} = S\epsilon$. As we take the energy E_0 of the ground configuration as standard,

$$\mathcal{K} - S\epsilon = (\mathcal{K} - SE_0) - SE$$

where $S_{12}E_0$ is the off-diagonal element considered. J. N. Murrell, *J. Am. Chem. Soc.*, **81**, 5037 (1959).

neglected. Nonempirical evaluations of the terms in eq. 6 are so difficult that we evaluate them semiempirically

$$\langle \Phi_G | H | \Phi(\theta_i^{-1}\phi_{j'}) \rangle - \langle \Phi_G | \Phi(\theta_i^{-1}\phi_{j'}) \rangle E_0 = \sqrt{2}(-KS_{ij'}) \quad (6')$$

The other important type of the off-diagonal elements are those between the CT and locally excited configurations (eq. 7). The semiempirical parameters K

$$\langle \Phi(\theta_i^{-1}\phi_{j'}) | H | \Phi(\phi_{i'}^{-1}\phi_{j'}) \rangle - \langle \Phi(\theta_i^{-1}\phi_{j'}) | \Phi(\phi_{i'}^{-1}\phi_{j'}) \rangle E_0 = - \left(i' | -\frac{1}{2}\Delta + V(D_i^+) + V(A) | i \right) - (j'j' | i'i) + 2(j'i | i'j') - S_{ii'}(\epsilon_{j'} - \epsilon_i - \epsilon_{i'} - J_{ii} - J_{i'i'}) + S_{ij'} \langle i' | V(D_i^+) | j' \rangle + \sum_k S_{ik} \{ \langle i' | V(D_i^+) | k' \rangle + (j'j' | i'k') - (j'k' | i'j') \} + \sum_k S_{ik} \{ \langle i' | V(A_i^+) | k \rangle + (j'j' | ik) - (j'k | ij') \} \simeq -K'S_{ii'} \quad (7)$$

and K' in eq. 6' and 7 are not exactly the same, but we set both $K \simeq 10$.⁸ For calculating the overlap integrals, Roothaan's expanded Hartree-Fock atomic orbital functions¹⁸ were used.

The interaction between the locally excited configurations of different molecules can be expressed as

$$\langle \Phi(\theta_i^{-1}\theta_j) | H | \Phi(\phi_{i'}^{-1}\phi_{j'}) \rangle - \langle \Phi(\theta_i^{-1}\theta_j) | \Phi(\phi_{i'}^{-1}\phi_{j'}) \rangle E_0 = 2(ji | j'i') - (jj' | i'i) - S_{jj'} \left(i | -\frac{1}{2}\Delta + V(A) + V(D) | i' \right) - S_{ii'} \left(j | -\frac{1}{2}\Delta + V(A) + V(D) | j' \right) \simeq 2(ji | j'i') \quad (8)$$

The off-diagonal term between two CT configurations can be expressed by the equation similar to the above. This is the interaction energy between two transition charge densities. For the interaction between the two CT configurations, the interaction energy was calculated by the point-charge approximation. On the other hand, the interaction energy between the two locally excited configurations was estimated by using the experimental transition dipoles because the wave functions of the locally excited configurations in which only the four orbitals are included are not good enough to give agreement between the calculated transition moments and the observed values. Also, the transition charge density of the lowest excited state Φ_{L2} of naphthalene is zero within LCAO-MO approximation.

Results and Discussion

The Structure of the Naphthalene-TCNB Complex. In a structure where the center of a donor molecule is located just above that of the acceptor and the long axis of one molecule is parallel to that of the other, the lowest CT configuration, $\Phi(\theta_2^{-1}\phi_2)$, can mix with the ground configuration because the orbitals θ_2 and ϕ_2 have same symmetry. The stabilization energy ΔE due to CT interaction was evaluated for this model and for two series of the geometrical models.

First, we allow one molecule to rotate around the axis perpendicular to molecular plane fixing the centers of the molecules. All four CT configurations under

(18) E. Clementi, "Tables of Atomic Functions," a supplement to the paper which appears in IBM J. Res. Develop., **9**, 2 (1965).

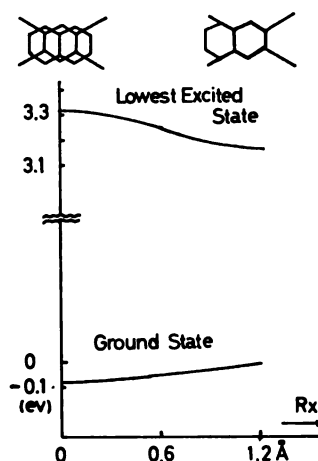


Figure 2. The potential curves calculated for the ground and lowest CT excited states. When $R_x = 0$, the center of TCNB molecule is located just above that of the naphthalene molecule. When $R_x = 1.2$ Å, there is the benzene ring of TCNB just over one benzene ring of naphthalene.

consideration stabilize the ground state, and the calculated stabilization energy is little dependent on the rotation angle θ ; for example, when $\theta = 0^\circ$, $\Delta E = -0.09$ eV, and, when $\theta = 90^\circ$, $\Delta E = -0.08$ eV. On the other hand, in these structures the lowest four locally excited configurations of the donor and acceptor and the four CT ones do not interact at all because of the symmetry of the orbitals.

Next, we try to shift one molecule along the x direction which is parallel to the long axis of molecules. The calculated potential curves for the ground and lowest excited states are shown in Figure 2. This time the stabilization energy changes from -0.09 to -0.01 eV with increasing R_x from 0 to 1.20 Å, where R_x is the x coordinate of the center of one molecule when the origin is taken to be the center of the other. When $R_x \neq 0$, the interaction between the lowest CT configuration and the lowest excited configuration within the donor and acceptor occurs, so that the lowest CT excited state is lowered from 3.32 to 3.17 eV with changing R_x from 0 to 1.20 Å. A similar result was obtained when one molecule is shifted along the short axis of the other molecule.

Thus the theoretical results seem to show that the stable structure in the ground state may be the structure in which the center of one molecule is located just above that of the other.

The crystal structure of TCNB-naphthalene complex has been determined by Kumakura, Iwasaki, and Saito.^{9,19} According to their results, the donor and acceptor molecules are stacked alternately in columns parallel to the c axis, and their planes are nearly perpendicular to this axis. Figures 3a and b show projections of TCNB and naphthalene molecules onto the plane perpendicular to the c axis and the $\{110\}$ face of the complex crystal, respectively. According to Figure 3a the center of one molecule is just above that of the other molecule, and the long axis of naphthalene molecules in the complex is at an angle of θ (θ is about 20°)

(19) The crystal is monoclinic and the space group is $C2/m$, with the two complexes in a unit cell. The complex crystallizes as needles, with the long axis parallel to c . The centers of TCNB molecules occupy $(0, 0, 0)$ and $(\frac{1}{2}, \frac{1}{2}, 0)$ positions in a unit cell, while those of naphthalene molecules are placed in $(0, 0, \frac{1}{2})$ and $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$ positions.

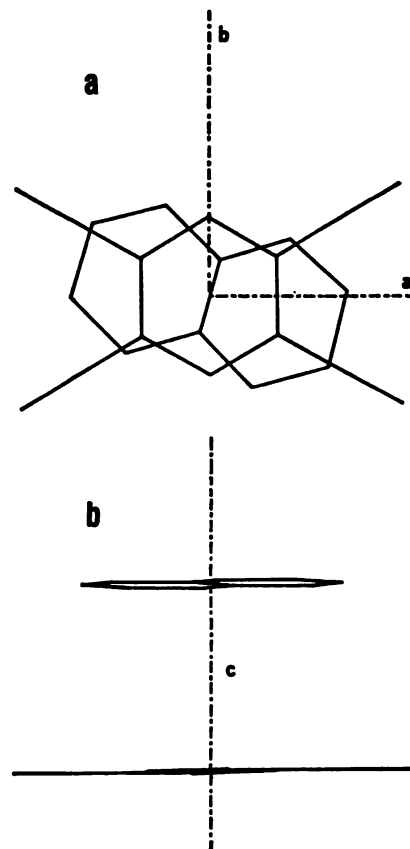


Figure 3. (a) Projection onto a plane perpendicular to the c axis. (b) Projection onto the $\{110\}$ face, in which the absorption measurements were made.

with respect to the a' axis which is parallel to the long axis of TCNB molecule.²⁰

Thus the structure in crystal is coincident with our theoretical expectation. From this it may be inferred that the stacking of the molecules in this crystal may be mainly controlled by the CT force.²¹ On the basis of the structure determined by the X-ray crystal analysis technique, the energy levels and wave functions of the ground and excited states of the complex have been calculated by the method described in the Theoretical Section. The results are given in Table I.

The Crystal Absorption Spectra. The visible and near-ultraviolet absorption spectra of the single crystal measured at room temperature are shown in Figure 4a. They have two peaks polarized parallel to the c axis and one peak polarized perpendicular to it. By comparing them with the solution spectra of TCNB, naphthalene, and the TCNB-naphthalene complex shown in Figure 4b, it is concluded that the first band at $25,000\text{ cm}^{-1}$ in crystal and in solution can be regarded as the CT band. The absorption intensity

(20) The angle may be either $+\theta$ or $-\theta$. This disorder does not affect the discussion on the polarization of the CT bands, but the polarization of the intramolecular local excitations of naphthalene in the $\{110\}$ face should be carefully discussed, because both short and long axes of naphthalene molecules are projected onto the $\{110\}$ face at different angles between molecules with an angle of $+\theta$ and $-\theta$.

(21) In some CT complex crystal, the steric factor, a methyl group, plays an important role in the way of stacking. The TCNB-TMPD complex is a case in point.²² On the other hand, in HMB-TCNB complexes, molecules are so nicely stacked that the CT force is strong (see ref 11).

(22) Y. Ohhashi, H. Iwasaki, and Y. Saito, *Bull. Chem. Soc. Japan*, in press.

Table I. Wave Functions of a 1:1 TCNB-Naphthalene Complex*

(a) Wave Functions of Ground and Lowest Four CT States						
Energy, W_i , ev	$W_i - W_0$, cm ⁻¹	Coefficients				
		Φ_0	Φ_{CT_1}	Φ_{CT_2}	Φ_{CT_3}	Φ_{CT_4}
W_0 -0.09	0	0.9886	0.1173	0.0421	-0.0604	0.0595
W_1 3.32	27,500	-0.1109	0.9908	-0.0504	0.0566	-0.0174
W_2 3.89	32,100	-0.0334	0.0340	0.9756	0.2138	-0.0149
W_3 4.00	33,000	0.0736	-0.0575	-0.2091	0.9731	0.0265
W_4 4.62	38,000	-0.0624	0.0113	-0.0124	-0.0244	0.9976

(b) Wave Functions of TCNB and Naphthalene Locally Excited States						
W_i , ev	$W_i - W_0$, cm ⁻¹	Coefficients				
		Φ_{L1}	Φ_{L2}	Φ_{L3}	Φ_{L4}	
W_1 3.93	32,400	0.9974	-0.0075	-0.060	+0.0381	
W_2 4.06	33,500	+0.0598	-0.0177	0.9980	0.0104	
W_3 4.35	35,800	-0.0384	-0.4523	-0.0150	0.8909	
W_4 4.74	38,200	-0.0099	0.8917	0.0117	0.4525	

The theoretical consideration has been made with the complex with geometrical orientation in crystal. The ground and lowest four CT configurations are little mixed with the TCNB and naphthalene locally excited configurations because of the molecular orbital symmetry.

io (A_{\parallel}/A_{\perp}) for light polarized parallel and perpendicular to the c axis is far larger than 25:1.

According to the X-ray crystal analysis data, TCNB and naphthalene molecules are stacked alternately in columns parallel to the c axis, and the centers of the molecules are on the c axis. Therefore we can safely say that the direction of the transition moment of the first CT band at 25,000 cm⁻¹ is nearly parallel to the line connecting the centers of the two component molecules. This fact supports the interpretation of this band as the first CT band.

The second band in the $\sim 33,000$ – $29,000$ -cm⁻¹ region is also polarized parallel to the c axis. This means that this band can be assigned to a CT transition as well. From the theoretical point of view, the appearance of two CT bands in the $\sim 25,000$ – $35,000$ -cm⁻¹ region is quite reasonable.

From the calculated energy levels given in Table I, the transition energies $W_i - W_0$ can be evaluated and are given in the same table. The results show that five absorption bands corresponding to the $W_0 \rightarrow W_i$ ($i = 1-5$) transitions appear in the $\sim 25,000$ – $38,000$ -cm⁻¹ region.

From the wave functions given in Table I, it is revealed that the $W_0 \rightarrow W_1$, $W_0 \rightarrow W_2$, and $W_0 \rightarrow W_4$ transitions are of CT character, and the $W_0 \rightarrow W_3$ and $W_0 \rightarrow W_5$ transitions are of local excitation. The first CT band at 25,000 cm⁻¹ clearly corresponds to the $W_0 \rightarrow W_1$ transition and is due to the transition from the highest occupied orbital (θ_2) of naphthalene to the lowest vacant orbital (ϕ_3) of TCNB. There are two possibilities for the interpretation of the second CT band. One of them is the transition from the second highest occupied (θ_1) orbital of naphthalene to the lowest vacant orbital (ϕ_2) of TCNB, and the other is the transition from the highest occupied orbital (θ_2) of naphthalene to the second lowest vacant orbital (ϕ_4) of TCNB (see Figure 1). The separation of $\Delta\nu_{CT}$ between the first and second CT bands may be expected to be 5200 cm⁻¹ in the former case from the corresponding values for naphthalene complexes containing tetracyanoethylene (TCNE) and chloranil as electron acceptor.² On the other hand, the $\Delta\nu_{CT}$ value for the latter case was calculated by us⁸ to be 6300 cm⁻¹ from the analysis of the absorption spectra of various TCNB complexes with substituted benzenes. The tentative $\Delta\nu_{CT}$ values for the two cases are rather close to each other, and either of

them can explain the observed position of the second CT band. Therefore, the observed second CT band may be due to both the above-mentioned transitions. The observed absorption intensity ratio of the first CT band to the second is about 1:0.88, while the calculated transition probability ratio of the first transition to the second plus the third one is 1:0.68.

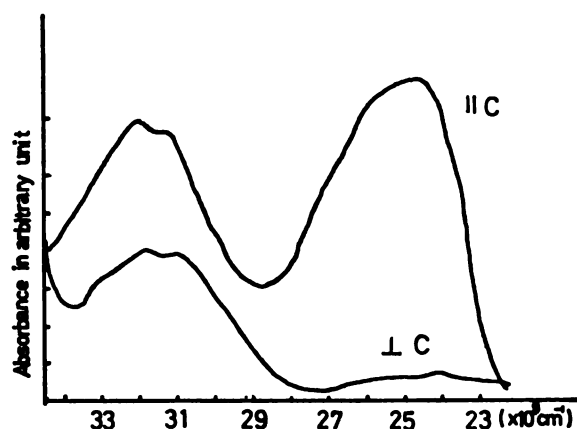


Figure 4a. The absorption spectra of the single crystal of the complex in the {110} face at room temperature. The ordinate is the absorbance in arbitrary units.

There appears in the 33,000–29,000-cm⁻¹ region another band which is polarized almost perpendicular to the c axis. From the direction of the transition moment, this band may be regarded as due to the intramolecular local excitations of the respective component molecules. In fact, the TCNB and naphthalene molecules show absorption bands with vibrational structures in this region as is shown in Figure 4b.²³ As the absorption intensity of TCNB local excitation is larger by about 10 times than that of naphthalene, the observed band at 31,000 cm⁻¹ perpendicular to the c axis is assigned to the TCNB local excitation. In the crystal,

(23) The first absorption band of the TCNB crystal which was observed in the previous paper⁸ is little perturbed by crystal field, and its position and vibrational structure are very similar to those of the solution spectrum. On the other hand, the absorption spectrum of the naphthalene crystal is known to be different from the spectrum in solution. In our case we should compare the absorption of naphthalene in the complex with that in solution or in solid mixed solution.

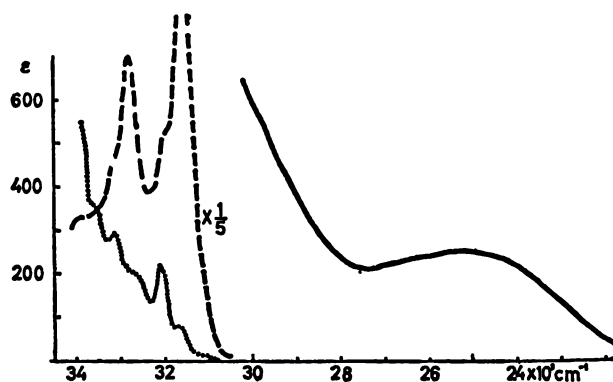


Figure 4b. The absorption spectra of naphthalene (---) and TCNB (—) in CH_2Cl_2 . The absorption spectrum of the CH_2Cl_2 solution containing naphthalene (0.065 M) and TCNB (0.0009 M) (—), the absorption intensity of which is shown in arbitrary units.

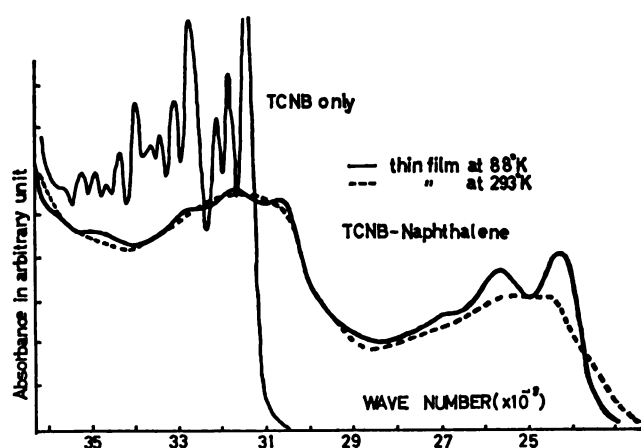


Figure 5. The absorption spectra of the thin film of the complex and TCNB only on a quartz plate. The ordinate is the absorbance in arbitrary unit: —, complex at 88°K; ---, complex at 298°K; —, TCNB only at 88°K.

the vibrational structure is blurred and the spectrum becomes broad as a whole. The reason for this is discussed in a later part of the present paper by taking into consideration the observed absorption spectra at low temperature.

In connection with the interpretation of the absorption spectrum of the CT complex, it seems to be interesting to measure it at low temperature. It is difficult, however, to do this with the single crystal principally because of technical difficulties. We prepared the thin film of the TCNB complex with naphthalene on a quartz plate and measured its absorption spectrum at 88°K.²⁴ The results are shown in Figure 5.²⁵ At 88°K vibrational structures in the first CT band appear

(24) We are indebted to Mr. T. Sakata for this method of absorption measurement at low temperature. He and the present authors have checked the reliability of this method with various samples. This method is known to give the results similar to those obtained by refraction method or by microscopic method with single crystals.

(25) The absorption intensity ratio of the 32,000- cm^{-1} bands to the 25,000- cm^{-1} band is about 2.1:1 in the spectra measured with the thin film of the CT complex, while the corresponding value for the single crystal is about 1.3:1. These results do not conflict with each other, because in the single crystal the CT band at 25,000 cm^{-1} was observed in the direction of c axis under the most optimal conditions, but the transition moments of the local excitation bands at 32,000 cm^{-1} with the polarization in the long axis of the component molecules are projected on the perpendicular direction to the c axis in the {110} plane with an angle φ ($\varphi = \tan^{-1} b/a' \approx 55^\circ 40'$).

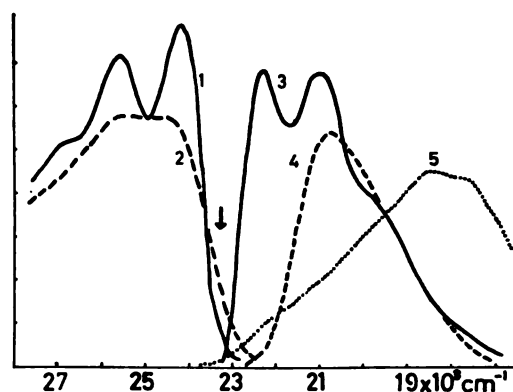


Figure 6. The absorption and fluorescence spectra of the complex: (1 and 2) the absorption spectra of the thin film on a quartz plate at 113 and 298°K, respectively (the ordinate is the absorbance in arbitrary unit); (3 and 4) the fluorescence spectra of the microcrystal at 77 and 298°K, respectively (the ordinate is the emission intensity); (5) the fluorescence spectra of the thin film at 298°K (see ref 28).

clearly at 24,300, 25,600, and 26,800 cm^{-1} , while the tail extending to the longer wavelength region of the first band at room temperature disappears. This seems to mean that the transition bands from thermally excited vibrational states of the ground state, the so-called hot bands, provide the explanation of the tail in the longer wavelength side of the first CT band.

The absorption bands of the complex in the shorter wavelength region, which are broad at room temperature, become a little sharp at 88°K and exhibit three indistinct peaks at 30,600, 31,800, and 32,700 cm^{-1} (see Figure 5). We also measured the absorption spectrum of TCNB itself under the same conditions. The result is shown in Figure 5 for the purpose of comparison. As is clearly seen in Figure 5, the vibrational structure of the latter is much more distinct than that of the former. From the above-mentioned facts, it might be inferred that the absorption spectrum of the complex at room temperature becomes broad for the following two reasons: first, because of the presence of hot bands due to the shallowness of the ground-state potential energy curve; second, because of the interaction of the locally excited configuration of TCNB with some high-energy configurations which were not considered in our theoretical study.²⁶

Fluorescence Spectra of Complex Crystal. The fluorescence spectra of the complex crystal at room and liquid N_2 temperatures are shown in Figure 6, together with the absorption spectra. The fluorescence spectra at liquid H_2 and liquid He temperatures are the same as at liquid N_2 temperature. A good mirror image relation between the fluorescence spectrum and the CT absorption spectrum is found at liquid N_2 temperature, so that the fluorescent state is concluded to be the lowest CT state. The overlap between the fluorescence and absorption spectra in the 23,200- cm^{-1} region is very small. This suggests that the geometric structure of the fluorescent state may be different from that of the ground state of the complex.

(26) Because of the relative orientation of donor and acceptor molecules in crystal and the symmetry of the excited states, both local excitations considered are little mixed with the lowest four CT configurations, and the interactions between the donor and acceptor local excitations may be small in view of the low transition intensities.

the case of the naphthalene-TCNB complex crystal. The Franck-Condon principle leads to the conclusion that the absorption intensity of the CT transition is high when both the ground state and the CT excited state are coupled with neither intramolecular nor intermolecular vibrations. Therefore the excited state corresponding to the longest wavelength absorption at $24,300\text{ cm}^{-1}$ seems to be coupled with some molecular vibrations. The similar consideration can be applied to the fluorescence.

At room temperature the mirror image relation between the absorption spectrum and the fluorescence spectrum of the microcrystal is not satisfied. One of the reasons for this may be the reabsorption corresponding to the long tail which was interpreted as the band. Another reason is that the fluorescence at room temperature may be a type of "excimer emission" in the perylene β crystal.²⁷ The formation of the "excited complex" might be possible at room temperature. The excited molecule is displaced over to the more stable structure, which may be induced by the interactions between the CT and localized electronic configurations.^{28,29}

Phosphorescence Spectra of the CT Complex in a Crystal. A phosphorescence was observed with the complex of the naphthalene-TCNB complex at low temperature. Figure 7 shows the phosphorescence spectra at liquid N_2 and liquid He temperatures, which are very different from each other. The spectra at liquid He temperature show the line structure with the background in the low-frequency region. The positions of the line spectra are given in Table II in comparison with those of the phosphorescence spectrum of naphthalene in the heptane and pentane matrix. The two spectra correspond well to each other in the $\text{N}-\text{O}$ band position and in vibrational structure. Therefore it is concluded that the phosphorescent state in the crystal is the naphthalene locally excited triplet state. Extra fine structure, thought to be due to the lattice vibrations, was observed for the crystal of the complex. The observation of lattice vibrations in the phosphorescence spectra may suggest that the emitting

Tanaka, *Bull. Chem. Soc. Japan*, **36**, 1237 (1963).

For the sake of the elimination of the reabsorption, the emission from a thin layer of powder was observed. But at room temperature emission of powder, which is made by crushing the crystal using mortar, appears in longer wavelengths than that of the microcrystal, as shown in Figure 6. At liquid N_2 temperature, however, emission of this powder is in agreement with that of the microcrystal. The usual phenomenon of powder emission cannot be simply explained although perhaps it may be related to the energy transfer to the traps. We could not obtain at room temperature the fluorescence spectra of crystal in which the reabsorption effects were completely eliminated.

In solution we found the "excimer" type of fluorescence for some complexes. In TCNB-benzene, -toluene, and -mesitylene the fluorescence spectra at room temperature appear in the very long wavelength but at liquid N_2 temperature they have the mirror image relation with the absorption spectra. We will discuss the phenomena in more detail in a future publication.

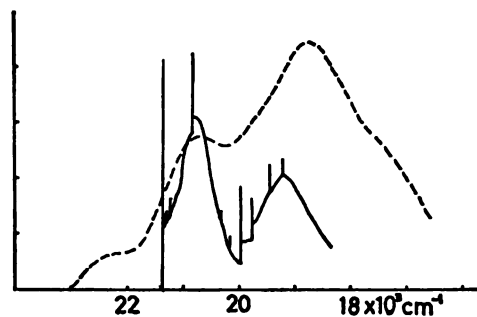


Figure 7. The phosphorescence spectra of the complex in crystalline state at 4.2°K (—) and 77°K (---). The ordinate is the plate blackness.

naphthalene is combined with the acceptor TCNB in the ground state and is not the extra naphthalene in crystal.

Table II. Maximum Wavelengths (cm^{-1}) of the Phosphorescence Spectra

Complex crystal (liquid He)	Naphthalene in pentane ^a (liquid N_2)	Naphthalene in heptane ^a (liquid N_2)
21,340 s 0	21,268 s 0	21,277 vs 0
21,320 w 20		
21,270 w 70		
21,230 w 110		
20,820 m 520	20,756 w 512	20,767 m 510
	20,506 vw 762	20,517 vw 760
20,320 w 1020	20,250 w 1018	20,259 w 1018
20,160 w 1180		20,119 w 1158
19,960 m 1380	19,888 s 1380	19,896 s 1381
19,760 m 1580	19,688 s 1580	19,700 s 1577
19,450 w 1690		
	19,376 m 1892	19,386 m 1891
19,240 w 2100	19,175 m 2093	19,183 m 2094

^a V. I. Mikhailenko, *et al.*, *Opt. Spectry.* (USSR), **20**, 29 (1966).

The spectra at liquid N_2 and H_2 temperatures are composed of broad bands, which appear in the same wavelength regions as those at liquid He temperature. Therefore the phosphorescence state at liquid N_2 and H_2 temperatures may also be related to the naphthalene triplet state, which is perturbed by the CT interaction. It is a problem why the complex crystal can emit the long-lived phosphorescence and why the temperature dependence of phosphorescence occurs. The most probable reason is that the emitting complexes are a type of traps in crystal.

Acknowledgment. The authors express their sincere thanks to Professor Y. Saito, Dr. F. F. Iwasaki, and Mr. S. Kumakura of our institute for their kindness in informing us of their X-ray analysis data on the TCNB-naphthalene complex prior to the publication.

Conformational Changes Involved in the Singlet-Triplet Transitions of Biphenyl¹

Peter J. Wagner

Contribution from the Department of Chemistry, Michigan State University, East Lansing, Michigan. Received November 4, 1966

Abstract: The lowest energy band in the $T^* \leftarrow S$ absorption spectrum of biphenyl in benzene solution appears at 75.5 kcal. Naphthalene and conjugated dienes are 2.5 times more effective than biphenyl at quenching triplet butyrophenone and at least 20 times more effective than biphenyl at quenching triplet benzophenone. The actual quenching efficiency of biphenyl decreases with increasing benzophenone concentration because of reversible energy transfer. From these absorption and quenching data, plus phosphorescence data in the literature, it is concluded that neither the highest energy band in the phosphorescence spectrum at 65.5 kcal nor the lowest energy band in the solution $T^* \leftarrow S$ absorption spectrum at 75.5 kcal represents the true $T^* \leftrightarrow S$ 0-0 transition of biphenyl, which occurs around 69.5 kcal and is a nonspectroscopic transition between a twisted ground state and a triplet state of grossly different geometry. Evidence that triplet biphenyl prefers to be planar is presented and discussed.

In recent measurements of the phosphorescence spectrum of biphenyl in frozen glasses, the highest energy band has been located at 65.5 kcal and assigned as the $T^* \rightarrow S$ 0-0 transition.² If the actual energy difference between the lowest vibrational levels of the ground and first triplet states were 65.5 kcal, biphenyl ought to quench higher energy (>68 kcal) ketone triplets at close to the diffusion-controlled rate in solution.³⁻⁵ Since biphenyl absorbs only negligibly at 3130 Å and is not known to undergo any photochemical changes, it seemed that it might be a choice quencher for use in studies of the triplet-state photochemistry of ketones. The work to be described grew out of a test of this assumption.

Results

Quenching of Butyrophenone Photoelimination. Biphenyl and several other aromatic and olefinic compounds with low-lying triplet states were used to quench type-II photoelimination of butyrophenone, whereby the excited molecule splits into ethylene and acetophenone. This reaction has been shown to proceed exclusively from the triplet state of the ketone.^{6,7} Pyrex tubes containing benzene solutions 0.20 *M* in ketone, 0.005 *M* in *n*-tetradecane as internal standard, and containing various concentrations of the different quenchers were degassed, sealed *in vacuo*, and irradiated in parallel such that each sample absorbed the same intensity of 3130- or 3660-Å radiation. The amount of acetophenone formed in each tube was then determined by glpc analysis. The highest conversion, in samples with no quencher, was 6%. Stern-Volmer plots, such as exemplified in Figure 1, were linear for each quencher,

their slopes yielding the $k_q\tau$ values listed in Table I. Since the lifetime of triplet butyrophenone, τ , is the same regardless of quencher, it is apparent that biphenyl is less efficient a quencher by a factor of 0.40 than are the other compounds studied, all of which are commonly assumed to be "diffusion-controlled" quenchers. The fact that the quenching efficiency of naphthalene appeared slightly higher than that of the others probably is not significant, since acetophenone and naphthalene were not completely separated under the analytical conditions employed, and a small systematic error may readily have been introduced.

Table I. Efficiencies of Various Compounds at Quenching Photoelimination of Butyrophenone

Compound	E_T^a	Wavelength, Å	$k_q\tau, M^{-1}$
1,3-Pentadiene	59 ^b	3130	670
2,5-Dimethyl-2,4-hexadiene	~58 ^b	3130	640
Biphenyl	~69.5 ^c	3130	275
Biphenyl		3660	276
Naphthalene	60.9 ^d	3660	750
<i>trans</i> -Stilbene	~50 ^e	3660	654
<i>cis</i> -Stilbene	58 ^e	3660	665

^a Triplet excitation energy, in kcal. ^b Reference 11. ^c Estimated in this work. ^d Reference 12. ^e Reference 13.

Quenching of Propiophenone Photoreduction. Isopropyl alcohol solutions 0.10 *M* in propiophenone and containing various concentrations (0-0.012 *M*) of naphthalene or biphenyl were degassed and irradiated in parallel in sealed Exax tubes at 3660 Å. The disappearance of propiophenone was monitored by ultraviolet analysis. Again Stern-Volmer plots were linear and yielded slopes equal to 204 and 136 M^{-1} for naphthalene and biphenyl, respectively. Cohen has reported a $k_q\tau$ value of ~170 M^{-1} for the acetophenone-isopropyl alcohol-naphthalene system.⁸

Quenching of Benzophenone Photoreduction. Biphenyl and several other compounds were employed to quench the photoreduction of benzophenone by benz-

(8) S. G. Cohen, D. A. Laufer, and W. V. Sherman, *ibid.*, **86**, 3060 (1964).

(1) Triplet Energy Transfer. I. Presented in part at the 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967.

(2) (a) E. Clar and M. Zander, *Chem. Ber.*, **89**, 749 (1956); (b) Y. Kanda, R. Shimada, and Y. Sakai, *Spectrochim. Acta*, **17**, 1 (1961); (c) V. Trusov and P. Teplyakov, *Opt. i Spektroskopiya*, **16**, 52 (1964); *Opt. Spectry.* (USSR), **16**, 27 (1964).

(3) K. Sandros and H. J. L. Bäckström, *Acta Chem. Scand.*, **16**, 956 (1962).

(4) G. Porter and F. Wilkinson, *Proc. Roy. Soc. (London)*, **A264**, 1 (1961).

(5) W. G. Herkstroeter and G. S. Hammond, *J. Am. Chem. Soc.*, **88**, 4769 (1966).

(6) P. J. Wagner and G. S. Hammond, *ibid.*, **88**, 1245 (1966).

(7) E. J. Baum, J. K. S. Wan, and J. N. Pitts, Jr., *ibid.*, **88**, 2652 (1966).

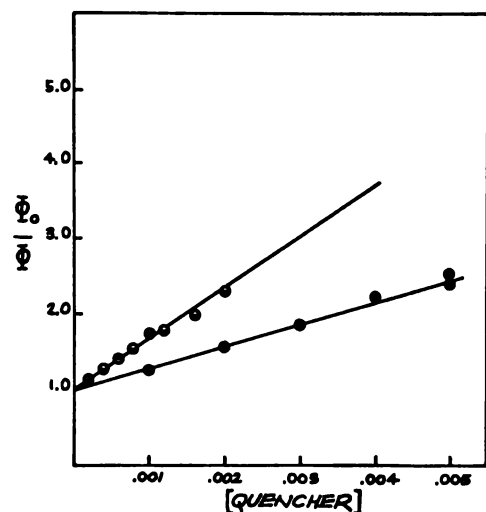


Figure 1. Stern-Volmer plots for quenching of butyrophenone elimination: \circ , *cis*-stilbene; \square , 2,5-dimethyl-2,4-hexadiene; \triangle , biphenyl.

col in benzene solution.^{9,10} Degassed, sealed Exaxs containing 0.050 *M* benzophenone, 0.20 *M* benzhydrol, and various concentrations of the quencher were irradiated in parallel at 3660 Å. Relative quantum yields for disappearance of benzophenone were measured by ultraviolet analysis. Stern-Volmer plots, as exemplified in Figure 2, were linear with the quenchers listed in Table II. Tables I and II both list literature values¹¹⁻¹³ for the triplet energies of the various quenchers.

Table II. Efficiencies of Various Compounds at Quenching of Benzophenone^a by 0.20 *M* Benzhydrol

Compound	E_T^b	S^c
Naphthalene	60.9 ^d	2470
2,5-Dimethyl-2,4-hexadiene	~58 ^e	2660
Triphenylene	66.6 ^d	360
Fluorene	67.6 ^d	63 ^f
Biphenyl	~69.5 ^g	17
Biphenyl ^h	~69.5 ^g	35
Biphenyl ⁱ	~69.5 ^g	80
<i>o</i> -Fluorobiphenyl ^j	>69.5 ^g	4.9
<i>o</i> -Chlorobiphenyl ^j	>69.5 ^g	0.9

^a Originally 0.050 *M* unless otherwise noted. ^b Triplet excitation energy in kcal. ^c Slope of Stern-Volmer plot. ^d Reference 12. ^e Reference 11. ^f Extrapolated to zero fluorene concentration. ^g Determined in this work. ^h 0.020 *M* benzophenone. ⁱ 0.0050 *M* benzophenone. ^j Only one concentration of quencher, 0.10 *M*.

The inefficiency of biphenyl at quenching triplet benzophenone is quite dramatic, naphthalene and the diene being some 145 times more effective. The two *ortho*-substituted biphenyls are even less effective than biphenyl itself. Triphenylene and fluorene display higher

W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Am. Chem. Soc.*, **83**, 2789 (1961).

W. M. Moore and M. Ketchum, *ibid.*, **84**, 1368 (1962).

R. E. Kellogg and W. T. Simpson, *ibid.*, **87**, 4230 (1965).

W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *ibid.*, **86**, 137 (1964).

G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Law, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *ibid.*, **86**, 197 (1964).

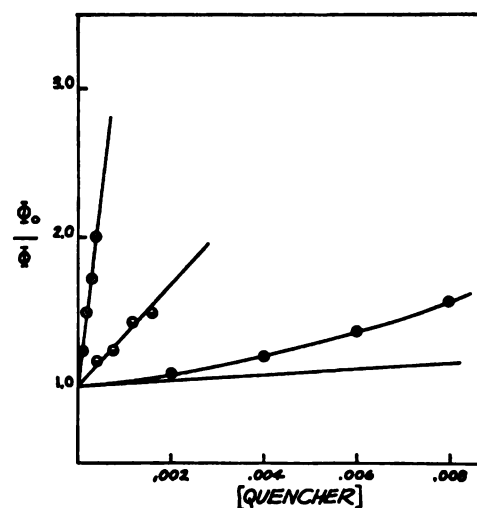


Figure 2. Stern-Volmer plots for quenching of the photoreduction of 0.05 *M* benzophenone: \circ , naphthalene or 2,5-dimethyl-2,4-hexadiene; \square , triphenylene; \bullet , fluorene; lowest line, biphenyl.

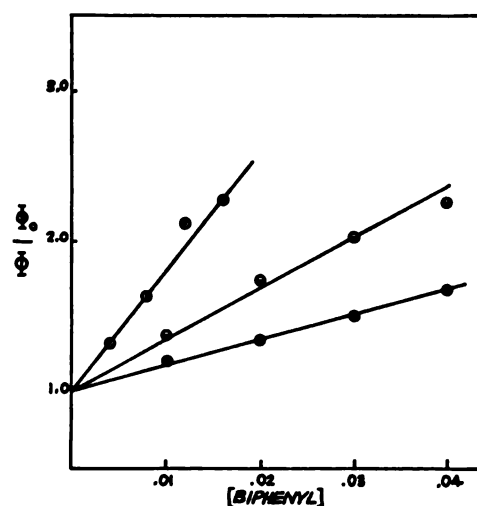


Figure 3. Stern-Volmer plots for quenching of the photoreduction of benzophenone by biphenyl: \circ , 0.005 *M* benzophenone; \square , 0.020 *M* benzophenone; \bullet , 0.050 *M* benzophenone.

energy phosphorescence bands than does biphenyl, and thus might be presumed to possess higher energy triplet states. Nonetheless they are appreciably better quenchers than biphenyl. Actually the quenching behavior of fluorene is somewhat anomalous in that Stern-Volmer plots bend upward. In systems where energy transfer is reversible,¹⁴ self-quenching or quenching by trace impurities could cause this behavior. The value for $k_q\tau$ recorded in Table II was calculated by extrapolating the slopes of the plot in Figure 2 to zero fluorene concentration.

Sandros¹⁴ has shown that reversible energy transfer is likely when quenching rate constants are several orders of magnitude below that of diffusion. Consequently a brief study was made of the effect of benzophenone concentration on the quenching efficiency of biphenyl. Two series of samples were prepared and analyzed as above, except that somewhat lower concentrations of biphenyl were used and benzophenone concentrations were 0.020 or 0.0050 *M*. Figure 3,

(14) K. Sandros, *Acta Chem. Scand.*, **18**, 2335 (1964).

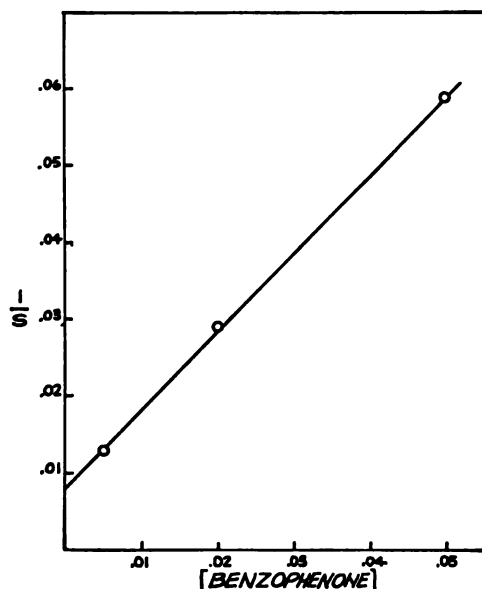


Figure 4. Plot of the reciprocal of the Stern-Volmer slopes in Figure 3 against benzophenone concentration.

which displays Stern-Volmer plots of the results, demonstrates the greater quenching efficiency of biphenyl at lower benzophenone concentrations. The Stern-Volmer slopes are included in Table II.

Straightforward kinetic analysis of reversible energy transfer yields the following modification of the usual Stern-Volmer equation (eq 1). In the system under

$$\frac{\Phi_0}{\Phi} = 1 + \frac{k_q\tau[Q]}{1 + \frac{k_{-q}[K]}{k_d'}} \quad (1)$$

consideration, τ represents the lifetime of triplet benzophenone in the presence of 0.20 *M* benzhydrol and no added quencher; k_q , the rate constant for energy transfer from triplet benzophenone to biphenyl; k_{-q} , the rate constant for energy transfer from triplet biphenyl to ground-state benzophenone; $[K]$, the concentration of benzophenone; $[Q]$, the concentration of biphenyl; and k_d' , the rate of decay of triplet biphenyl.

Equation 1 describes the inverse relationship between the slopes of the Stern-Volmer plots and ketone concentration. Letting S equal the slope of a given Stern-Volmer plot, the following expression results.

$$\frac{1}{S} = \frac{1}{k_q\tau} \left(1 + \frac{k_{-q}[K]}{k_d'} \right) \quad (2)$$

Figure 4 depicts the linear adherence of the present results to eq 2. The intercept of 0.0080 yields a value of 125 *M*⁻¹ for $k_q\tau$, and the slope of 0.95 yields a value of 118 *M*⁻¹ for k_{-q}/k_d' .

After corrections for reversibility, the rate of energy transfer from triplet benzophenone to biphenyl turns out to be 1/20th the "diffusion-controlled" rate to naphthalene and the diene.

Although no detailed studies were carried out, it is very probable that the S values for fluorene and for triphenylene also depend on benzophenone concentration, so that the true values of $k_q\tau$ for them are appreciably greater than those listed in Table II.

T* ← S Absorption of Biphenyl. Since the phosphorescence spectrum of biphenyl does not allow correct

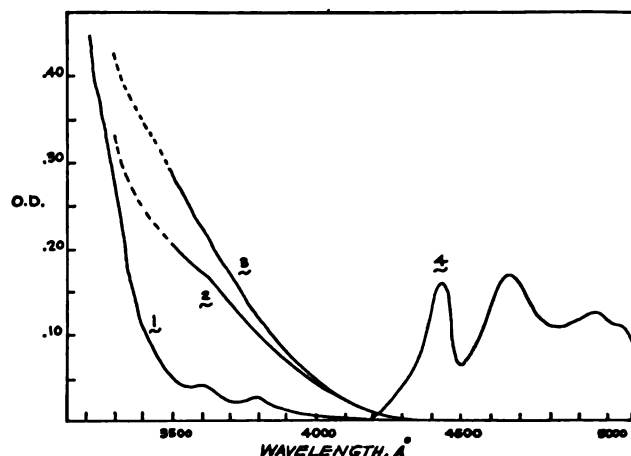


Figure 5. Long-wavelength electronic absorption spectra of biphenyls, all in 5-cm cells: (1) 1.5 *M* biphenyl in benzene *vs.* benzene; (2) 1.0 *M* biphenyl, 6 *M* methyl iodide in 2,2,4-trimethylpentane *vs.* 6 *M* methyl iodide in 2,2,4-trimethylpentane; (3) 0.7 *M* *p*-bromobiphenyl in benzene *vs.* benzene; (4) low-wavelength end of a typical phosphorescence spectrum of biphenyl at 77°K in a glass (ref 21).

prediction of its quenching efficiency, a search for the T* ← S absorption spectrum of biphenyl was undertaken. A 1.5 *M* benzene solution of biphenyl in a 5-cm cell displays weak, almost featureless absorption beginning around 4200 Å, there being two weak but quite distinct maxima at 3790 Å ($\epsilon \sim 0.004$) and at 3600 Å ($\epsilon \sim 0.006$). Any further structure is masked by intense absorption at wavelengths below 3500 Å. This feeble absorption system is assigned to a spin-forbidden T* ← S transition for several reasons. Bubbling nitrogen through the cell to remove oxygen decreases the intensity,¹⁵ while inclusion of methyl iodide in the solvent enhances the intensity. Moreover, 4-bromobiphenyl also absorbs more strongly in the same region. No band structure, however weak, could be detected in these presumed heavy atom enhanced¹⁶ T* ← S transitions. Typical absorption curves, together with a phosphorescence spectrum from the literature, are presented in Figure 5. Kearns, using the phosphorescence excitation technique, has also found almost featureless T* ← S absorption for biphenyl in exactly the same region reported here.¹⁷

It is apparent that there is little, if any, overlap between emission and absorption and that there is a 10-kcal difference between the highest energy phosphorescence band at 65.5 kcal and the lowest energy absorption band at 75.5 kcal.

Discussion

Spectroscopic Transitions of Biphenyl. The T* ↔ S emission and absorption spectra of biphenyl yield estimates of its triplet excitation energy which seem to differ by 10 kcal. This problem of nonoverlapping emission and absorption spectra is not a new one and is a direct result, of course, of the Franck-Condon principle.¹⁸ When the lowest vibrational levels

(15) (a) D. F. Evans, *Nature*, **176**, 777 (1955); (b) D. Craig, J. Hollas, and G. King, *J. Chem. Phys.*, **29**, 974 (1958).

(16) For a review, see S. K. Lower and M. A. El-Sayed, *Chem. Rev.*, **66**, 199 (1966).

(17) A. P. Marchetti and D. R. Kearns, *J. Am. Chem. Soc.*, **89**, 768 (1967).

(18) For an excellent early discussion, see P. Pringsheim, "Fluores-

ground and excited states possess significantly different equilibrium geometries, true spectroscopic 0-0 transitions are forbidden, and the divergent apparent bands observed in emission and absorption spectra represent transitions from one vibrationally relaxed to a vibrationally excited mode of the other state. In the present case of biphenyl, it would appear that there exists a gross geometric difference between the ground state and the excited triplet state. The highest 0-0 band in the phosphorescence spectrum at 65.5 kcal probably should be reinterpreted as a transition from the triplet state in its equilibrium geometry to a vibrationally or rotationally excited ground state. The rise of the $T^* \leftarrow S$ absorption band at 75.5 kcal probably represents a transition from vibrationally and rotationally relaxed ground state to a nonequilibrium configuration of the excited triplet. The true 0-0 energy difference must lie somewhere intermediate between 65.5 and 75.5 kcal and represents a *nonspectroscopic* transition which is forbidden in radiative processes but allowed in bimolecular energy-transfer reactions. The long tail out to 4200 Å in the $T^* \leftarrow S$ emission spectrum probably can be attributed to quenching by the small percentages of ground-state molecules in nonequilibrium geometries, as will be discussed later.

Any exact interpretation would not be justified by spectroscopic data alone, but it is the only one consistent with the quenching results now to be discussed. **Triplet-Energy Transfer Involving Biphenyl.** The data in Tables I and II for naphthalene, the stilbenes, and the dienes provide further evidence that the efficiency of triplet-energy transfer in solution is equally low for all compounds whose triplet energies are sufficiently lower than that of the donor. Biphenyl clearly acts as such a "diffusion-controlled" quencher toward three ketones studied. The marked inefficiency which biphenyl quenches triplet benzophenone indicates that the triplet energy of biphenyl is at least as low as that of the ketone.

Rate constants for triplet-energy transfer from the studied ketones to biphenyl can be estimated. Flash spectroscopic studies^{3,5} have indicated that naphthalene, stilbenes, and conjugated dienes all quench triplets with excitation energies as high as those of the ketones with what seems to be a maximum bimolecular quenching rate constant of $5 \times 10^9 M^{-1} \text{sec}^{-1}$ in benzene. The rate constant for quenching of triplet butyrophenone ($E_T \sim 72.5 \text{ kcal}^{19}$) by biphenyl is thus calculated as $2 \times 10^9 M^{-1} \text{sec}^{-1}$, while that for the quenching of triplet benzophenone ($E_T = 69.5 \text{ kcal}^{19}$) by biphenyl is $2.5 \times 10^8 M^{-1} \text{sec}^{-1}$. Quenching rate constants have not been measured in isopropyl alcohol; however, the rate constant for diffusion can be calculated from viscosity²⁰ as $4.5 \times 10^9 M^{-1} \text{sec}^{-1}$. If it is assumed that naphthalene quenches triplet propiophenone ($E_T = 64 \text{ kcal}^{12}$) with this rate constant, that for biphenyl would be $3 \times 10^8 M^{-1} \text{sec}^{-1}$. This value is somewhat lower than that estimated for the lower energy butyrophenone, but it is noteworthy that the efficiency of

triplet-energy transfer to biphenyl is measurably less than maximal even in a fairly viscous solvent and with a quite high-energy donor.

The inefficiency in the quenching of triplet butyrophenone by biphenyl is reasonably readily explained. In order for vertical-energy transfer to take place, in which process the geometry of the biphenyl remains constant, a donor with at least a 75.5-kcal triplet energy is required. However, as will be discussed below, the vibrationally relaxed triplet of biphenyl, of a geometry substantially different from that of the ground state, lies no more than 70 kcal above the ground state. Consequently, energy transfer to biphenyl involves *nonvertical* transitions in which the geometry of the biphenyl changes appreciably. The steric requirements for such an energy-transfer process are undoubtedly greater than for vertical-energy transfers, and the observed difference in the rates with which biphenyl and the "diffusion-controlled" quenchers quench triplet butyrophenone is some measure of this steric effect. An identical explanation has been advanced by Hammond and his co-workers for the behavior of the stilbenes.^{5,13}

It was hoped that the triplet energy of propiophenone was sufficiently large that vertical-energy transfer to biphenyl would be possible. Whatever the reason, energy transfer seems to be not much more efficient than from the lower energy triplet butyrophenone.

The quenching results with benzophenone are the most informative. A quenching rate constant of $2.5 \times 10^8 M^{-1} \text{sec}^{-1}$ suggests that energy transfer may be slightly endothermic.¹⁴ The first problem, then, in determining the true triplet energy of biphenyl involves ascertaining the true triplet energy of benzophenone. Hammond and co-workers¹³ have reported that the 0-0 band in the phosphorescence spectrum of benzophenone in hydrocarbon solvents occurs at 68.5 kcal. Kearns and Case, however, have noted a 2-kcal separation between phosphorescence and absorption 0-0 bands.¹⁹ Consequently, the true triplet excitation energy of benzophenone in benzene probably is approximately 69.5 kcal. As pointed out above, with butyrophenone as donor, the rate constant for energy transfer does not seem to exceed $2 \times 10^9 M^{-1} \text{sec}^{-1}$. The further decrease by a factor of 8 upon going to triplet benzophenone donor could be compounded of further steric restrictions plus new energetic requirements. Unfortunately, there is no way of guessing the contribution of steric effects alone in depressing the rate of nonvertical-energy transfer when biphenyl must be twisted all the way to its equilibrium triplet geometry. If the further steric effect were minor, the eightfold total rate decrease would imply that energy transfer was approximately 1 kcal endothermic. If, however, severe steric requirements are the major contributor to the total rate decrease, energy transfer could be thermoneutral or even slightly exothermic. Therefore $69.5 \pm 1.0 \text{ kcal}$ is perhaps the best estimate that can be made for the true 0-0 energy for the $T^* \leftrightarrow S_0$ transition of biphenyl. Such a value is in good agreement with the suggested interpretation of the spectroscopic data, being somewhat less than midway between the two divergent 0-0 bands.

Since these experiments provide no knowledge of the lifetime of triplet biphenyl, a discussion of the value of

and Phosphorescence," Interscience Publishers, Inc., New York, 1949, pp 299-303.

D. R. Kearns and W. A. Case, *J. Am. Chem. Soc.*, **88**, 5087

A. D. Osborne and G. Porter, *Proc. Roy. Soc. (London)*, **A284**, 1950.

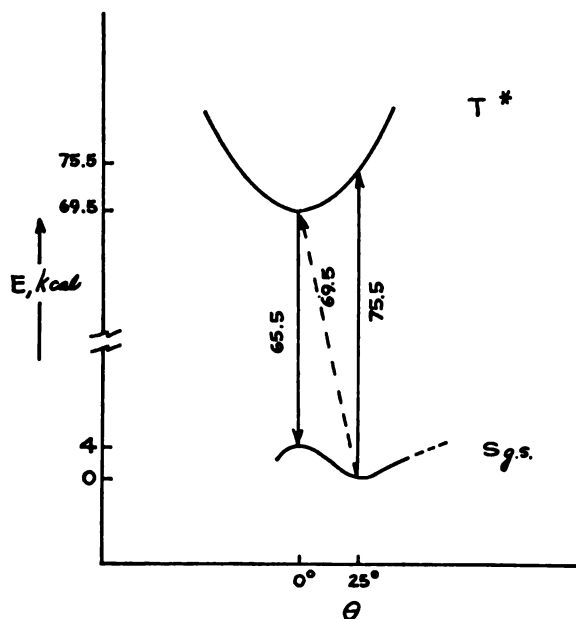


Figure 6. Spectroscopic (solid lines) and nonspectroscopic (dashed line) $T^* \leftrightarrow S$ transitions in biphenyl. Curves represent supposed potentials for the two states as a function of dihedral angle θ between the rings.

k_{-q}/k_d' obtained from the slope of Figure 4 would not be profitable. As soon as flash spectroscopic studies allow determination of the value of k_d' , a comparison of k_q and k_{-q} values ought to provide an even better estimate of the triplet energy of biphenyl.

The Triplet State of Biphenyl. The spectroscopic data and the quenching results considered together indicate that the geometry of biphenyl in its triplet state must differ considerably from that of its ground state. The most stable conformation of ground-state biphenyl depends strongly on the medium. The dihedral angle between the two rings is 40–45° in the gas phase,²¹ 20–25° in solution,²² and 0° in the crystalline state.²³ Consequently, the triplet state in solution must deviate considerably from a 20–25° twist, and a large body of evidence points to a perfectly planar conformation.

ortho substituents are well known to increase the dihedral angle in biphenyls and consequently would be expected to make for better quenching if the triplet state were more twisted than the ground state and worse quenching if the triplet state tended toward planarity. The latter effect is observed. In 1944 Lewis and Kasha reported that *ortho* substituents shift the phosphorescence spectrum of biphenyl to higher energies,²⁴ presumably because of steric crowding in planar excited states.

Hirota has provided seemingly incontrovertible evidence regarding the geometry of triplet biphenyl. He measured the $T^* \leftarrow S$ absorption spectra of a few compounds by a modified phosphorescence excitation method, in which crystals of the subject compound were doped with a compound of lower triplet energy to trap the excitation.²⁵ The $T^* \leftarrow S$ spectrum of biphenyl so obtained displays a 0–0 band at 65.5 kcal in exact

agreement with the highest energy phosphorescence band. Consequently the 65.5-kcal transition in biphenyl must take place between planar conformations of both ground and triplet states. Such a transition is a true 0–0 transition in the crystal, but not in solution where the most stable conformation of the ground state is twisted.

Figure 6 depicts a schematic energy diagram for the various $T \leftrightarrow S$ transitions of biphenyl in solution, the curves representing potentials for twisting around the C–C bond connecting the two rings. The two vertical solid arrows represent spectroscopic transitions between states of identical geometry, while the slanted dotted line represents the nonspectroscopic transition which can take place in the relatively slow nonvertical energy-transfer process. The potential for twisting triplet biphenyl is steeper than that for the ground state in accord both with theoretical expectations and with the experimental observation that the 0–0 energy is somewhat less than midway between the highest energy phosphorescence band and the lowest energy absorption band.

The combination of spectroscopic and quenching results indicate that the ground-state conformation which possesses the equilibrium geometry of the triplet state is about 4 kcal excited relative to the favored ground-state conformation. Theoretical estimates predict a very shallow potential for twisting the rings in biphenyl,^{26,27} and 5 kcal is the largest estimate²⁷ yet made for the difference between twisted and planar ground-state biphenyl. Of course the impossibility of resolving optical isomers of 2,2'-disubstituted biphenyls unless the *ortho* substituents are extremely bulky is strong experimental evidence for the low activation energy required to twist the rings of biphenyl.

Choosing the maximum at 3790 Å in the $T^* \leftarrow S$ absorption spectrum of biphenyl as the "lowest energy spectroscopic transition" instead of some point on the long tail out to 4200 Å may have seemed somewhat arbitrary, and in a sense was. With the shallow potential for twisting the rings, a fairly large percentage of ground-state molecules must exist with twists between 0 and 25°, and for that matter greater than 25°. For example, if a planar molecule is excited 4 kcal and one twisted 10° only 2 kcal, simple Boltzmann statistics predict that 0.2 and 4% of the ground state molecules will be planar and twisted 10°, respectively, at room temperature. Figure 6 illustrates that $T^* \leftarrow S$ absorption by biphenyl molecules twisted less than the favored 20–25° occurs at longer wavelengths than absorption by the majority of molecules which are in the favored ground-state conformation. The long tail, then, most likely is composed of spectroscopic transitions by small percentages of ground-state molecules in nonequilibrium conformations, and is not particularly unusual except in its 400-Å length. The band at 3790 Å is not, then, the lowest energy $T^* \leftarrow S$ spectroscopic transition occurring in biphenyl, but it is the lowest energy spectroscopic transition from the lowest vibrational-rotational level of the ground state. It is important to note that the suggested interpretation of combined quenching and phosphorescence data implies that it would be incorrect to call some point near 69.5

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(26) F. Adrian, *ibid.*, **28**, 608 (1958).

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in the absorption spectrum the 0-0 transition. Absorption at this energy represents a transition between two states both of which are weakly torsionally relaxed.

Since the triplet state of biphenyl seems to be planar, sensitized racemization of optically active biaryls should occur with ease. Mislow has already reported direct photoracemization of several biaryls.²⁸ In regard, the effects of substituents on the quenching efficiency of biphenyl promise to be very interesting, and k_q , k_{-q} , and k_d' all ought to vary considerably, and study of such effects is in progress.

The fact that the triplet energy of biphenyl is higher than that of benzophenone can be estimated from its phosphorescence spectrum helps clarify some photochemistry. Zimmerman reported that biphenyl is only 1/10th as effective as benzophenone at quenching the photorearrangement of a substituted unsaturated ketone.²⁹ He measured the triplet energy of the ketone as 71 kcal, but found it difficult to reconcile this value with a 65.5-kcal triplet energy for biphenyl. The matter is of some importance because of the considerable speculation and controversy regarding the nature of the reacting triplets of enones. The higher value for the triplet energy of biphenyl is more consistent with a ketone triplet of 71-kcal triplet energy.

Experimental Section

Reagents. Reagent grade benzene was washed with sulfuric acid, dried, and distilled from phosphorus pentoxide. Reagent isopropyl alcohol was distilled from sodium.

Materials. Propiophenone (Eastman) and butyrophenone (Eastman) were distilled under reduced pressure and then recrystallized several times from pentane. Eastman White Label benzophenone was recrystallized from ligroin. Columbia Organics tetradecane required extensive washings with sulfuric acid before distillation and distillation under reduced pressure. Matheson Coleman and Bell benzhydrol was used without further purification. Benzophenone, biphenyl, fluorene, *trans*-stilbene, 2-fluorobiphenyl (Eastman Organics), and 2-chlorobiphenyl (K & K Laboratories) were all recrystallized once from ethanol. Aldrich triphenylene was recrystallized several times until white. The melting points of the solid quenchers checked with those reported in the literature. Aldrich *cis*-stilbene was distilled under reduced pressure. Biperylene was distilled and analyzed by glpc analysis as *cis*- and *trans*-piperylene and 2% cyclopentene. Aldrich 2,5-dimethyl-2,4-hexadiene was recrystallized from itself.

Absorption Spectra. A Cary 14 spectrophotometer was employed and solutions were contained in 5-cm cells. Concentration results are presented in Figure 5.

Preparation of Samples. For the propiophenone system, one solution 0.50 *M* in propiophenone was prepared by weighing appropriate amount of ketone in a 25-ml volumetric flask and diluting to volume with isopropyl alcohol. Stock solutions 0.020 *M* in naphthalene and 0.029 *M* in biphenyl were prepared similarly.

A 2-ml portion of the ketone solution was pipetted into each of nine 10-ml volumetric flasks, one of which was immediately filled to volume with solvent. From 1 to 4 ml of each of the quencher solutions was pipetted into each of the other flasks before they were filled to volume. Then 2.6 ml of each solution was placed in separate Exax tubes with a syringe. The tubes were standard 13 × 100 culture tubes which had been washed and dried before being constricted about 1 in. from the top to allow sealing. The tubes with the samples in them were attached to a vacuum line and put through three freeze-pump-thaw cycles before being sealed *in vacuo* at 0.002 mm.

Samples were prepared quite similarly for the benzophenone and butyrophenone systems except that benzene was used as solvent and the ketone stock solutions were 0.250, 0.100, or 0.0250 *M* in benzophenone and 1.00 *M* in benzhydrol in the first case and 1.00 *M* in butyrophenone and 0.02–0.03 *M* in tetradecane in the latter.

Irradiation of Samples. In any given run degassed tubes containing four different concentrations of each of several quenchers were irradiated in parallel with two or three samples containing only ketone, all for the same length of time. Irradiations were performed in a "merry-go-round" apparatus,³⁰ consisting essentially of a rotating turntable with the light source and filters at the center and windows of identical area allowing radiation to enter the various sample compartments. This design ensured that the same intensity radiation impinged upon each sample. Since each sample contained the same concentration of ketone, the amount of irradiation absorbed by each sample was identical; since each tube contained the same volume of liquid, the relative amount of reaction in each tube was directly proportional to the quantum yield. Corning No. 7-83 filter combinations were used to isolate the 3660-Å line of a Hanovia 450-w medium-pressure mercury lamp, and a 1-cm path of 0.002 *M* potassium chromate in 5% aqueous potassium carbonate was used to isolate the 3025–3130-Å lines. The entire apparatus was immersed in a water bath, and the temperature during irradiation was maintained at 25 ± 1°.

Analyses of Samples. The disappearance of propiophenone and benzophenone was measured on a Gilford Model 200 spectrophotometer. Samples with no quencher were carried to approximately 50% conversion. Analyses were made at 3400, 3500, 3600, and 3700 Å for benzophenone and 3400, 3450, and 3500 Å for propiophenone. Measured per cent reactions varied by less than 1% at the various wavelengths. The propiophenone and dilute benzophenone samples were analyzed in 10-mm cells, the 0.050 *M* benzophenone samples in 1-mm cells. The dilute ketones did not absorb all the light incident upon them, and corrections for this were made in calculating relative quantum yields.

The photoelimination of butyrophenone was monitored by measuring the yields of acetophenone formed by glpc analysis. All analyses were performed on an Aerograph Model 600-D Hy-Fi with a 6 ft × 1/8 in. column containing 4% QF-1 and 1% Carbowax 20M on 60–80 mesh Chromosorb P, with a column temperature of 105–110° and a nitrogen flow of 30 ml/min. A Leeds and Northrup Model H recorder fitted with a disk integrator allowed the area ratios of acetophenone to tetradecane to be measured with 1% reproducibility. Area ratios were converted to mole ratios by calibrating the column with known mixtures.

Acknowledgment. Grants from the National Science Foundation and the Office of Naval Research are gratefully acknowledged. A grant from Research Corporation allowed preliminary work to be begun and is particularly appreciated. Professor Kearns very generously provided preprints of his work.

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Kinetics of Proton Transfer and Tautomerism in Aqueous Diacetylacetone. A Temperature-Jump Investigation

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Abstract: Diacetylacetone (2,4,6-heptanetrione) is a pseudo-acid with a pK of 7.43. Kinetic measurements with the temperature-jump relaxation technique have been carried out in the acidic and basic pH regions at 25° and ionic strength 0.1. Two concentration- and pH-dependent relaxation times were observed in the millisecond time region: one in acidic and one in basic solutions. The nmr spectra of the solutions established that the predominant anionic species had the structure $\text{CH}_3\text{COCH}_2\text{COCH}=\text{CO}^-\text{CH}_3$ (KHE^-). The structures of the main protonated forms could not be deduced from the nmr data. On the basis of the nmr results and the concentration dependence of the acidic relaxation time, the latter was attributed to the process $\text{H}^+ + \text{KHE}^- \rightleftharpoons \text{KHKH}$, where KHKH is the triketone form of the acid. The forward rate constant was found to be $2.6 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$. The mechanism for hydrolysis was found to be considerably more complicated and involved the hydrolysis of two or more anionic species by means of a cyclic mechanism. Only an effective (over-all) rate constant could be measured for the reaction of the molecules with OH^- : $k_{\text{eff}} = 2.5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$. On a Brønsted plot of $\log k$ vs. pK_a , both rate constants correlated well with data for other ketones.

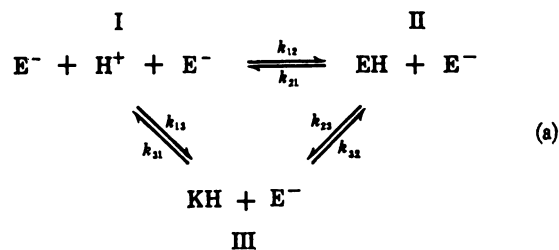
Eigen and his co-workers have amply demonstrated that the rate of "normal" proton transfer in simple acid-base systems is diffusion controlled; that is, the rate-determining step is the diffusion of the partners to a critical distance.^{2,3} For such reactions, the rate constant for the reaction of H^+ with an anion is on the order of 10^{10} – $10^{11} \text{ M}^{-1} \text{ sec}^{-1}$; that for the reaction of OH^- with a protonated species is on the order of $10^{10} \text{ M}^{-1} \text{ sec}^{-1}$. Exceptions to these generalizations are well understood⁴ and occur (a) if steric factors reduce the angle acceptable for successful encounter, (b) in systems which are strongly internally hydrogen bonded (e.g., the reaction of OH^- with the enol of acetylacetone), (c) within the class of acids known as "pseudo-acids," in which a proton is removed directly or indirectly from a carbon atom. It is with an example of this class that this paper is concerned.

Proton transfers in pseudo-acids are characterized by reaction rates^{2,3} which range from "very slow" (e.g., the neutralization of CH_2NO_2^- with H^+ , which can be observed with conventional techniques⁴) to virtually diffusion controlled. Within a series of closely related compounds, the rates of protonation and hydrolysis are a direct function of the pK of the acid.^{3,5} An important class of pseudo-acids are ketones which can exist in two or more tautomeric forms. The present paper reports the results of a kinetic study, using the temperature-jump relaxation technique, on the triketone diacetylacetone (2,4,6-heptanetrione). This compound can exist in several tautomeric forms both as the molecule and anion. The possibilities⁶ are shown in Table I. The symbols KH and EH refer to keto and enol portions of the molecule, respectively.⁷ To date there

has been no detailed investigation of the relative amounts of the various species present nor a study of the mechanism interrelating them.

Reaction Mechanisms

Acidic Region. Eigen, *et al.*,⁸ have shown that protonation and deprotonation equilibria in aqueous solutions of tautomeric substances involve a reaction scheme (a) in which the keto and enol forms of the molecule as well as the anion participate. The conversion I–II



EH = enolic form, KH = keto form, and E^- = enolate anion

involves the recombination of a proton with the enolate to yield the enolic form of the substance. The conversion I–III involves the same partners, but now yielding the ketone. Reaction II–III describes the anion catalyzed keto–enol conversion in which the proton is directly removed from one tautomer by the enolate ion with the generation of the other tautomeric form. This simple mechanism involving only one anion and one each of the keto and enol forms will be shown to be inadequate to explain fully the results obtained in the present work. Nevertheless, the general features of this mechanism and the concentration dependence of the relaxation time apply.

Mechanism a as a whole is characterized by two relaxation times, which may be separated by several orders of magnitude. The shorter of these (τ_1) is associated exclusively with the fast (diffusion-controlled) conver-

(1) Address to which correspondence should be sent.

(2) M. Eigen, *Angew. Chem.*, **75**, 489 (1963); *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

(3) M. Eigen, W. Kruse, G. Maass, and L. DeMaeyer, *Progr. Reaction Kinetics*, **2**, 287 (1964).

(4) D. Turnbull and S. Maron, *J. Am. Chem. Soc.*, **65**, 212 (1943).

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(6) Some especially unlikely structures (e.g., the trienol) have not been considered.

(7) Note that KHEH_1 signifies the form with a ketone at one end and an enol at the first C–O at the other end, etc.

(8) M. Eigen, G. Ilgenfritz, and W. Kruse, *Chem. Ber.*, **98**, 1623 (1965); see also G. Ilgenfritz, Diplomarbeit, University of Göttingen, 1963.

Table I. Possible Tautomeric and Resonance Structures for Diacetylacetone and Its Anions

1. Protonated forms		2. Enolate anions*	
KHKH	$\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\overset{\text{O}}{\parallel}\text{CCH}_2\overset{\text{O}}{\parallel}\text{CCH}_3$	KHE ⁻	$\left\{ \begin{array}{l} \text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\overset{\text{O}}{\parallel}\text{CCH}=\overset{\text{O}^-}{\text{CCH}_3} \\ \text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\overset{\text{O}^-}{\text{C}}=\text{CH}\overset{\text{O}}{\parallel}\text{CCH}_3 \end{array} \right.$
KHEH ₁	$\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_2\overset{\text{O}\cdots\text{HO}}{\parallel}\text{CCH}=\text{CCH}_3$		
KHEH ₂	$\text{CH}_3\overset{\text{O}\cdots\text{HO}}{\parallel}\text{CCH}=\text{CH}\overset{\text{O}}{\parallel}\text{CCH}_3$	EHE ₁ ⁻	$\left\{ \begin{array}{l} \text{CH}_3\overset{\text{OH}\cdots\text{O}^-}{\text{C}}=\text{CH}\overset{\text{O}}{\parallel}\text{CCH}_3 \\ \text{CH}_3\overset{\text{OH}\cdots\text{O}}{\text{C}}=\text{CH}\overset{\text{O}^-}{\text{C}}\overset{\text{O}}{\parallel}\text{CCH}_3 \end{array} \right.$
EHEH ₁	$\text{CH}_3\overset{\text{OH}}{\text{C}}=\text{CH}\overset{\text{O}\cdots\text{HO}}{\text{C}}\overset{\text{O}}{\parallel}\text{CCH}_3$		
EHEH ₂	$\text{CH}_3\overset{\text{OH}}{\text{C}}=\text{CH}\overset{\text{OH}\cdots\text{O}}{\text{C}}=\text{CH}\overset{\text{O}}{\parallel}\text{CCH}_3$	EHE ₂ ⁻	$\left\{ \begin{array}{l} \text{CH}_3\overset{\text{O}^-\cdots\text{HO}}{\text{C}}=\text{CH}\overset{\text{O}}{\parallel}\text{CCH}_3 \\ \text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}=\text{CH}\overset{\text{OH}\cdots\text{O}^-}{\text{C}}\overset{\text{O}}{\parallel}\text{CCH}_3 \end{array} \right.$

* Resonance structures for the anion with the charge localized on carbon not shown.

sion I-II during the restoration of which the slower processes remain virtually unchanged. The longer relaxation time (τ_2) is a function of the kinetic parameters for the two slow steps (I-III, II-III) as well as of the equilibrium parameters of the step I-II. When the two steps are widely separated in time, the two relaxation times are⁸

$$\tau_1^{-1} = k_{12}([H] + [E]) + k_{21} \quad (1)$$

and

$$\tau_2^{-1} = \frac{k_{12}K_{\text{EH}}([H] + \frac{[E]}{1+\alpha})}{K_{\text{EH}} + [H] + \frac{[E]}{1+\alpha}} + k_{21} + \frac{k_{22}[E]}{K_{\text{EH}} + [H] + \frac{[E]}{1+\alpha}} \left([H] + \frac{[E]}{1+\alpha} \right) + k_{22}[E] \quad (2)$$

where the brackets refer to the equilibrium values of the concentrations⁹ and the equilibrium constant K_{EH} is defined by

$$K_{\text{EH}} = \frac{[H][E]}{[EH]} \quad (3)$$

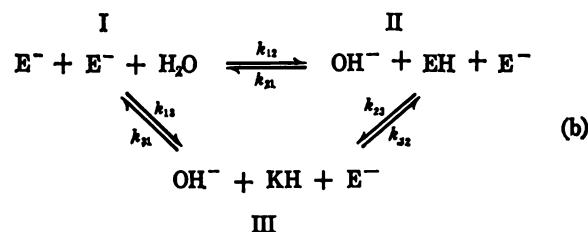
The quantity α is a correction term resulting from coupling the slow relaxation time to a rapid indicator equilibrium (to permit the relaxation to be followed by optical means) and is given by

$$\alpha = \frac{[H]_{\text{In}}}{K_{\text{In}} + [H]} \quad (4)$$

where K_{In} is the acid dissociation constant for the indicator.

(9) Charges are omitted for simplicity.

Basic Region. The simplest reaction scheme (i.e., hydrolysis of an anion to yield enol and keto forms) may be represented by



III

where the conversion I-II represents the (rapid) protonation of the enolate anion to yield the enol. The two (slower) conversions I-III and II-III involve protonation yielding the keto form and the enolate catalyzed interconversion, respectively. The two relaxation times are

$$\tau_1^{-1} = k_{21}([EH] + [OH]) + k_{12} \quad (5)$$

and

$$\tau_2^{-1} = k_{21} \left(\frac{[KH]}{1+\beta} \frac{[OH]}{K'_{\text{EH}} + [OH]} + \frac{[EH]}{1+\beta} + [OH] \right) + k_{12} \frac{[OH]}{K'_{\text{EH}} + [OH]} + \frac{[EH]}{1+\beta} + k_{22}[E] \frac{K'_{\text{EH}} + [EH]/(1+\beta)}{K'_{\text{EH}} + [OH]} + k_{22}[E] \quad (6)$$

where K'_{EH} is the hydrolysis equilibrium constant¹⁰ of

(10) Throughout this paper, primed symbols will be used to indicate that the equilibrium constant so designated is a hydrolysis equilibrium constant.

the enol form and $\beta = [HIn]/(K'_{In} + [OH])$ is again an indicator correction term.

Experimental Section

Materials. The disodium salt of diacetylacetone was prepared¹¹ by the hydrolysis of 2,6-dimethyl- γ -pyrone. A solution of 19 g of 2,6-dimethyl- γ -pyrone¹² in 100 ml of absolute ethanol was treated with 19 ml of 16 *N* NaOH and slowly brought to boiling. The resultant yellow precipitate was collected, repeatedly washed in cold alcohol, and dried. The residue was recrystallized twice from 95% ethanol, vacuum dried, and stored at -10° . The spectrum of the fresh salt was found to compare well with that given by Schwarzenbach, *et al.*¹³

It was found necessary to store the compound in a frozen condition prior to use. A pale yellow aqueous solution at pH 13 turned deep red-brown after 4 days, apparently because of polymerization. Acidic solutions showed no visible evidence of instability over short periods of time. During the course of the experimental work, the compound was prepared freshly for each run.

The solutions were made using sufficient 1 *M* KNO₃ to maintain a constant ionic strength of 0.1. The *pK* of diacetylacetone at 25° and zero ionic strength¹⁴ (7.43) was converted to the concentration equilibrium constant at 0.1 ionic strength by using the relation $K = K^0/\gamma_{\pm}^2$ where K^0 is the zero ionic strength value and γ_{\pm} is the mean ionic activity coefficient. The value¹⁴ $\gamma_{\pm} = 0.79$ was used, yielding $K = 6.1 \times 10^{-8}$. The indicators used in this investigation and their approximate *pK* values¹⁵ at ionic strength 0.1 were methyl red (4.96), chlorophenol red (6.00), phenol red (8.0), cresol red (8.3), and phenolphthalein (9.7).

Kinetic Measurements. All kinetic runs were carried out on a temperature-jump relaxation spectrometer similar to that described by Czerlinski and Eigen.¹⁶ The solution temperature was adjusted such that the final temperature (following the jump) was 25°. In each (acid and base) pH region only a single relaxation time was observed in the time range accessible (1 sec–5 μ sec). The resultant relaxation curves were photographed with a 35-mm camera system. Their relaxation times were evaluated from enlargements made from the negatives. Blank experiments involving only the indicator system, or diacetylacetone solution without indicator, were also carried out.

Results.

Kinetic Measurements. Acidic Region. The results of experiments between pH 5.0 and 6.5 at 25° are shown in Table II. The over-all anion concentration $[E]_z$ (calculated from the pH and the equilibrium constant) is given in column 4. This number could consist of several different anionic species (*cf.* Table I).

It is clear that the relaxation time is a function of $[H] + \{[E]/(1 + \alpha)\}$ and not of $[E]$ or $[E]^2/(1 + \alpha)$. Compare, for example, entries 1 and 5 in Table II, which have different enolate concentrations by a factor of 3 but whose relaxation times are within 10% of each other. The indicator correction term brings the two concentration functions (column 7) to about the same value. The differences in these correction terms lie in the pH differences and the change of the indicator (*i.e.*, pK'_{In} differences; see eq 4). A graph of τ^{-1} vs. $[H] + \{[E]/(1 + \alpha)\}$ yields a straight line, the slope of which is $k_{12} = 2.6 \times 10^6 M^{-1} \text{sec}^{-1}$. An estimate may be made of K_{EH} , the equilibrium constant defined by eq 3, by calcu-

Table II. Acid pH Region. Tabulation of Results

No.	C^0, M	pH ^a	Indicator ^b	$[E]_z \times 10^4, M$	α	τ, msec	$\frac{[H] + \{[E]_z/(1 + \alpha)\} \times 10^4}{M}$
1	1.67×10^{-3}	5.00	MR	8.03	0.40	6.0	7.00
2	8.35×10^{-3}	5.00	MR	4.02	0.40	10.0	4.14
3	8.35×10^{-3}	5.08	MR	4.85	0.48	9.7	4.32
4	8.35×10^{-3}	5.60	CPR	15.7	1.60	5.5	6.4
5	8.35×10^{-3}	5.75	CPR	22.0	2.10	5.5	7.3
6	8.35×10^{-3}	5.85	CPR	27.6	2.80	4.7	7.45
7	8.35×10^{-3}	6.00	CPR	38.3	3.84	4.45	8.0
8	8.35×10^{-3}	6.03	CPR	41.2	4.10	4.4	8.2
9	8.35×10^{-3}	6.25	CPR	66.2	5.76	3.8	9.9
10	8.35×10^{-3}	6.52	CPR	115	7.70	3.1	13.2
11	4.17×10^{-3}	5.00	MR	2.01	0.40	14.0	2.70
12	4.17×10^{-3}	5.05	MR	2.25	0.44	9.0	2.69
13	2.08×10^{-3}	5.10	MR	1.25	0.50	16.9	1.84
14	1.67×10^{-3}	5.08	MR	0.97	0.48	17.0	1.71
15	8.35×10^{-4}	5.00	MR	0.40	0.40	31.5	1.56
16	8.35×10^{-4}	5.00	MR	0.40	0.40	16.4	1.56
17	4.17×10^{-4}	5.00	MR	0.20	0.40	18.0	1.41

^a $[H]$ was calculated from the measured pH by dividing the hydrogen ion activity by γ_{\pm} (≈ 0.79). ^b MR = methyl red, CPR = chlorophenol red; indicator concentrations = $2 \times 10^{-5} M$.

lating the value which would cause a just detectable deviation of the curve from a straight line. The result is $K_{EH} \geq 1.5 \times 10^{-3}$. The third term in eq 2 (and hence the conversion II–III) apparently does not make a measurable contribution to the relaxation time at the concentrations and pH's used.

Basic Region. The processes occurring in this region were considerably slower than in the acidic region; the measured relaxation times varied between approximately 1 sec and 70 msec (see Table III). The fourth column in Table III tabulates the total concentration of protonated species ($[HX]_z$) calculated from the over-all concentration and the measured pH. A close examination of eq 6 shows that only the first term fits the results in Table III. The fourth term varies directly as $[E]$, the enolate concentration. Since above pH 8.5 virtually all the compound is present in this form, a pH-independent relaxation time would result. The third term can assume several limiting forms depending on which terms are large in the denominator, but in no case can the experimentally observed form be obtained. On the other hand, the first term in eq 6 (corresponding to the conversion I–III) fits the observed concentration and pH dependence exactly. A graph of τ^{-1} vs. C^0 (over-all concentration) should yield a straight line at constant pH, the vertical intercept of which should be $k_{21}[OH]$. Furthermore, if $K'_{EH} \gg [EH] + [OH]$, a series of straight lines with slopes virtually independent of pH (since $1 + \beta \approx 1$) will be observed. Figure 1 shows that the linear relationship anticipated clearly holds for the results at pH 8.87. The ratio of the vertical intercept to the hydroxyl ion concentration is $2.1 \times 10^6 M^{-1} \text{sec}^{-1}$. If straight lines are drawn through the points at pH 9.2 and 9.4, the division of the observed intercepts by the hydroxyl ion concentration yields the values 2.8 and $2.7 \times 10^6 M^{-1} \text{sec}^{-1}$, respectively. The difference between these numbers is not considered significant; as a result it may be concluded that the value of k_{21} is $(2.5 \pm 0.4) \times 10^6 M^{-1} \text{sec}^{-1}$.

(11) G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, 23, 1162 (1940).

(12) Obtained from EGA-Chemie KG., Keppler and Reif, Steinheim/Albach, West Germany.

(13) G. Schwarzenbach, K. Lutz, and E. Felder, *Helv. Chim. Acta*, 27, 576 (1944).

(14) See, *e.g.*, C. W. Davies, "Ion Association," Butterworth Inc., Washington, D. C., 1962.

(15) In general, the *pK* values of the indicators were not available for the exact conditions of this investigation. Since, however, the literature values may vary by 0.2 or 0.3 *pK* unit, depending on the source, no attempt was made to correct for a slight difference in temperature or ionic strength.

(16) G. Czerlinski and M. Eigen, *Z. Elektrochem.*, 63, 652 (1959).

Table III. Basic pH Region. Tabulation of Results

No.	C_0 , M	pH ^a	Indicator ^b	$[HX]_Z$ ^c $\times 10^4, M$	β	τ , msec
1	3.35×10^{-3}	8.95	P	8.05	0.22	113, 108
2	2.16×10^{-3}	8.12	CR (1×10^{-5})	31.0	1.49	217
3	2.16×10^{-3}	8.42	CR (1×10^{-5})	16.6	0.70	157
4	2.16×10^{-3}	8.72	CR (1×10^{-5})	8.75	0.27	160
5	2.16×10^{-3}	8.87	P	6.21	0.28	112
6	2.16×10^{-3}	9.00	P	4.65	0.26	100
7	2.16×10^{-3}	9.20	P	2.24	0.20	80
8	2.16×10^{-3}	9.37	P	2.02	0.16	65, 90
9	1.67×10^{-3}	8.87	P	4.80	0.28	165
10	1.67×10^{-3}	8.93	P	4.22	0.27	125
11	1.67×10^{-3}	9.20	P	1.74	0.20	94
12	1.67×10^{-3}	9.37	P (1.5×10^{-5})	1.56	0.12	80
13	1.67×10^{-3}	9.40	P (2×10^{-5})	1.46	0.15	70
14	1.67×10^{-3}	9.38	P (2.5×10^{-5})	1.52	0.19	72, 74, 85
15	1.67×10^{-3}	9.37	P (4×10^{-5})	1.56	0.32	94, 96, 112
16	1.67×10^{-3}	9.38	P (1×10^{-4})	1.52	0.76	78, 88
17	1.67×10^{-3}	9.39	P (1×10^{-4})	1.49	0.76	74, 90
18	1.67×10^{-3}	9.40	P (2.5×10^{-4})	1.46	1.89	108
19	1.07×10^{-3}	8.30	PR (1×10^{-5})	10.7	0.80	290, 330
20	1.07×10^{-3}	8.28	PR (2×10^{-5})	11.1	1.72	305, 318
21	1.07×10^{-3}	8.35	PR (5×10^{-5})	9.65	3.42	435
22	8.35×10^{-4}	8.00	CR	15.1	3.74	1000
23	8.35×10^{-4}	8.34	CR	7.62	1.75	540
24	8.35×10^{-4}	8.72	CR	3.42	0.53	320
25	8.35×10^{-4}	8.80	P	2.93	0.30	160
26	8.35×10^{-4}	8.87	P	2.40	0.28	190
27	8.35×10^{-4}	8.90	P	2.25	0.28	170
28	8.35×10^{-4}	8.93	P	2.10	0.27	144, 174
29	8.35×10^{-4}	9.20	P	0.87	0.20	125
30	8.35×10^{-4}	9.35	P	0.81	0.16	118
31	8.35×10^{-4}	9.40	P	0.73	0.14	83
32	8.35×10^{-4}	9.46	P	0.64	0.13	72
33	4.17×10^{-4}	8.88	P	1.18	0.28	296
34	2.08×10^{-4}	8.87	P	0.60	0.28	405, 350

^a [OH] was calculated from the measured pH by dividing the hydroxyl ion activity by 0.79. ^b CR = cresol red, PR = propyl red, P = enolphthalein; indicator concentrations, where not indicated in parentheses, were $2 \times 10^{-5} M$. ^c The symbol $[HX]_Z$ is used to designate total concentration of protonated forms; see Table I.

It can be easily shown that a single set of reaction partners (*i.e.*, a single enolate anion and one ketone and one alcohol, respectively) as represented in mechanisms a and b are not sufficient to explain the kinetics in both the acidic and the basic regions. For example, if we assume the reaction in basic solutions is the hydrolysis given by mechanism b (where KH and EH now refer to a pair of related protonated forms of the molecule; see Table I), the slow relaxation time is given essentially by the first term in eq 6 with $K'_{BH} \gg [OH] + \{[EH]/(1 + \beta)\}$. We conclude therefore that $K'_{BH} = 1.4 \times 10^{-3}$ or larger.¹⁷ This gives $K_{BH} (= [H][E]/[EH]) \leq 7.1 \times 10^{-12}$.

Now if the same partners are to account for the relaxation process observed in the acidic pH range, we use simply mechanism a with τ^{-1} given by eq 2, and the terms involving k_{21} and k_{22} are negligible. The equilibrium constant K_{BH} for the rapid step I-II is fixed by the basic solution results, and so τ^{-1} reduces to

$$\tau^{-1} = k_{12}K_{12} + k_{21} = k_{21}(1 + K_{12}K_{12}) \cong k_{21} \quad (7)$$

Since $k_{21} = K_{12}k_{12} = k_{12}(6.8 \times 10^{-8})$, $\tau \cong 2 \times 10^7/k_{12}$. If k_{12} is between the (reasonable) values 10^4 – $10^7 M^{-1} s^{-1}$ (see Figure 3), then τ would lie between 2 and 100 sec and be independent of concentration and pH. Thus, the acidic analog of the basic relaxation time could not yield an observable relaxation in the acidic pH range.

(17) If only part of the protonated form exists as the ketone, $[KH]/[HX]_Z$ where f is the fraction of HX in the form KH.

Nmr Measurements. The proton resonance spectra of diacetylacetone (determined at room temperature on an A-60 nmr spectrometer) in the basic and acidic

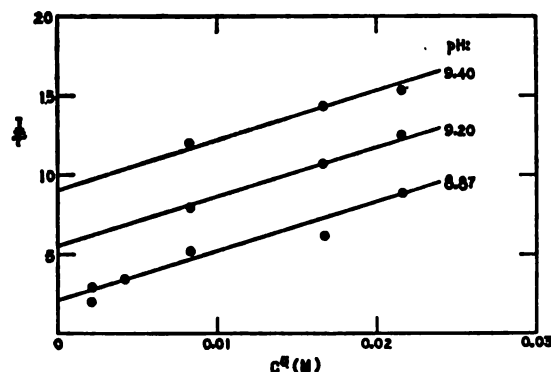


Figure 1. Variation of the relaxation time in basic solutions with the over-all concentration at several pH values.

pH regions are shown in Figure 2. The spectrum of a 1 M solution of acetylacetone at pH 4 was also run for comparison. The latter showed four peaks in the proper ratios to account for 85% ketone and 15% enol in aqueous solution. The resonances for the groups $CH_3C=$, CH_3C- , $-CH_2-$, and $-CH=$ occur at 1.95, 2.14, 3.72, and 5.60 ppm, respectively, relative to TMS. The spectrum for the anions of diacetylacetone

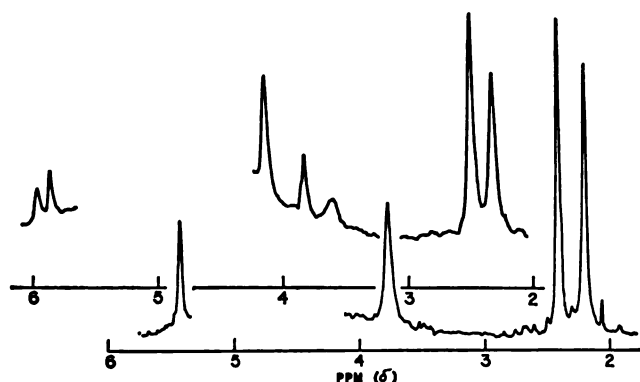


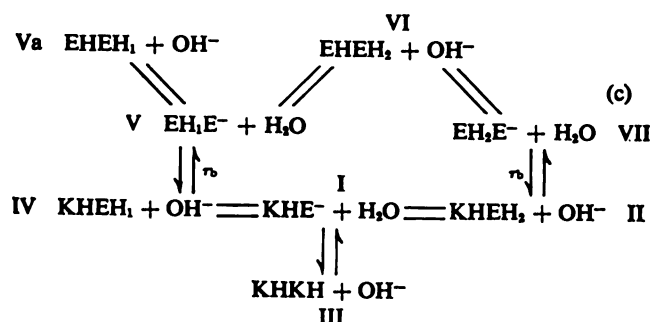
Figure 2. Nmr spectra of 0.5 *M* diacetylacetone: upper spectrum, pH 4.0; lower spectrum, pH 10.0 (water resonances are not shown).

indicates also only four peaks, associated with the above-mentioned groups in the ratio 3:3:2:1. The only structure consistent with the latter is the anionic form KHE^- (see Table I); *i.e.*, of the three anions possible, KHE^- is the only one detectable¹⁸ by nmr. The more complicated acidic spectrum shows once more two different methyl peaks, but in addition there are several other peaks, the integrals of which are in no simple proportions to each other. The only conclusion that can be reached is that the protonated species exists as a mixture of various forms.

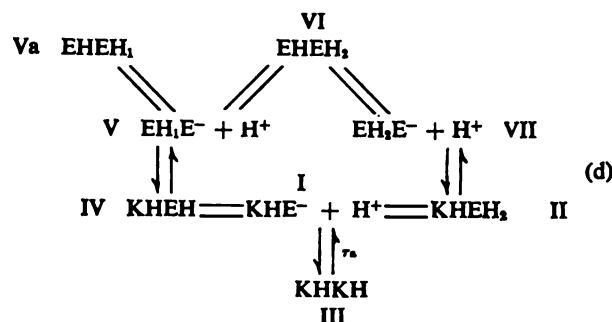
Discussion

While it is clear that one of the two relaxation times observed is associated with the direct protonation of the enolate anion and the other with the hydrolysis of one or more protonated forms, it is desirable to relate the relaxation phenomena to specific species.

The mechanism interrelating all species in Table I is given for the basic pH region by (c) where the slow



steps are represented by arrows and the rapid equilibria



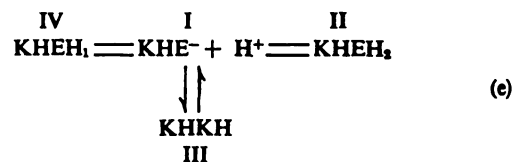
(18) Presumably the species EHE_1^- and EHE_2^- are also present, but at much smaller concentrations.

libria by \rightleftharpoons signs. The analogous reaction scheme for the acidic region is (d). Although there are eight equilibria shown in these two mechanisms, there can be no more than seven relaxation times for each, since the circular interconnection reduces the number of independent concentration variables by one. There are only two long relaxation times: one is associated with the isolated slow step I–III (and the equilibria preceding it); the other is associated with the “parallel” pathways¹⁹ II–VII and IV–V. The task remains of making an assignment of the observed relaxation times to specific steps. The following observations are relevant.

1. Only two relaxation times were observed, one each in the basic and acidic pH regions. If, for example, the effect in basic solutions corresponds to the processes II–I–III, it is clear by the analysis above (eq 7 and text) why the exact acidic counterpart ($\text{KHEH}_2 = \text{KHE}^- + \text{H}^+ \rightleftharpoons \text{KHKH}$) would not be observed in the acidic solutions. Thus, of the four slow steps in mechanisms c and d, all are needed to account for the two times.

2. The magnitude of the relaxation effect is *ca.* tenfold larger in the acidic region than in the basic region. In both pH regions, the size of the effects decreases as the quantities $[\text{HX}]_2$ and $[\text{E}]_2$ decrease relative to $[\text{OH}]$ and $[\text{H}]$, respectively.²⁰ In the acidic region, the relaxation effect disappears just as $[\text{E}]_2$ decreases to become virtually identical with $[\text{H}]$. The effect in the basic region, however, is much smaller to begin with and disappears well before the sum of the protonated species becomes small compared to $[\text{OH}]$.

Both observations are consistent with the assignment of the relaxation effect in acidic solutions to equilibria involving major constituents; in basic solutions, to equilibria involving minor constituents. The best assignment of relaxation times is that shown by the position of τ_a (acidic) and τ_b (basic) in mechanisms c and d. The final mechanism in the acidic region then becomes



the slow relaxation time (τ_a) of which is given by eq 5, where now

$$\frac{1}{K_{\text{BH}}} = \frac{1}{K_{12}} + \frac{1}{K_{14}} = \frac{[\text{KHEH}_1] + [\text{KHEH}_2]}{[\text{H}][\text{KHE}]}$$

Under the condition $K_{\text{BH}} \gg [\text{H}] + [\text{KHE}]/(1 + \alpha)$, this reduces to the experimentally observed form. It is also apparent that since KHE^- is the only major anion present (see nmr results), its concentration is virtually equal to the total anion concentration. We conclude therefore that the rate constant k_{12} has the value $2.6 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ and $K_{\text{BH}} \geq 1.5 \times 10^3$ (see acid results).

The interpretation of the relaxation observed in the basic region is somewhat more involved. If one

(19) They are effectively parallel because of the rapid interconversion between states VII and V on the one hand and between II and IV on the other.

(20) The optimum conditions for observing a reaction coupled to a pH indicator are $[\text{OH}] \ll [\text{HX}]$ in the basic region and $[\text{H}] \ll [\text{E}]$ in the acidic region, where the symbols HX and E^- refer to the reactants which yield the relaxation effect.

$$\frac{\bar{k}[\text{OH}]\left[K'_{14}\frac{[\text{KHEH}_1]}{1+\beta}(1+K_{42})(1+K_{57})+K'_{14}K'_{56}+(1+K_{57})K'_{14}\frac{[\text{EHEH}_2]}{1+\beta}+[\text{OH}]\right]}{[\text{OH}]\left\{(1+K_{57})\frac{[\text{KHEH}_1](1+K_{42})+[\text{EHEH}_2]}{1+\beta}+[\text{OH}]+K'_{14}(1+K_{42})+K'_{56}(1+K_{42})\right\}+R} +$$

$$\frac{\bar{k}[\text{OH}]\left[\frac{[\text{KHEH}_1](1+K_{42})+[\text{EHEH}_2]}{1+\beta}+[\text{OH}]+K'_{14}(1+K_{42})\right]}{[\text{OH}]\left\{(1+K_{57})\frac{[\text{KHEH}_1](1+K_{42})+[\text{EHEH}_2]}{1+\beta}+[\text{OH}]+K'_{14}(1+K_{42})+K'_{56}(1+K_{42})\right\}+R} \quad (8)$$

the equilibrium V-Va in mechanism d, the on time τ_b becomes²¹ as shown in eq 8 the equilibrium constants are defined as

$$K'_{14} = \frac{[\text{KHEH}_1][\text{OH}]}{[\text{KHE}]} \quad K_{57} = \frac{[\text{EH}_2\text{E}]}{[\text{EH}_1\text{E}]}$$

$$K'_{56} = \frac{[\text{EHEH}_2][\text{OH}]}{[\text{EH}_1\text{E}]} \quad K_{42} = \frac{[\text{KHEH}_2]}{[\text{KHEH}_1]}$$

effective rate constants (characterizing the pathways IV-V and II-VII) are given by $\bar{k} = K_{42}k_{27}$ and $\bar{k} = k_{54} + K_{57}k_{72}$. The term R in denominator contains all terms not multiplied by

$$+ K_{42}) \times$$

$$\frac{+ K_{57}[\text{EHEH}_2] + K'_{56}[\text{KHEH}]}{1 + \beta} + K'_{14}K'_{56} \quad]$$

eq 8 may reduce to several forms depending on assumptions made concerning the relative values of K_{56} in the denominator. It is clear that the R must be large compared to those multiplied by K_{56} in order that the experimentally observed form be obtained. In addition, if $K'_{14}K'_{56}$ is the largest term in the brackets in the expression for R , there finally

$$\frac{\bar{k}[\text{OH}]}{1 + K_{42}} \times$$

$$\left[\frac{K'_{57}[\text{EHEH}_2] + [\text{KHEH}_1] + [\text{KHEH}_2]}{K'_{56}(1 + \beta)} + 1 \right] +$$

$$\frac{1}{K'_{56}} \left[\frac{[\text{KHEH}_1]}{1 + \beta} + \frac{[\text{EHEH}_2]}{(1 + K_{42})(1 + \beta)} + K'_{14} \right] \quad (9)$$

equation now has the correct concentration dependence. From Figure 1 the over-all rate constant $\bar{k}/(1 + K_{42}) = 2.5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$ and $1 + K_{42} = 7.5 \times 10^3$. It is not possible to decide unambiguously which of the terms $(k_{54} + K_{42}k_{27})$ in eq 9 is the larger contribution.

It might be asked if the assignment of relaxation times in the acidic and basic regions could just as well be reversed; i.e., is there any ambiguity in the assignment of τ_a and τ_b ? If one were to interchange the two times, the assignment is immediately apparent. The time τ_b must indeed be accounted for by step I-III coupled with I-II. The acidic τ , however, can easily be shown to be completely inconsistent with the

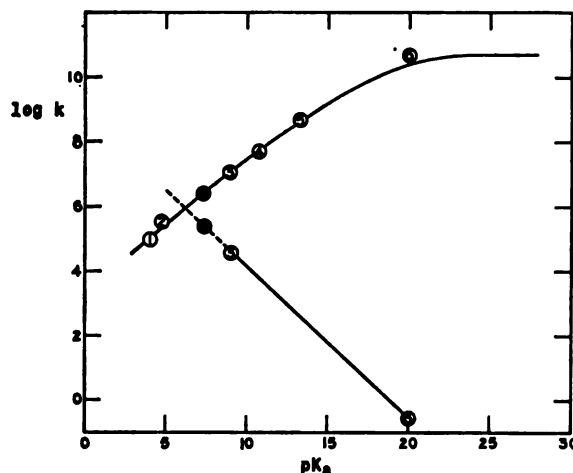


Figure 3. Brønsted plot for acid and base rate constants in some ketones: solid circles, diacetylacetone; others, (1) barbituric acid, (2) Meldrum's acid, (3) acetylacetone, (4) ethylacetylacetone, (5) diethylmalonic acid, (6) acetone. Upper curve is k_a , lower is k_b .

parallel paths V-IV and VII-II. If one again neglects the equilibrium V-Va, an expression for τ_a analogous to eq 8 is obtained where now $\bar{k} = k_{57} + K_{42}k_{27}$. In order to obtain an equation of the proper form, it is necessary to assume that an "R" term²² in the denominator is negligible. This requires, among others, that $K_{56} \ll [\text{H}]$. On the other hand, it is also required that $K_{56} \geq 1.5 \times 10^{-3}$ (see acid results), a result which is irreconcilable with the lower limit of K_{56} necessary in the denominator. Thus we conclude that the assignment of the relaxation times in the acidic and basic regions can be unambiguously made.

It is now well established that a correlation exists between the rate constants for proton transfer in pseudo-acids and the pK_a of the system (Brønsted relation). Figure 3 shows a Brønsted plot for a series of closely chemically related pseudo-acids.²⁴ Most of the rate constants have been directly measured;²⁵ i.e., they are not obtained from the ionization rate and the pK_a . The acid recombination rate constants all lie on a smooth curve, with the result for diacetylacetone falling precisely where expected. Data are more scanty for the basic reaction ($\text{HB} + \text{OH}^-$); it is clear, however, that the basic rate constant involving diacetylacetone correlates well with a linear extrapolation of the other points. This correlation is remarkable inasmuch as the value measured was an effective or over-all

(23) Containing all terms not multiplied by $[\text{H}]$.

(24) If all rate data for acids of varying chemical composition (e.g., trifluoroacetylacetone, nitromethane) were examined, the qualitative correlation would still exist, but several curves would be necessary to adequately represent all the data. For example, the reaction of OH^- with HCN ($pK = 9.1$) is just 10-fold less than diffusion-controlled: J. Stuehr, *et al.*, *J. Chem. Phys.*, **38**, 587 (1963).

Appendix.

eq 8 requires that $K'_{56} \gg (1 + K_{57})[\text{EHEH}_2]$ and $K'_{14} \gg$

rate constant (see eq 8). There are at least three explanations: (1) the correlation is purely fortuitous; (2) the pK of the molecules involved is also about 7.4; or (3) the basic reaction involves the same molecule or anion²⁵ as the acidic. The latter is eliminated, however, by the fact that an examination of mechanism c shows that there is no anion or molecule common to two slow processes. For the second possibility, we must have a single step predominating, a condition which is fulfilled either if $K_{43} \gg 1$ (in which case $k_{\text{eff}} \cong k_{43}$) or $K_{43} \ll 1$ ($k_{\text{eff}} \cong k_{45}$).

In such a relatively complicated system, it was clearly necessary to have carried out measurements in both pH regions. If measurements had been restricted to acidic solutions, one would have concluded that virtually any two-step mechanism could account for the results.²⁶ The kinetic parameters for acidic and basic diacetylacetone are summarized in Table IV. Thus, by carry-

Table IV. Equilibrium and Rate Constants for Aqueous Diacetylacetone at 25° and 0.1 Ionic Strength

Acidic		Basic	
$K_2 = 6.8 \times 10^{-4}$			
$\left. \begin{matrix} k_{14} \\ k_{13} \\ k_{16} \\ k_{78} \end{matrix} \right\} \sim 3 \times 10^{10} M^{-1} \text{sec}^{-1a}$	all	$\left. \begin{matrix} k_{45} \\ k_{47} \\ k_{44} \\ k_{21} \end{matrix} \right\} \leq 3 \times 10^{10} M^{-1} \text{sec}^{-1b}$	all
$k_{13} = 2.6 \times 10^6 M^{-1} \text{sec}^{-1}$ $K_{14} \geq 1.5 \times 10^{-3}$ $K_{13} \geq 1.5 \times 10^{-3}$		$\frac{k}{1 + K_{43}} = 2.5 \times 10^6 M^{-1} \text{sec}^{-1c}$	

^a Estimated on the basis of diffusion-controlled reactions. ^b Internally hydrogen-bonded molecules hydrolyze with rates ranging from the diffusion-controlled limit to considerably more slowly. ^c Over-all rate constant defined by eq 8.

ing out and interpreting measurements in both pH regions, the general features of the protonation-deprotonation mechanism could be established with a high degree of certainty.

(25) But not both; see eq 7 and related text.

(26) For example, a mechanism consisting of one protonated form and two anions ($E_1^- + H^+ = KH \rightleftharpoons E_2^- + H^+$) is easily shown to be compatible with the acid results. The relaxation time for an analogous hydrolysis, however, cannot be fitted to the observed concentration dependence.

Appendix

Derivation of Eq 8. For a small perturbation from equilibrium ($\delta C_i \ll C_i$), the rate of restoration of equilibrium for the parallel paths IV-V and II-VII is given by

$$\frac{d(\delta C_5 + \delta C_6 + \delta C_7)}{dt} = -\frac{d(\delta C_1 + \delta C_4 + \delta C_8)}{dt} = k_{44}(C_4\delta C_{OH} + C_{OH}\delta C_4) + k_{27}(C_3\delta C_{OH} + C_{OH}\delta C_3) - k_{54}\delta C_5 - k_{72}\delta C_7 \quad (\text{A-1})$$

where the symbols C_i refer to the concentrations of the chemical species indicated in mechanism c. This equation may be put in the form

$$\frac{d\delta C_i}{dt} = -\frac{1}{\tau}\delta C_i \quad (\text{A-2})$$

by using the conservation relationships

$$\sum_{i=1}^8 \delta C_i = 0 \quad (i \neq 3) \quad (\text{mass conservation}) \quad (\text{A-3})$$

$$\delta C_2 + \delta C_4 + \delta C_6 + \delta C_{H_2O} = 0 \quad (\text{proton conservation}) \quad (\text{A-4})$$

$$\delta C_{OH} + \delta C_{H_2O} = 0 \quad (\text{hydroxyl conservation}) \quad (\text{A-5})$$

and the preequilibrium relationships

$$K_{56}\delta C_5 = C_6\delta C_{OH} + C_{OH}\delta C_6 \quad (\text{A-6})$$

$$K_{14}\delta C_1 = C_4\delta C_{OH} + C_{OH}\delta C_4 \quad (\text{A-7})$$

$$\delta C_2 = K_{43}\delta C_4 \quad (\text{A-8})$$

$$\delta C_7 = K_{57}\delta C_5 \quad (\text{A-9})$$

The elimination of all δC_i variables except one from eq A-3-A-9 and substitution into A-1 yields an equation of the form of eq A-2, from which τ^{-1} (eq 8) follows directly.

Acknowledgment. This work was supported in part by the Division of General Medical Sciences, Public Health Service, in the form of a postdoctoral fellowship (1962-1963). The author wishes to express his thanks to Dr. Manfred Eigen for many helpful discussions during the course of this work. Special thanks are due to Dr. T. J. Swift for his part in obtaining and interpreting the nmr spectra.

Nuclear Magnetic Resonance Spectrum of Oriented (Cyclobutadiene)iron Tricarbonyl¹

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New York, New York 10027. Received February 18, 1967

Abstract: The geometry of the four-proton system in (cyclobutadiene)iron tricarbonyl has been determined from the proton magnetic resonance spectrum in liquid crystal solution. The observed spectrum is characteristic of a geometry with only two independent direct magnetic dipole coupling constants. The observed splittings do not quite fit those expected from a square geometry. The possibility of a rectangular proton configuration was considered. This geometry could be a result either of a stable structure in the isolated molecule or a distortion of a square structure by the nematic solvent. Using a computer simulation program, it was possible to fit the observed spectrum with a rectangle in which the ratio of unequal sides is 0.9977 ± 0.0045 . Assuming reasonable bond lengths and coplanarity of the carbon and hydrogen skeletons, this corresponds to a change of 0.5° in the C-C-H angle. At worst, this is a very small departure from square symmetry and represents a limit on the extent to which the proton geometry can be rectangular and still yield a spectrum consistent with experimental results. The alternative possibility of a proton configuration rotating rapidly in the asymmetric force field of the liquid crystal environment is also considered.

In 1956, Longuet-Higgins and Orgel² predicted the stability of complexes of cyclobutadiene with transition metal carbonyls. In 1965, Pettit³ reported a thesis of the first stable cyclobutadiene complex, (cyclobutadiene)iron tricarbonyl, CIT (see Figure 1). The geometry of the cyclobutadiene system is unknown, but, for this reason, it is of interest to study the proton configuration. Analysis of the nmr spectra of molecules dissolved in a nematic liquid crystal solvent can lead to a determination of the anisotropic magnetic dipole coupling constant.⁴ Since the anisotropic dipole-dipole interaction is sensitive to interproton distances, it is possible to study the proton geometry by analysis of the nematic pmr spectrum.

Nematic Four-Spin Spectra

A method for analysis of nmr spectra of molecules in a nematic solution has been developed by Saupe,⁴ and the nematic pmr spectrum of CIT was predicted assuming that the protons are in a square and a rectangular configuration. In both structures, the degree of orientation of the molecule (and therefore of the proton system) is given by a single parameter S_{zz} , which is defined as

$$S_{zz} = \frac{1}{2} \langle 3 \cos^2 \theta - 1 \rangle$$

where θ is the angle between the magnetic field and the molecular symmetry axis (see Figure 1). The brackets signify a time average of the angular function. The dipolar Hamiltonian for the four protons, modified for partial orientation in a liquid crystal matrix, is for a rectangle (in cps)

$$\mathcal{H}^{(1)} = \frac{\gamma^2 \hbar}{4\pi} S_{zz} \sum_{i < j}^4 (3I_{zi}I_{zj} - \vec{I}_i \cdot \vec{I}_j) R_{ij}^{-3}$$

¹ Research supported in part through National Science Foundation Grant No. NSF-GP-3559.

² H. C. Longuet-Higgins and L. E. Orgel, *J. Chem. Soc.*, 1969 (6).

³ G. F. Emerson, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **87**, (1965).

⁴ A. Saupe, *Z. Naturforsch.*, **19A**, 161 (1964).

where γ is the proton gyromagnetic ratio, and R_{ij} is the distance between nuclei i and j . For a square proton configuration, the Hamiltonian is

$$\mathcal{H}^{(1)} = \frac{\gamma^2 \hbar}{4\pi R^3} S_{zz} \sum_{i < j}^4 (3I_{zi}I_{zj} - \vec{I}_i \cdot \vec{I}_j)$$

where R is the ortho internuclear distance. For both cases, the Zeeman Hamiltonian is

$$\mathcal{H}^{(0)} = -\frac{\gamma H_0}{2\pi} (1 - \sigma - 2S_{zz}\Delta\sigma/3) \sum_{i=1}^4 I_{zi}$$

H_0 is the magnitude of the external field, σ is the isotropic average of the chemical shift tensor, and $\Delta\sigma$ is the difference between the chemical shift measured perpendicular and parallel to the four-proton plane. Symmetric eight- and ten-line spectra are predicted for the square and rectangular structures, respectively. The splittings and intensities for both cases are given in Table I. The center of symmetry of both spectra is given by

$$\nu = \frac{\gamma H_0}{2\pi} (1 - \sigma - 2S_{zz}\Delta\sigma/3)$$

2. Experimental Section

The nematic pmr spectrum of CIT was obtained in a 25 mole % solution of 4,4'-di-*n*-hexyloxyazobenzene at 76° and is shown in Figure 2. It appears to be a symmetric eight-line multiplet. Tetramethylsilane was used as an internal reference. The measured splittings and intensities are given in Table II. Intensities were obtained with a Varian V-3521 integrator.

3. The Proton Geometry

(a) Square Structure. A visual examination of the spectrum (see Figure 2) would lead to the conclusion that the protons are in a square configuration since there are eight lines. Normalized to the smallest splittings (ΔS_4 and $\Delta\nu_4$), the four splittings are

Theoretical (Table Ia)	1:2.80944:4.6561:6.65611
Experimental (Table II)	1:2.699 \pm 0.107:4.8 \pm 0.17:6.493 \pm 0.25

It can be seen that, within experimental error, the observed splittings are not quite in the same ratio as the

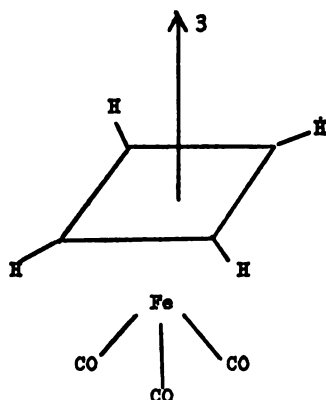


Figure 1. Molecular structure and direction of ordering axis (3) in (cyclobutadiene)iron tricarbonyl (CIT).

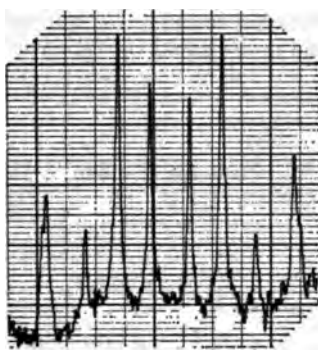
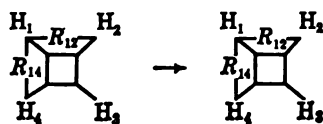


Figure 2. Nematic proton nmr spectrum of (cyclobutadiene)iron tricarbonyl.

theoretical splittings. The possibility that the spectrum actually consists of ten lines, two pairs of which are unresolved (*i.e.*, that the structure is a rectangle), was then considered. An estimate was made of the extent to which the proton structure could differ from a square (*i.e.*, become rectangular) and still fit the observed spectrum.

(b) Rectangular Structure. A possible continuous transition from square to rectangle may occur as



In this case, R_{12} becomes less than R_{14} . Since $B_{ij} = 3\gamma^2\hbar S_{33}/4\pi R_{ij}^3$, B_{12} becomes greater than B_{14} . If the proton chemical shift anisotropy is assumed to be negative, S_{33} must be positive to explain the relative position of the isotropic and nematic spectra. Then, since $R_{12} > R_{14} > R_{13}$, $B_{12} < B_{14} < B_{13}$. Using these inequalities, the transition of the stick-plot spectrum from square to rectangle was made and is shown in Figure 3. The only difference between the two spectra is that the innermost line pair, S_4 , in the "square" spectrum splits into the two "rectangular" line pairs, R_4 and R_5 . The separation between lines in the two pairs (on the same side of the center of symmetry) is given by (see Figure 3 and Table Ib)

$$\frac{1}{\pi}(B_{12} - B_{14}) = \frac{1}{2}(\Delta R_4 - \Delta R_5) \quad (1)$$

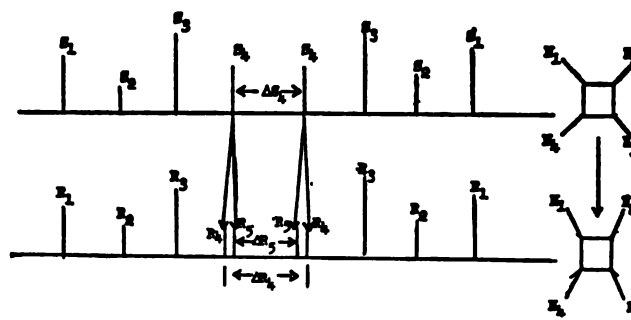


Figure 3. Change in nmr spectrum of four protons as structure changes from a square to a rectangle.

Experimentally, only four pairs of lines are obtained, and the half-width at half-height of the innermost pair is 3.0 cps. It was assumed that a line of the inner-

Table I. Theoretical Splittings and Intensities for Symmetric Four-Spin Spectra

Line pair ^a	Splitting	Intensity
a. Square Configuration: $B = (3\gamma^2\hbar/4R^3)S_{33}$		
S_1	$\Delta S_1 = \frac{B}{\pi} \left(2 + \frac{1}{2\sqrt{2}} \right)$	2
S_2	$\Delta S_2 = \frac{B}{\pi} \left(2 - \frac{1}{2\sqrt{2}} \right)$	1
S_3	$\Delta S_3 = \frac{B}{3\pi} \left[\left(2 + \frac{1}{2\sqrt{2}} \right)^2 + 8 \left(1 - \frac{2}{2\sqrt{2}} \right)^2 \right]^{1/2}$	3
S_4	$\Delta S_4 = \frac{B}{\pi} \left(\frac{1}{2\sqrt{2}} \right)$	2
b. Rectangular Configuration: $B_{ij} = (3\gamma^2\hbar/4R_{ij}^3)S_{33}$		
R_1	$\Delta R_1 = \frac{1}{\pi}(B_{12} + B_{13} + B_{14})$	2
R_2	$\Delta R_2 = \frac{1}{\pi}(B_{12} - B_{13} + B_{14})$	1
R_3	$\Delta R_3 = \frac{1}{3\pi} \{ (B_{12} + B_{13} + B_{14})^2 + 4[(B_{12} - B_{13})^2 + (B_{12} - B_{14})^2 + (B_{13} - B_{14})^2] \}^{1/2}$	3
R_4	$\Delta R_4 = \frac{1}{\pi}(B_{12} + B_{13} - B_{14})$	1
R_5	$\Delta R_5 = \frac{1}{\pi}(-B_{12} + B_{13} + B_{14})$	1

^a See Figure 3.

Table II. Observed Splittings and Intensities in the CIT Proton Nmr Spectrum

Splitting, cps	Intensity
$\Delta\nu_1 = 331.15 \pm 2.25$ (outermost pair)	2
$\Delta\nu_2 = 227.88 \pm 1.66$	1
$\Delta\nu_3 = 137.67 \pm 1.57$	3
$\Delta\nu_4 = 51.00 \pm 1.93$ (innermost pair)	2

most (observed) pair is actually a superposition of two "unresolved" lines. The separation between these two "unresolved" lines is given by eq 1. In order to place

nit on this separation, it is necessary to find the minimum splitting which is possible between two overlapping lines (*i.e.*, R_4 and R_5) which are not resolved. For this purpose, a computer simulation program was written. The lines were given a Lorentzian shape and half-width at half-height of 3.0 cps. It was found that the maximum separation consistent with experiment is 1.0 cps. Using (1), the following relation then holds

$$\frac{1}{\pi}(B_{12} - B_{14}) \leq 1.0 \text{ cps} \quad (2)$$

If $B_{12} - B_{14} = 0$, the proton configuration is a square. Thus, (2) places an upper limit on the distortion from a square structure. The separation between outer pairs, R_1 and R_2 , is given by (see Table Ib)

$$\Delta R_1 - \Delta R_2 = \frac{2B_{13}}{\pi} \quad (3)$$

The splitting between the outermost pair is given by (Table Ib)

$$\Delta R_1 = \frac{1}{\pi}(B_{12} + B_{13} + B_{14}) \quad (4)$$

Subtracting (3) from (4), the following is obtained.

$$\frac{1}{\pi}(B_{12} + B_{14}) = \Delta R_1 - \frac{1}{2}(\Delta R_1 - \Delta R_2) \quad (5)$$

and the maximum departure from the square structure, $\frac{1}{\pi}(B_{12} - B_{14})$ is set equal to the limiting value of 1.0

Using the observed splittings (Table II), eq (5) yields the following dipolar coupling constants (cps): $B_{12} = 440.64 \pm 4.18$, $B_{13} = 162.23 \pm 4.40$, $B_{14} = 437.50 \pm 4.18$. Under the above assumptions, these parameters fit the observed splittings.

The ratio of the interproton distances, R_{12}/R_{14} , is a meaningful estimate of the distortion of a square structure, since $R_{12}/R_{14} = 1$ for a square. Since $B_{ij} = \frac{1}{4\pi} \frac{\gamma^2 \hbar^2}{R_{ij}^3}$, this ratio can be obtained for the minimum distortion from a ratio of the above dipolar coupling constants.

$$\frac{R_{12}}{R_{14}} = \left(\frac{B_{14}}{B_{12}} \right)^{1/3} = 0.9977 \pm 0.0045$$

Worst, this represents a very small departure from square symmetry and places a limit on the extent to which the structure can depart from square symmetry and still fit the observed spectrum.

Other work points to a square structure for the carbon skeleton.⁵ A square configuration for the protons would then be reasonable. Assuming that this is the most stable geometry in the isolated molecule, the following explanation for the distortion is offered: a pressure is exerted on the C-H bonds as the molecule dissolves in the nematic solvent, and this squeezes the protons into a rectangular configuration. This explanation has been used on the distortion of the C-H bonds in the methyl groups of tetramethylsilane in the nematic solvent.⁶ The changes are of the same magnitude ($\sim 0.5^\circ$ change in the C-C-H angle). It is im-

J. D. Fitzpatrick, L. Watts, G. F. Emerson, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 3254 (1965).
L. C. Snyder and S. Meiboom, *J. Chem. Phys.*, **44**, 4057 (1966).

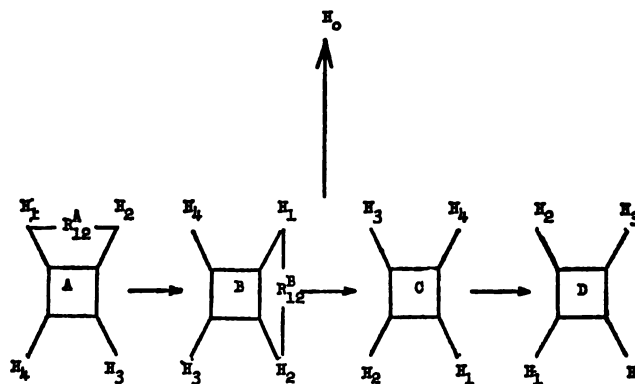


Figure 4. Rotation of the distorted cyclobutadiene ring in an asymmetric liquid crystal force field.

portant to note here that if the line widths were smaller, the maximum separation without resolution (eq 2) and the deviation from square structure would be smaller. It is expected that this would be the case with better sample temperature homogeneity.

(c) Rotationally Averaged Structure. The alternative possibility that the four-proton system is rotating rapidly in an asymmetric force field due to the liquid crystal environment was then considered. It is assumed that the anisotropy in distortion is such that the four protons are squeezed into a rectangle, the long side of which is parallel to the external field direction. The change in proton geometry as the cyclobutadiene ring rotates about its symmetry axis is shown in Figure 4. The four orientations shown are 90° apart in the angle between the external field direction and a given internuclear vector. It can be seen that the para internuclear distance (R_{13} and R_{24}) remains constant in magnitude during a rotation, while the ortho distance (R_{12} , R_{23} , R_{34} , and R_{41}) is averaged

$$\langle R_{\text{ortho}} \rangle = \frac{1}{2}(R_{12}^A + R_{12}^B)$$

This leads to a dipolar Hamiltonian modified for this type of distortion and rotational averaging

$$\mathcal{H}^{(1)} = (\gamma^2 \hbar / 4\pi S_{33}) \left[\langle R_{\text{ortho}}^{-3} \rangle \sum_{i < j} (3I_{ii}I_{jj} - \vec{I}_i \cdot \vec{I}_j) + R_{\text{para}}^{-3} \sum_{k < l} (3I_{kk}I_{ll} - \vec{I}_k \cdot \vec{I}_l) \right]$$

The first term inside the bracket is summed over all ortho nuclear pairs, and the second term over all para nuclear pairs. The spectrum resulting from this Hamiltonian is almost identical with that predicted for a square. The only difference is that the cube of the ratio of the para-to-ortho internuclear distance (derivable from the observed splittings) is not the same as that in a square. For the square, the following relation holds

$$\left(\frac{R_{\text{para}}}{R_{\text{ortho}}} \right)^3 = 2.828$$

From a least-squares analysis of the observed spectrum, the relation between the averaged distances is

$$\left\langle \left(\frac{R_{\text{para}}}{R_{\text{ortho}}} \right)^3 \right\rangle = 2.72 \pm 0.74$$

Without a more detailed knowledge of the force fields which produce the distortion, it is difficult to interpret the above result.

4. Scalar Nuclear Coupling

The scalar nuclear spin-spin coupling has been neglected in the preceding analysis. In a complete analysis, only the most intense line pair (S_3 or R_3 , Table I) is dependent on this parameter. Since the structure is very close to a square, and since the dependence on J_{ij} of the lines in the pair S_3 is much simpler than in the pair R_3 , only S_3 will be considered. When scalar coupling is included in the spin Hamiltonian the line pair, S_3 , is actually two pairs of lines, the separation between the lines in the two pairs (on the same side of the center of symmetry) being given by

$$\frac{1}{2}(\Delta S_{3a} - \Delta S_{3b}) = 3J_{12} = 3J_{\text{ortho}} \quad (\text{cps})$$

where ΔS_{3a} and ΔS_{3b} would be the splittings between the two pairs of lines if they could be resolved. Again, since the most intense lines appear to be singlets (see Figure 2), it is only possible to put a limiting value on their separation (without resolution), and hence on J_{ortho} . Using computer simulation (see section 3b), this was estimated to be 4.0 cps, so that $3J_{\text{ortho}} \leq 4.0$ cps and $J_{\text{ortho}} \leq 1.3$ cps. Because of line-width effects (see preceding section), it is likely that J_{ortho} is even

smaller. This result agrees with experimental observations by Pettit⁷ in the nmr spectrum of a derivative of CIT, in which $J_{\text{ortho}} = 0.0$ cps.

5. Proton Chemical Shift Anisotropy

The center of the nematic spectrum is 10.8 cps downfield from the isotropic spectrum. In order to estimate the proton chemical shift anisotropy, S_{33} , must be known. A value for S_{33} can be calculated by the following procedure: (1) the observed splittings are matched to the theoretical square (see Table Ia) splittings to yield S_{33}/R^3 (this is reasonable since the observed spectrum is very close to that predicted for a square; see section 3a); (2) using C-C and C-H bond lengths of 1.4 and 1.1 Å, respectively, and assuming coplanarity of the carbon and hydrogen skeletons, the interproton distance, R , is found to be 2.96 Å. S_{33} then equals ± 0.02 . Using this value for S_{33} , a chemical shift anisotropy of ± 13 ppm is obtained. This is relatively large, being about the magnitude of shift anisotropies observed for acetylenic protons.⁸

Acknowledgment. The authors are grateful to Professor R. Pettit for supplying the cyclobutadiene compound.

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Energetics of the Ionization and Dissociation of $\text{Mn}_2(\text{CO})_{10}$, $\text{Re}_2(\text{CO})_{10}$, and $\text{ReMn}(\text{CO})_{10}$ ¹

Harry J. Svec and Gregor A. Junk

Contribution from the Institute for Atomic Research and Department of Chemistry, Iowa State University, Ames, Iowa. Received November 5, 1966

Abstract: The mass spectra of $\text{Re}_2(\text{CO})_{10}$, $\text{Mn}_2(\text{CO})_{10}$, and $\text{ReMn}(\text{CO})_{10}$ have been established and compared with the mass spectra of the monometal carbonyls. The electron-impact ionization potentials and the appearance potentials of the major fragment ions have been measured. These data are used to calculate specific and average bond dissociation energies for the ions. Metal-CO bond energies for $\text{Re}_2(\text{CO})_{10}^+$ are shown to be greater than those of $\text{Mn}_2(\text{CO})_{10}^+$. Metal-CO bond energies for $\text{ReMn}(\text{CO})_{10}^+$ are related to those observed for the Re_2 and Mn_2 compounds. A similar relative scale is predicted for the metal-CO bond energies of the neutral molecules. The calculated metal-metal dissociation energies (ev) of the neutral decacarbonyls and their ions to produce $\cdot\text{M}(\text{CO})_5$ and $\text{M}(\text{CO})_5^+$ are: Mn-Mn, 0.96, and $[\text{Mn-Mn}]^+$, 0.82; Re-Re, 2.22, and $[\text{Re-Re}]^+$, 2.08; Re-Mn, 2.67, and $[\text{Re-Mn}]^+$, 2.65. The ionization and dissociation mechanisms are discussed in terms of "isolated ionization" at one of the metal atoms in a dimetal carbonyl, and this model is tested by experimental observations.

Mass spectrometric studies of polynuclear carbonyls^{2,3} and derivatives^{4a} have been published recently. King² has worked primarily with the tri- and tetrametal carbonyls, while Preston and Reed^{4a} and Lewis *et al.*,^{4b} have concentrated their activities on the derivatives of dimetal carbonyls. No ionization

and appearance potential measurements are reported by these authors. Winter and Kiser³ report the ionization potentials of $\text{Mn}_2(\text{CO})_{10}$ and $\text{Co}_2(\text{CO})_8$, and the appearance potentials of some fragment ions from these materials are used to calculate $\Delta H_f(\text{ion})$ values. Fragmentation patterns are also reported. These mass spectral patterns are important for the relationships to the quasi-equilibrium theory⁵ and for structural information.³ However, the energetics of the various fragmentations are also of fundamental importance.

(1) Work was performed in the Ames Laboratory of the U. S. Atomic Energy Commission. Contribution No. 1979.

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ron-impact studies may be used to gain an insight the validity of the proposed bonding in the metal onyls. In addition, conclusions about structure, l on fragmentation pattern correlations, may times be verified by appearance-potential meas- ents. Finally, bond dissociation energies which f thermochemical interest are obtained from elec- impact data.

have measured the energy required to produce ent ions from the decacarbonyls of Re_2 , Mn_2 , ReMn primarily to obtain bond dissociation ener- and to study the mechanisms of ionization and ciation. The strength of the metal-CO bonds and metal-metal bonds reported here may not be ably accurate because of unknown kinetic and tion energies. The possible errors due to these s should be about equal for the series, $\text{Mn}_2(\text{CO})_{10}$, $\text{Re}_2(\text{CO})_{10}$, and $\text{ReMn}(\text{CO})_{10}$. Thus, at least a good ve scale of bond energies is expected.

Experimental Section

Instrumentation. A General Electric mass spectrometer with cations⁴ previously described was used to obtain the data d here. No additional modifications were required for this

Electron-Impact Measurements. The vanishing current⁷ pro- was used to measure the onset potentials. Simultaneous ng of the dimetal compounds and the xenon voltage cali- gas was used.

Materials. The $\text{Re}_2(\text{CO})_{10}$ and $\text{Mn}_2(\text{CO})_{10}$ were purchased from organics, Inc., and used without further purification. The mple of $\text{ReMn}(\text{CO})_{10}$ was kindly furnished by Dr. H. D. University of California, Los Angeles, Calif.

Results and Discussion

Mass Spectra. Line diagrams of the 55-ev mass a are shown in Figure 1. Only the dimetal ent ions are shown since these fragments cause of the total ion current. The total intensity of the metal ions is less than 20% of the total dimetal ntensity for each sample. The ratios of these ities are: $\Sigma \text{Mn}(\text{CO})_x^+ / \Sigma \text{Mn}_2(\text{CO})_x^+ = 0.20$; $\text{CO})_x^+ / \Sigma \text{Re}_2(\text{CO})_x^+ = 0.05$; and $[\Sigma \text{Mn}(\text{CO})_x^+ \text{Re}(\text{CO})_x^+] / \text{ReMn}(\text{CO})_x^+ = 0.12$. The apparent ence for ruptures of the metal-CO bonds is a ion of the lower strength of these bonds compared he metal-metal bonds. The greater intensity of onometal fragments for the manganese compound its that the metal-metal bond is weaker than the e bond. This conclusion based on the 55-ev spectra is supported by appearance-potential rements discussed in the sections on dissociation es. The enhanced tendency to form the higher ragment from $\text{Re}_2(\text{CO})_{10}$ compared to $\text{Mn}_2(\text{CO})_{10}$ s the expected periodic trend in the metal-CO energies as the molecular weight increases within ition metal group.

numerical tabulation of Winters and Kiser⁸ $\text{Mn}_2(\text{CO})_{10}$ has been converted to the per cent total tion and is included as the broken bar graph in 1. Their spectrum contains more of the lighter ragment, and this is probably due to a combina- f sampling and instrumental factors.

A. Junk and H. J. Svec, *Anal. Chem.*, **37**, 1629 (1965); Paper presented at the Twelfth Annual Conference on Mass Spec- y and Allied Topics, Montreal, June 1964.

H. Field and J. L. Franklin, "Electron Impact Phenomena," ic Press Inc., New York, N. Y., 1957, p 30.

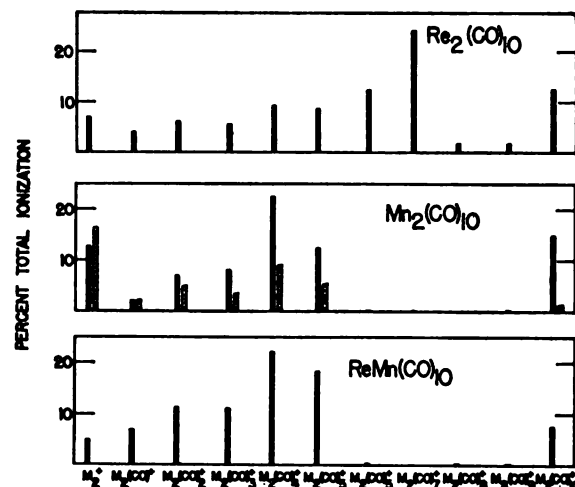


Figure 1. Mass spectra of dimetal decacarbonyls in per cent total ionization: solid bar, this report; broken bar, Winters and Kiser.⁸

The only ion currents observed here which are the result of metastable transitions are recorded in Table I. No attempt was made to observe other metastable ion

Table I. Observed Metastable Transitions

Process	Calcd <i>m/e</i>	Obsd <i>m/e</i>
$\text{Mn}_2(\text{CO})_{10}^+ \rightarrow \text{Mn}(\text{CO})_5^+ +$	97.5	97.5
$\text{Mn}(\text{CO})_5^+$		
$\text{Mn}_2(\text{CO})_8^+ \rightarrow \text{Mn}_2(\text{CO})_7^+ + \text{CO}$	169.5	169.3
$\text{Mn}_2(\text{CO})_6^+ \rightarrow \text{Mn}_2(\text{CO})_5^+ + \text{CO}$	197.1	197.0

currents by varying instrumental parameters such as sensitivity and repeller potential. Others undoubtedly exist, and the observation of these are important because they support the decomposition proposals^{3,4b,5,8,9} of successive loss of CO groups in the unimolecular dissociation of metal carbonyls.

A possible rearrangement ion current was observed in the fragmentation of $\text{ReMn}(\text{CO})_{10}$. Seven per cent of the total is due to a $[\text{Re}(\text{CO})_6]^+$ ion current. Rearrangements involving migrations other than hydrogen are rare. Only one other such rearrangement, the OH group migration to form the *m/e* 46 ion current from amino acids,¹⁰ has been positively confirmed at our laboratory. However, recent research reports from

Table II. Ionization Potentials of Dimetal Decacarbonyls

Sample	Ionization potential, ev		
	This report	Winters and Kiser ⁸	Metal atoms
$\text{Mn}_2(\text{CO})_{10}$	8.58	8.55	7.43
$\text{Re}_2(\text{CO})_{10}$	8.27	...	7.87
$\text{ReMn}(\text{CO})_{10}$	8.15	...	7.43, 7.87

(8) An extensive report of observed metastable transitions of some monometal carbonyls has recently been published by R. W. Winters and J. H. Collins, *J. Phys. Chem.*, **70**, 2057 (1966).

(9) B. Cantone, F. Grasso, and S. Pignataro, *J. Chem. Phys.*, **44**, 3115 (1966).

(10) G. A. Junk and H. J. Svec, *J. Am. Chem. Soc.*, **85**, 839 (1963).

Table III. Appearance Potentials and Heats of Formation of the $M_x(\text{CO})_z^+$ Ions from $\text{Mn}_x(\text{CO})_{10}$, $\text{Re}_x(\text{CO})_{10}$, and $\text{ReMn}(\text{CO})_{10}$

Ion	AP, ev ^a	Process	$\Delta H_f(\text{ion})$, kcal/mole
Mn^+	22.13	$\text{Mn}_2(\text{CO})_{10}^b \rightarrow \text{Mn}^+ + \text{Mn} + 10(\text{CO})?$?
$\text{Mn}(\text{CO})^+$	18.21	$\rightarrow \text{Mn}(\text{CO})^+ + \text{Mn} + 9(\text{CO})$?
$\text{Mn}(\text{CO})_2^+$	14.80	$\rightarrow \text{Mn}(\text{CO})_2^+ + ?$?
$\text{Mn}(\text{CO})_3^+$	9.40	$\rightarrow \text{Mn}(\text{CO})_3^+ + \text{Mn}(\text{CO})_2$?
Mn_2^+	18.73	$\rightarrow \text{Mn}_2^+ + 10(\text{CO})$	309 (312) ^c
$\text{Mn}_2(\text{CO})_2^+$	16.43	$\rightarrow \text{Mn}_2(\text{CO})_2^+ + 8(\text{CO})$	201
$\text{Mn}_2(\text{CO})_3^+$	15.34	$\rightarrow \text{Mn}_2(\text{CO})_3^+ + 7(\text{CO})$	152
$\text{Mn}_2(\text{CO})_4^+$	13.98	$\rightarrow \text{Mn}_2(\text{CO})_4^+ + 6(\text{CO})$	94 (95)
$\text{Mn}_2(\text{CO})_5^+$	11.91	$\rightarrow \text{Mn}_2(\text{CO})_5^+ + 5(\text{CO})$	20 (37)
$\text{Mn}_2(\text{CO})_{10}^+$	8.58	$\rightarrow \text{Mn}_2(\text{CO})_{10}^+$	-188 (-189)
Re^+	37.55	$\text{Re}_2(\text{CO})_{10}^d \rightarrow \text{Re}^+ + ?$?
$\text{Re}(\text{CO})_2^+$	10.35	$\rightarrow \text{Re}(\text{CO})_2^+ + \text{Re}(\text{CO})_2$...
$\text{Re}(\text{CO})_3^+$	13.30	$\rightarrow \text{Re}(\text{CO})_3^+ + ?$?
Re_2^+	28.96	$\rightarrow \text{Re}_2^+ + 10(\text{CO})$	319
$\text{Re}_2(\text{CO})^+$	26.26	$\rightarrow \text{Re}_2(\text{CO})^+ + 9(\text{CO})$	231
$\text{Re}_2(\text{CO})_2^+$	23.55	$\rightarrow \text{Re}_2(\text{CO})_2^+ + 8(\text{CO})$	142
$\text{Re}_2(\text{CO})_3^+$	21.46	$\rightarrow \text{Re}_2(\text{CO})_3^+ + 7(\text{CO})$	67
$\text{Re}_2(\text{CO})_4^+$	19.31	$\rightarrow \text{Re}_2(\text{CO})_4^+ + 6(\text{CO})$	-9
$\text{Re}_2(\text{CO})_5^+$	16.71	$\rightarrow \text{Re}_2(\text{CO})_5^+ + 5(\text{CO})$	-95
$\text{Re}_2(\text{CO})_6^+$	15.01	$\rightarrow \text{Re}_2(\text{CO})_6^+ + 4(\text{CO})$	-160
$\text{Re}_2(\text{CO})_7^+$	13.55	$\rightarrow \text{Re}_2(\text{CO})_7^+ + 3(\text{CO})$	-220
$\text{Re}_2(\text{CO})_8^+$	10.89	$\rightarrow \text{Re}_2(\text{CO})_8^+ + 2(\text{CO})$	-308
$\text{Re}_2(\text{CO})_9^+$	9.57	$\rightarrow \text{Re}_2(\text{CO})_9^+ + \text{CO}$	-365
$\text{Re}_2(\text{CO})_{10}^+$	8.27	$\rightarrow \text{Re}_2(\text{CO})_{10}^+$	-421
Mn^+	25.67	$\text{ReMn}(\text{CO})_{10}^e \rightarrow \text{Mn} + ?$?
Re^+	30.93	$\rightarrow \text{Re} + ?$?
$\text{Mn}(\text{CO})^+$	19.05	$\rightarrow \text{Mn}(\text{CO})^+ + ?$?
$\text{Re}(\text{CO})_2^+$	10.80	$\rightarrow \text{Re}(\text{CO})_2^+ + \text{Mn}(\text{CO})_2$...
$\text{Re}(\text{CO})_3^+$	9.36	$\rightarrow \text{Re}(\text{CO})_3^+ + \text{Mn}(\text{CO})_3 (?)$?
ReMn^+	25.98	$\rightarrow \text{ReMn}^+ + 10(\text{CO})$	314
$\text{ReMn}(\text{CO})^+$	23.00	$\rightarrow \text{ReMn}(\text{CO})^+ + 9(\text{CO})$	219
$\text{ReMn}(\text{CO})_2^+$	19.75	$\rightarrow \text{ReMn}(\text{CO})_2^+ + 8(\text{CO})$	118
$\text{ReMn}(\text{CO})_3^+$	16.94	$\rightarrow \text{ReMn}(\text{CO})_3^+ + 7(\text{CO})$	26
$\text{ReMn}(\text{CO})_4^+$	14.65	$\rightarrow \text{ReMn}(\text{CO})_4^+ + 6(\text{CO})$	-53
$\text{ReMn}(\text{CO})_5^+$	12.12	$\rightarrow \text{ReMn}(\text{CO})_5^+ + 5(\text{CO})$	-137
$\text{ReMn}(\text{CO})_{10}^+$	8.16	$\rightarrow \text{ReMn}(\text{CO})_{10}^+$	-360

^a Reproducibility of all AP values reported here are from ± 0.05 to 0.2 ev. ^b ΔH_f° of $\text{Mn}_2(\text{CO})_{10} = -385.9$ kcal/mole from calorimetric measurements: F. A. Cotton and K. R. Mouchamp, *J. Chem. Soc.*, 533 (1960). ^c Values calculated from Winters and Kiser data.³ ^d ΔH_f° of $\text{Re}_2(\text{CO})_{10} \approx -611$ kcal/mole from AP data. No calorimetric value available. ^e ΔH_f° of $\text{ReMn}(\text{CO})_{10} \approx -548$ kcal/mole from AP data. No calorimetric value available.

Stanford¹¹ suggest that migration of bulky groups may occur more frequently than previously suspected. The absence of a comparable rearrangement ion current (if indeed the observed ion current is the result of a rearrangement process) due to a $\text{M}(\text{CO})_6^+$ fragment in the mass spectrum of either $\text{Mn}_2(\text{CO})_{10}$ or $\text{Re}_2(\text{CO})_{10}$ suggests that the structure of $\text{ReMn}(\text{CO})_{10}$ may be considerably different in the spatial configuration of the CO groups.

Ionization Potentials. The ionization potentials are recorded in Table II. Our value for $\text{Mn}_2(\text{CO})_{10}$ is in excellent agreement with the value reported by Winters and Kiser.³ The ionization potentials of the metal atoms are listed in column 4 for comparison. Since the CO ionization potential is about 14.0 ev, it appears as if ionization of these metal carbonyls involves removal of one of the valence electrons from the metal atom.

Appearance Potentials. The appearance potentials for the major fragment ions are listed in column 2 of Table III. Values of $\Delta H_f(\text{ion})$ are tabulated in column 4. For comparison, values calculated from the appearance-potential data of Winters and Kiser³ are given in parentheses. The decomposition reactions for forming the various dimetal ions are uncomplicated, and the processes listed in column 3 are undoubtedly

(11) P. Brown and C. Djerassi, *J. Am. Chem. Soc.*, 88, 2469 (1966), and references cited therein.

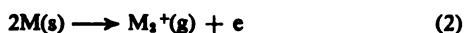
correct. However, the reactions for forming the mono-metal fragments are questionable due to at least two possible reaction paths. Hence, no $\Delta H_f(\text{ion})$ values are recorded for these fragment ions. Calorimetric measurements on $\text{Re}_2(\text{CO})_{10}$ and $\text{ReMn}(\text{CO})_{10}$ have not yet been reported so ΔH_f° values for these materials are not available. We have estimated some values (see Standard Heat of Formation section) and these are used in the calculation of the $\Delta H_f(\text{ion})$ values given for the $\text{Re}_2(\text{CO})_z^+$ and $\text{ReMn}(\text{CO})_z^+$ fragment ions. The appearance potentials for the $\text{M}_x(\text{CO})_z^+$ fragment ions listed in Table III are plotted on the energy diagrams shown in Figure 2. The higher energy required to form each successively lighter fragment ion is experimental confirmation for the proposed stepwise decomposition mechanism.

Standard Heat of Formation Calculations. The $\Delta H_f(\text{Mn}_2^+)_g$ listed in Table III is 309 kcal/mole or 13.43 ev. This value can be used to approximate values for $\Delta H_f(\text{Re}_2^+)_g$ and $\Delta H_f(\text{ReMn}^+)_g$ from the fragmentation of their respective decacarbonyls. The approximation is based on the 6.00-ev difference between the $\Delta H_f^\circ(\text{Mn}_2^+)_g = 13.43$ ev and the ionization potential of $\text{Mn}(g) = 7.43$ ev. The difference between the ionization potential of $\text{Re}(g)$ and the $\Delta H_f(\text{Re}_2^+)_g$ is also assumed to be 6.00 ev. Since the ionization potential of $\text{Re}(g)$ is 7.87 ev, the value of $\Delta H_f(\text{Re}_2^+)_g$ is estimated to be 13.87 ev. The $\Delta H_f(\text{ReMn}^+)_g$ value is then in-

terpolated to be intermediate between the values of Re_2^+ and Mn_2^+ or 13.66 ev. These $\Delta H_f(\text{ion})$ values and the appearance potentials of Re_2^+ and ReMn^+ are used in the equation

$$\Delta H_f(\text{M}_2^+) = \text{AP}(\text{M}_2^+) - 10[\Delta H_f^\circ(\text{CO})] + \Delta H_f^\circ[\text{M}_2(\text{CO})_{10}]_g \quad (1)$$

to calculate the standard heats of formation. The calculated values are -611 kcal/mole for $\text{Re}_2(\text{CO})_{10}$ and -548 kcal/mole for $\text{ReMn}(\text{CO})_{10}$. It is difficult to estimate the probable error in these values. In the interpolation to obtain the value for $\Delta H_f(\text{Re}_2^+)_g$, the heat of sublimation of Re and Mn are assumed to be equal. It is also assumed that the metal-metal bond strengths are equal. Both assumptions are erroneous since the ΔH_{subl} for Re and the bond energy of Re-Re are both greater than the corresponding values for Mn. However, in the process



errors due to the assumptions tend to cancel one another. Since the bond-energy error is probably greatest, we consider these heat of formation values for $\text{Re}_2(\text{CO})_{10}$ and $\text{ReMn}(\text{CO})_{10}$ to be maximum (negative) values.

Metal-CO Dissociation Energies. The specific bond dissociation energies for the various ions have been calculated for the AP data and are listed in Table IV.

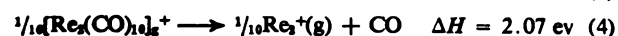
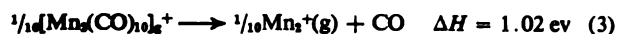
Table IV. Specific Bond Dissociation Energies of Ions

Dissociation process	Dissociation energy, ev		
	Mn_2	Re_2	ReMn
$\text{M}_2(\text{CO})_{10}^+ \rightarrow \text{M}_2(\text{CO})_9^+$	0.7 ^a	1.3	0.8 ^a
$\text{M}_2(\text{CO})_9^+ \rightarrow \text{M}_2(\text{CO})_8^+$	0.7 ^a	1.3	0.8 ^a
$\text{M}_2(\text{CO})_8^+ \rightarrow \text{M}_2(\text{CO})_7^+$	0.7 ^a	2.7	0.8 ^a
$\text{M}_2(\text{CO})_7^+ \rightarrow \text{M}_2(\text{CO})_6^+$	0.7 ^a	1.5	0.8 ^a
$\text{M}_2(\text{CO})_6^+ \rightarrow \text{M}_2(\text{CO})_5^+$	0.7 ^a	1.7	0.8 ^a
$\text{M}_2(\text{CO})_5^+ \rightarrow \text{M}_2(\text{CO})_4^+$	2.1	2.6	2.5
$\text{M}_2(\text{CO})_4^+ \rightarrow \text{M}_2(\text{CO})_3^+$	1.4	2.2	2.3
$\text{M}_2(\text{CO})_3^+ \rightarrow \text{M}_2(\text{CO})_2^+$	1.0	2.1	2.8
$\text{M}_2(\text{CO})_2^+ \rightarrow \text{M}_2(\text{CO})^+$	1.2	2.7 ^b	3.2
$\text{M}_2(\text{CO})^+ \rightarrow \text{M}_2^+$	1.2	2.7 ^b	3.0

^a These are average values calculated from the dissociation of the first five CO groups. ^b These are average values calculated from the dissociation of the last two CO groups.

The almost equal energy required to dissociate the first five metal-CO bonds from $\text{ReMn}(\text{CO})_{10}^+$ and $\text{Mn}_2(\text{CO})_{10}^+$ suggests that these dissociations in $\text{ReMn}(\text{CO})_{10}^+$ are due to Mn-CO bond ruptures. The near-equal energy required to dissociate the last five CO groups from $\text{ReMn}(\text{CO})_{10}^+$ and $\text{Re}_2(\text{CO})_{10}^+$ agrees with this suggested process. The negligible intensities of fragment ions between $\text{M}_2(\text{CO})_{10}^+$ and $\text{M}_2(\text{CO})_5^+$ (see Figure 1) for both the Mn_2 and ReMn decacarbonyls also support this proposal.

The average metal-CO bond dissociation energies from Table IV are



It is not possible to calculate the dissociation energies of the neutral molecules because of unknown ionization potentials and valence-state excitation energies for

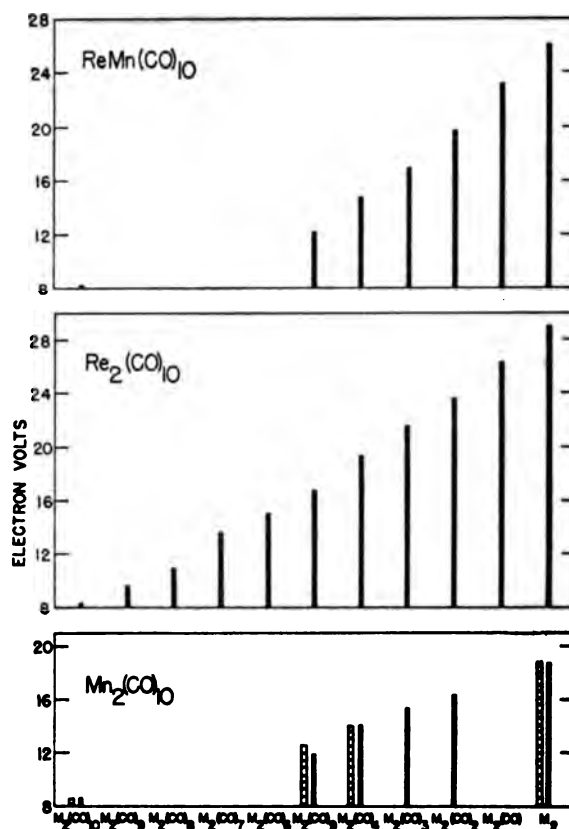


Figure 2. Appearance potentials of $\text{M}_2(\text{CO})_{10}^+$ ions from $\text{Mn}_2(\text{CO})_{10}$, $\text{Re}_2(\text{CO})_{10}$, and $\text{ReMn}(\text{CO})_{10}$: solid bar, this report; broken bar, Winters and Kiser.³

Re_2 , Mn_2 , and ReMn . However, it was shown for all the monometal carbonyls¹² that the bond dissociation energies of the ions are 0.3 to 0.5 ev per bond higher than the neutral dissociation energies. If this difference is true for the dimetal carbonyls, the neutral dissociation energies are 0.6, 1.7, and 1.4 ev per metal-CO bond in $\text{Mn}_2(\text{CO})_{10}$, $\text{Re}_2(\text{CO})_{10}$, and $\text{ReMn}(\text{CO})_{10}$.

Metal-Metal Dissociation Energies. The ionization potential of the $\cdot\text{M}(\text{CO})_5$ radical and the appearance potential of $\text{M}(\text{CO})_5^+$ from $\text{M}_2(\text{CO})_{10}$ are required to calculate the metal-metal dissociation energy of the decacarbonyls according to the equation

$$D[(\text{CO})_5\text{M}-\text{M}(\text{CO})_5] = \text{AP}[\text{M}(\text{CO})_5^+] - \text{IP}[\text{M}(\text{CO})_5] \quad (6)$$

Bidinosti and McIntyre¹³ have recently measured the ionization potential of the $\cdot\text{Mn}(\text{CO})_5$ radical and report a value of 8.44 ev, but no measurement of the ionization potential of the $\cdot\text{Re}(\text{CO})_5$ radical is currently available. However, the difference in the ionization potentials of $\cdot\text{Mn}(\text{CO})_5 = 8.44$ ev and $\text{Mn}_2(\text{CO})_{10} = 8.58$ ev is only 0.14 ev. We have assumed that this relationship is valid for $\cdot\text{Re}(\text{CO})_5$ and $\text{Re}_2(\text{CO})_{10}$, and the ionization potential of $\cdot\text{Re}(\text{CO})_5$ is estimated to be 0.14 ev below the ionization potential of $\text{Re}_2(\text{CO})_{10}$ (see Table II) or 8.13 ev. These values for the ionization potentials of $\cdot\text{Mn}(\text{CO})_5$ and $\cdot\text{Re}(\text{CO})_5$ radicals and the appearance potentials for $\text{Re}(\text{CO})_5^+$ and $\text{Mn}(\text{CO})_5^+$ (from Table I) were used in eq 6 to calculate the metal-metal dissociation energies listed in Table V. As expected, the Re-Re

(12) Unpublished work from this laboratory.

(13) D. R. Bidinosti and N. S. McIntyre, Chem. Commun., 555 (1966).

Table V. Metal-Metal Bond Dissociation Energies for $M_2(CO)_{10}$ (Ions and Neutral Molecules)

Process	ΔH , ev
$(CO)_5Mn-Mn(CO)_5 \rightarrow Mn(CO)_5 + Mn(CO)_5$	0.96 ^a
$[(CO)_5Mn-Mn(CO)_5]^+ \rightarrow Mn(CO)_5 + Mn(CO)_5^+$	0.82
$(CO)_5Re-Re(CO)_5 \rightarrow Re(CO)_5 + Re(CO)_5$	2.22
$[(CO)_5Re-Re(CO)_5]^+ \rightarrow Re(CO)_5 + Re(CO)_5^+$	2.08
$(CO)_5Re-Mn(CO)_5 \rightarrow Re(CO)_5 + Mn(CO)_5$	2.67
$[(CO)_5Re-Mn(CO)_5]^+ \rightarrow Re(CO)_5^+ + Mn(CO)_5$	2.65
$[(CO)_5Re-Mn(CO)_5]^+ \rightarrow Re(CO)_5 + Mn(CO)_5^+$... ^b

^a This value compares favorably with the 0.82-ev value reported by Bidinosti and McIntyre¹³ and is considerably lower than the 1.48-ev value calculated by Cotton and Mouchamp (see footnote *b* Table III) from calorimetric measurements. While the explanation for this discrepancy is not yet resolved, the relative scale of bond energies reported here should be reasonably accurate. ^b The low intensity of $Mn(CO)_5^+$ ion current made appearance-potential measurement unfeasible. For this reason no internal check on the $ReMn$ dissociation energy calculated from this process was possible.

bond dissociation energy turns out to be greater than the $Mn-Mn$ bond dissociation energy. The explanation for the even higher value for the bond energy of $Re-Mn$ may be related to what was observed by Saalfeld and Svec¹⁴ with the dihydride, $H_2Si-GeH_2$, in which overlap of vacant d orbitals in the mixed metal compounds tend to stabilize the metal-metal bond.¹⁵ The difference in the electronegativities of Mn and Re may also contribute to the strength of the metal-metal bond in the mixed metal compound.

The metal-metal bond energy values of the ions follow the same trend as the neutral molecules, with the mixed compound having the highest value. Although the ions have less bond energy in each case, the difference is rather small indicating that charge has relatively little effect on the metal-metal bond.

Ionization and Dissociation Mechanism. It has been suggested that ionization of metal carbonyls¹⁶ involves removal of one of the valence electrons from the metal atom. The highest probability for localization of the resultant positive charge from an "isolated ionization concept"¹⁷ is therefore on the metal atom from which the electron is removed. To test this suggestion, the average dissociation energies of the metal-CO bonds from $M(CO)_6$, $M(CO)_6^+$, and $M_2(CO)_{10}^+$ have been investigated. These dissociation energies, calculated from the appearance-potential data in Tables III and IV and our studies of monometal carbonyls,¹² are listed in column 2 of Table VI. The estimated average dissociation energies are taken from chromium and tungsten hexacarbonyl data.¹² The average metal-CO bond dissociation energy for $Cr-CO$ and $Cr-CO^+$ are taken to be roughly equal to that expected for

(14) F. A. Saalfeld and H. J. Svec, *J. Phys. Chem.*, **70**, 1753 (1966).

(15) The relative bond strengths, $Mn-Re > Re-Re > Mn-Mn$, reported here are in agreement with the findings of H. M. Gager, J. Lewis, and M. J. Ware, *Chem. Commun.*, 616 (1966).

(16) A. Foffani and S. Pignataro, *Z. Physik. Chem. (Frankfurt)*, **45**, 79 (1965).

(17) H. J. Svec and G. A. Junk, *J. Am. Chem. Soc.*, **89**, 790 (1967).

Table VI. Observed and Estimated Dissociation Energies of $M-CO$ Bonds in Dimetal Decacarbonyls

Proposed process	Dissociation energy, ev	
	Obsd av	Estd av ^a
$(CO)_5Mn-Mn^+(CO)_5 \rightarrow Mn-Mn^+(CO)_5 + 5(CO)$	0.7	1.1 ^b
$Mn-Mn^+(CO)_5 \rightarrow Mn-Mn^+ + 5(CO)$	1.4	1.4 ^c
$(CO)_5Re-Re^+(CO)_5 \rightarrow Re-Re^+(CO)_5 + 5(CO)$	1.7	1.9 ^d
$Re-Re^+(CO)_5 \rightarrow Re-Re^+ + 5(CO)$	2.5	2.3 ^e
$(CO)_5Mn-Re^+(CO)_5 \rightarrow Mn-Re^+(CO)_5 + 5(CO)$	0.8	1.1 ^b
$Mn-Re^+(CO)_5 \rightarrow Mn-Re^+ + 5(CO)$	2.7	2.3 ^e

^a Taken from unpublished data from this laboratory. ^b The ΔH for the process: $1/6Cr(CO)_6 \rightarrow 1/6Cr + CO$. ^c The ΔH for the process: $1/6Cr^+(CO)_6 \rightarrow 1/6Cr^+ + CO$. ^d The ΔH for the process: $1/6W(CO)_6 \rightarrow 1/6W + CO$. ^e The ΔH for the process: $1/6W^+(CO)_6 \rightarrow 1/6W^+ + CO$.

$Mn-CO$ and $Mn-CO^+$. The same approximation is made in the case of W and Re . The proposed bond ruptures are listed in column 1 of Table VI. No preferred charge localization exists between the metal atoms of the symmetrical carbonyls, and the choice listed is arbitrary. However, the charge is shown on the Re atom in the case of $ReMn(CO)_{10}$. The reason for this choice is the lower ionization potential observed for $Re_2(CO)_{10}$ compared with $Mn_2(CO)_{10}$ and the expectation that the lower energy process should occur preferentially. The agreement of the observed dissociation energies and the crudely estimated values suggests that the model proposed for ionization and dissociation is correct.

The almost equal average bond dissociation energy for the loss of the first five CO groups from $Mn_2(CO)_{10}$ (0.7 ev per bond) and $ReMn(CO)_{10}$ (0.8 ev per bond) supports this proposal, as does the close agreement of the dissociation of the last five CO groups from $Re_2(CO)_{10}$ (2.5 ev per bond) and $ReMn(CO)_{10}$ (2.7 ev per bond). Other observations which support this localized charge proposal are: the similarity of the mass spectra of $ReMn(CO)_{10}$ to $Mn_2(CO)_{10}$ from the parent ion to the $M_2(CO)_5^+$ ion; the similarity of the remainder of the spectrum of $ReMn(CO)_{10}$ to that observed for the $Re_2(CO)_5^+$ to Re_2^+ fragment ions from $Re_2(CO)_{10}$; and the high intensity of the $Re(CO)_5^+$ (100 units) relative to the $Mn(CO)_5^+$ (<1 unit). Thus, we conclude that the site of ionization of these complex molecules can be considered to be "isolated" and that low-energy processes are favored in the fragmentation; i.e., the metal-CO bonds of the uncharged metal atom are the first to be ruptured. This observation is of fundamental mechanistic importance and should prove useful in future interpretations of the mass spectra of polymetal carbonyls and ligand-substituted metal carbonyls.

Acknowledgments. The authors are indebted to Dr. H. D. Kaesz of the University of California, Los Angeles, Calif., for furnishing the pure sample of $ReMn(CO)_{10}$ and to Mr. William Stebbings for assisting in the data accumulation.

The Catalytic Addition of Fluorine to a Carbonyl Group. Preparation of Fluoroxy Compounds¹

Max Lustig, A. R. Pitochelli, and John K. Ruff

Contribution from Rohm and Haas Company, Redstone Research Laboratories, Huntsville, Alabama 35807. Received November 21, 1966

Abstract: The low-temperature metal fluoride catalytic fluorination of carbonyl halides and fluoroalkyl acid fluorides provides a simple method for the preparation of fluoroxyfluoroalkanes in high yields. In addition to some known fluoroxy derivatives the new compounds, 1-fluoroxy-1,1,2,2-tetrafluoroethane, $\text{FOCF}_2\text{CF}_2\text{H}$, octafluoro-1,4-bis(fluoroxy)butane, $\text{FO}(\text{CF}_2)_4\text{OF}$, decafluoro-1,5-bis(fluoroxy)pentane, $\text{FO}(\text{CF}_2)_5\text{OF}$, 1-fluoroxy-2-difluoroaminotetrafluoroethane, $\text{CF}_2(\text{NF}_2)\text{CF}_2\text{OF}$, and 1-fluoroxy-2-difluoroaminohexafluoropropane, $\text{CF}_3\text{CF}(\text{NF}_2)\text{CF}_2\text{OF}$, are also prepared by this method. Some chemical and physical properties of the new compounds are given.

ough the first example of a fluoroxyalkane has been known for 19 years,² it was not until recently other members of this class of compounds have been prepared.^{3,4} The techniques of fluorination employed in these preparations have varied from the high-temperature, catalyzed, flow fluorination of CH_3OH , or COF_2 to produce CF_3OF to the lower temperature fluorination of alcohols.^{3,4} A new low-temperature fluorination procedure has been developed which, in the presence of a suitable catalyst, permits the condensation of fluorine across a carbon-oxygen double bond. Fluoroxyfluoroalkanes can be prepared by this method in high yields.

Experimental Section

Materials. The perfluoroalkyl acid fluorides were prepared from the corresponding chlorides by reaction with KF in 3-methylphenyl hexafluoroacetone was obtained from General Chemical Co., Allied Chemical Corp., and used without further purification. The difluoroamino acid fluoride derivatives were available from other study.⁵

Safety. Explosions have been encountered on occasion upon the use of the new bis- and α -difluoroaminohypofluorites. Workers should be properly shielded.

General Preparative Procedure. A 10-g sample of cesium fluoride, which had been dried overnight at 175–200° under vacuum and ground in a nitrogen-filled drybox, was loaded into a 150-ml Hoke cylinder containing approximately 30 1/8-in. diameter stainless steel balls. The cylinder was then shaken for several hours to ensure fine grinding of the cesium fluoride. A 1.72-mmol of COF_2 was condensed into the reactor at –196°, and nitrogen (1.73 mmoles) was allowed to expand into the reactor at room temperature. The reactor was then placed in a –78° dry ice/acetone bath and allowed to stand for 4 hr. After cooling the reactor to –78°, any unreacted fluorine was pumped out through a trap containing KOH. The condensable product was then removed by distillation. This procedure was employed for all the compounds at the same temperature and for the same time interval above except for $\text{HCF}_2\text{C}(\text{O})\text{F}$ (cf. Discussion), which was allowed to react with fluorine at 0°. A summary of the experimental data is given in Table I.

General Purification Procedure. Reaction mixtures containing known compounds CF_3OF , $\text{C}_2\text{F}_5\text{OF}$, $\text{C}_3\text{F}_7\text{OF}$, and $(\text{CF}_3)_2\text{CHO}$ were prepared for analysis first by subjecting them to vapor chromatography using the column recommended in the literature.⁶ The ¹⁹F nmr and infrared spectra of the pure components were then compared with those published.³ Purification of the fluoroxyfluoroalkyl compounds was performed by vacuum-

line fractionation. The butane derivative was retained in a trap set at –126° while the pentane was held in a –95° trap. Any unreacted acyl fluoride was removed by allowing the mixture to stand over water at room temperature for no longer than 0.5 hr. The purification of $\text{CF}_3\text{CF}(\text{NF}_2)\text{CF}_2\text{OF}$ was accomplished by vacuum-line fractionation through a trap set at –126° in which it was retained. No purification of $\text{NF}_2\text{CF}_2\text{CF}_2\text{OF}$ was necessary since it was obtained in quantitative yield.

Analyses. Although some analyses are given, they were generally difficult to obtain because several of the samples exploded during handling. For the fluorine analysis, samples were reduced with lithium in *n*-propylamine within high-pressure Pyrex tubes containing Fischer-Porter Teflon valves. Conventional techniques were then employed. The Dumas method was used to determine nitrogen in gaseous samples; carbon was determined by the conventional Pregl combustion method using fresh MgO mixed with the catalyst in the combustion tube (see Table I for some results).

Molecular Weights. Molecular weights were obtained by vapor density measurements (refer to Table I).

Melting Points. The melting points of $\text{FO}(\text{CF}_2)_4\text{OF}$ and $\text{FO}(\text{CF}_2)_5\text{OF}$ were measured by immersing samples contained in 5-mm o.d. Pyrex tubes into a 1:1 v/v pentane-isopentane cold bath which warmed at a rate of ca. 0.5°/min (see Table I).

Infrared Spectra. The infrared spectra of the new materials were obtained using gaseous samples in cells having a 10-cm path length employing a Perkin-Elmer Model 21 spectrometer. The following are the frequencies in cm^{-1} (relative intensities) for $\text{FO}(\text{CF}_2)_4\text{OF}$: 1333 (m), 1284 (s), 1250 (sh), 1227 (s), 1203 (sh), 1176 (m), 1136 (s), 1096 (w), 1061 (w), 962 (m), 917 (m), 886 (s), 862 (m), 821 (w), 803 (m), 782 (s), 763 (s), 738 (w), 717 (w), 680 (w); for $\text{FO}(\text{CF}_2)_5\text{OF}$: 1348 (sh), 1332 (m), 1258 (sh), 1227 (vs, complex), 1174 (s), 1148 (s), 1110 (m), 1036 (w), 1014 (w), 897 (wm), 877 (wm), 855 (wm), 820 (w), 793 (wm), 778 (wm), 752 (s), 727 (ms), 705 (w), 694 (w); for $\text{CF}_2(\text{NF}_2)\text{CF}_2\text{OF}$: 1333 (ms), 1253 (vs), 1218 (vs), 1176 (sh), 1159 (s), 8018 (ms), 977 (s), 936 (s), 893 (wm), 881 (w), 781 (s); and for $\text{CF}_3\text{CF}(\text{NF}_2)\text{CF}_2\text{OF}$: 1311 (ms), 1277 (s), 1252 (vs), 1183 (m), 1136 (wm), 1099 (w, complex), 1011 (m), 968 (sh), 963 (m), 932 (m), 984 (wm, complex), 813 (wm), 766 (w), 741 (wm).

The infrared spectra of all the new compounds exhibit multiple bands in the region (1400–1000 cm^{-1}) which are assigned to C–F stretching vibrations. They also show several weak-to-medium intensity absorptions in the O–F⁺ and C–O⁺ domain (917–855 cm^{-1}). The difluoroamino derivatives have absorptions between 1020 and 925 cm^{-1} , and some of these may be assigned to the N–F stretching motions.

¹⁹F Nmr Spectra. The ¹⁹F nmr spectra were obtained on CCl_4F solutions of the fluoroxy derivatives at room temperature employing a Varian Model V4310 spectrometer operating at 40 Mc at room temperature. Resonances for $\text{FO}(\text{CF}_2)_4\text{OF}$ are located at δ –146.7, 92.5, 122.7 having an area ratio of 1.0:2.0:2.1, respectively, while the spectrum of $\text{FO}(\text{CF}_2)_5\text{OF}$ shows absorptions at δ –146.9, 92.9, and 124.0 having the respective area ratio, 1.0:2.1:3.1. 1-Fluoroxy-2-difluoroaminotetrafluoroethane has resonances at δ –147.0, –17.3, 92.5, and 115.2; the area ratio was measured to be 1.0:1.8:1.9:1.9, respectively, and $\text{CF}_3\text{CF}(\text{NF}_2)\text{CF}_2\text{OF}$ has

¹For a preliminary report on this method of preparation, see J. K. Ruff, A. R. Pitochelli, and M. Lustig, *J. Am. Chem. Soc.*, **88**, 4531 (1966).
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Table I. Preparation of Fluoroxo Compounds

Substrate (mmoles)	Fluorine, mmoles	Product(s) (mmoles)	Vapor density mol wt		Additional data
			Calcd	Found	
COF ₂ (1.72)	1.73	CF ₃ OF (1.67)	104	105	Trace of CF ₄ present
CF ₃ C(O)F (1.59)	1.61	C ₂ F ₅ OF (1.53)	154	151	Traces of CF ₄ and C ₂ F ₄
C ₂ F ₅ C(O)F (1.82)	1.83	C ₂ F ₅ OF (1.77)	204	202	
(CF ₃) ₂ CO (1.05)	1.07	(CF ₃) ₂ CFOF (1.03)	204	205	Trace of CF ₄
F(O)C(CF ₃) ₂ C(O)F (1.38)	2.76	FO(CF ₃) ₂ OF (1.13)	270	273	Anal. Calcd for C ₄ F ₁₀ O ₃ : C, 18.07; F, 70.3. Found: C, 17.78; F, 66.5. Mp -119 ± 0.6° Mp -102.9 ± 0.3°
F(O)C(CF ₃) ₂ C(O)F (0.427)	0.854	FO(CF ₃) ₂ OF (0.425)	320	316	
NF ₂ CF ₂ C(O)F (0.22)	0.25	NF ₂ CF ₂ CF ₂ OF (0.22)	187	184	
CF ₃ CF(NF ₂)C(O)F (1.80)	2.01	CF ₃ CF(NF ₂)CF ₂ OF (1.71)	237	239	Anal. Calcd for C ₃ F ₈ NO: C, 15.19; N, 5.91. Found: C, 15.47; N, 6.21.
FCONF ₂ (0.756)	0.970	NF ₂ COF ₂ CF ₂ OF (0.753) (0.551) (0.200)			
FCONF ₂ (0.872)	10.5	NF ₂ CF ₂ OF (0.871) (0.872)			
COCl ₂ (1.13)	1.15	COCl ₂ Cl ₂ CF ₂ OF (0.55) (0.54) (0.57)			
CO ₂ (1.47)	3.40	CF ₃ (OF) ₂ (1.44)	120	118	Trace of CO ₂

bands at ϕ -150.7, -24.3, 72.8, 86.1, and 167.2 (area ratio 1.0:1.8:3.1:2.01:1.0, respectively).

The nmr spectra of these compounds are rather diagnostic. They all have resonances near ϕ -150 which are assigned to the fluoroxo fluorine atoms. Both CF₃(NF₂)CF₂OF and CF₃CF(NF₂)CF₂OF have an absorption assigned to the NF₂ group fluorine atoms at -17.3 and -24.3, respectively. The NF₂ group fluorine resonance lies at higher field when the group is bound to a CF₃ than when it is attached to a CF. The positions of these N-F fluorine absorptions are close to those found in the respective α -difluoroaminoacyl fluorides.⁸ Other resonances for FO(CF₃)₂ are located at ϕ 92.5 (terminal CF₃) and 122.9 (central CF₃); for FO(CF₃)₂OF at 92.9 (terminal CF₃ groups) and 124.0 (three central CF₃ groups); for CF₃(NF₂)CF₂OF at 92.5 (CF₃ group adjacent to OF) and 115.2 (CF₃ adjacent to NF₂); and for CF₃CF(NF₂)CF₂OF at 72.8 (CF₃), 86.1 (CF₂), and 167.2 (CF). These tentative assignments are based on field positions, area ratios, and comparison of the spectra of these new compounds with each other as well as with published information.^{8,9}

Alkaline Hydrolysis. Both FO(CF₃)₂OF (52.2 mg) and FO(CF₃)₂OF (80.0 mg) were admitted into bulbs containing 50 ml of 0.996 N NaOH solution and allowed to stand at room temperature for 3 hr. The aqueous phases were titrated to determine the amount of hydroxide consumed as well as analyzed for fluoride. The vapor phases were measured by their pressure-volume-temperature relationships and subjected to mass spectral analysis. The analytical results are summarized in Table II.

Table II. Alkaline Hydrolysis

Products, moles/mole of reactant	FO-(CF ₃) ₂ OF	FO-(CF ₃) ₂ OF	Theory
F ⁻	5.9	5.7	6.0
O ₂	0.9	0.9	1.0
OH ⁻ (consumed)	8.7	8.5	8.0

The alkaline hydrolysis of both FO(CF₃)₂OF and FO(CF₃)₂OF followed the general equation

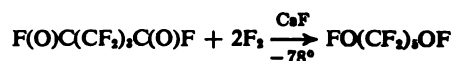
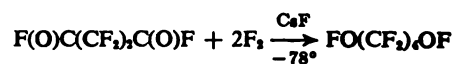


The presence of trace quantities of perfluorocarbons and the larger than theoretical quantities of OH⁻ consumed is explained by the known decarboxylation of perfluorinated acids in alkaline solution.

Results and Discussion

Cesium fluoride has been shown to catalyze the addition of fluorine across the sulfur-oxygen double bond of thionyl fluoride.⁷ It was postulated that the active

intermediate in the fluorination was the SF₆O⁻ ion. Since cesium fluoride was reported to react with carbonyl fluoride to form CsOFCF₃,⁸ an attempt was made to determine whether cesium fluoride would catalyze the addition of fluorine across the C=O bond of several fluorocarbon derivatives. This was found to occur readily and high yields of the corresponding fluoroxo compounds could be obtained when the reactions were allowed to progress at -78° in a static system. The following conversions to known compounds were easily accomplished: COF₂ → CF₃OF, 97% yield; CF₃COF → C₂F₅OF, 96% yield; C₂F₅COF → C₂F₅OF, 97% yield; and (CF₃)₂CO → (CF₃)₂CFOF, 98% yield.¹ When the technique was extended to include the two diacyl fluorides derived from perfluorosuccinic and perfluoroglutaric acids, the corresponding bis(fluoroxo) compounds were produced. These reactions were car-



ried out using close to stoichiometric amounts of fluorine in order to eliminate C-C bond cleavage that is commonplace with fluorinations carried out at elevated temperatures. The advantage of this catalyzed method of fluorination becomes obvious in comparing the yield in the preparation of the only other known example of a bis(fluoroxo) compound, FO(CF₃)₂OF (approximately 2%),⁴ with the yields obtained in this study. The yields of the monofluoroxo derivatives are also much higher than those previously reported, and essentially no purification of the compounds is necessary for most purposes.

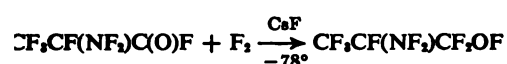
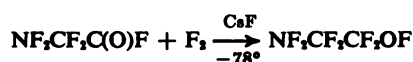
The high-temperature fluorination of carbon dioxide has been reported to produce only the known fluoroxo compound, CF₃OF.⁹ However, in the presence of cesium fluoride the catalytic addition of fluorine occurs, and CF₃(OF)₂ is obtained in nearly quantitative yield. Some variation in the conversion was noted, and this

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to depend on the history of the cesium fluoride used. Better results were obtained with a catalyst that had been previously used to convert the acid chloride derivatives to fluoroxy compounds. Identification of $\text{CF}_2(\text{OF})_2$ was achieved by vapor density, molecular weight and by a comparison of its infrared and ^{19}F nmr spectra with those previously obtained.¹⁰ This method of fluorination could not be extended to compounds containing an atom or group other than fluorine or a perfluoroalkyl group bonded to the carbon. Displacement occurred and only the perfluoro compound derived from the related acid fluorides was observed upon fluorination. For example, reaction of COCl_2 with 1 equiv of fluorine at -78° in the presence of CsF produced only CF_3OF and chlorine in small amounts. Unreacted COCl_2 was also recovered. Fluorination of FCONF_2 with excess fluorine at -78° yielded NF_3 and CF_3OF as the major products. However, the catalyzed fluorination of the α -substituted aminoacyl fluorides, $\text{NF}_2\text{CF}_2\text{C}(\text{O})\text{F}$ and $\text{CF}_3\text{CF}_2\text{C}(\text{O})\text{F}$, produced the corresponding fluoroxy compounds in high yield. Both products are stable in



the solid phase in Pyrex at room temperature.

The fluorination of HCF_2COF at 0° produced an unstable material which was contaminated with small amounts of COF_2 , HCF_3 , and CF_4 . Purification of this material by either vacuum-line fractionation or gas chromatography resulted in spontaneous and often violent decomposition. The main products in this position were COF_2 and HCF_3 . The ^{19}F nmr

of G. Thompson, private communication.

spectrum of the crude product consisted of an unresolved broad singlet at $\delta -131$ (OF), an unresolved singlet at $\delta 99.9$ (C-F), and a doublet at $\delta 136.4$ (C-F) ($J_{\text{HF}} = 56$ cps). The relative area ratio of the peaks is 1.0:2.1:1.9. This spectrum is consistent with the formulation of the compound as $\text{HCF}_2\text{CF}_2\text{OF}$. The infrared spectrum of the crude material showed no absorptions attributable to a carbonyl group but exhibited a weak band in the fluoroxy region which was not observed in the starting material. The instability of this hydrogen-containing fluoroxy compound is in agreement with previous observations.^{3,4}

The presence of a metal fluoride is necessary in these reactions although its role is not known with certainty. For example, when either CF_3COF or $(\text{CF}_3)_2\text{C}=\text{O}$ was allowed to stand with 1 equiv of fluorine at -78° in a Pyrex reactor, no reaction was observed and the carbonyl derivatives were quantitatively recovered. However, in the presence of an alkali metal fluoride the formation of the corresponding fluoroxy compound was complete in 1 hr (on the 1-2-mmole scale). It is probable that the metal fluoride either reacts directly with or polarizes the carbon-oxygen double bond to such an extent that a polar intermediate is formed, which is the active species in the fluorination. Support for this assumption was obtained by fluorination of CsOCF_3 at -78° in a static system. Fluoroxytrifluoromethane was formed in quantitative yield. Furthermore, when $(\text{CF}_3)_2\text{C}=\text{O}$ was allowed to react with an excess of CsF , it was completely absorbed and could not be removed *in vacuo* at ambient temperature. Fluorination of the preabsorbed $(\text{CF}_3)_2\text{C}=\text{O}$ under similar conditions also produced $(\text{CF}_3)_2\text{CFOF}$.

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Spectroscopic Studies of Isotopically Substituted Metal Carbonyls. I. Vibrational Analysis of Metal Pentacarbonyl Halides^{1a}

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Abstract: All of the infrared absorptions including the many minor peaks hitherto neglected in the spectra of the pentacarbonyl halides $M(CO)_5X$ ($M = Mn, Re$; $X = Cl, Br, I$) have been assigned to the carbonyl stretching modes of the all-¹²C derivative (95% natural abundance) and the principal monoisotopic species $M(^{12}CO)_4(^{13}CO)X$ (4% ¹³C-*cis* and 1% ¹³C-*trans* to X). Calculations using an energy-factored block of the (FG^{-1}) matrix for the carbonyl stretching modes (but without any other predetermined constraints on the force field) have given all five force constants in the block. These support the proposed assignments and also verify previous models for the force fields in these molecules. The ¹³C absorptions have been experimentally verified through enrichment; axial and radial CO groups are observed to be approximately equally enhanced by ¹³C exchange in disagreement with interpretations of previous radiocarbon tracer studies.

Although the infrared carbonyl stretching absorptions of $M(CO)_5X$ derivatives have received a great deal of attention,²⁻⁵ certain of their features have not yet been satisfactorily explained. It remains to assign the many minor peaks often attributed⁶ but actually never proved to be absorptions of ¹³C-substituted molecules occurring in natural abundance. These, as we will show below, are a source of valuable information. Also, while it is not the subject of the present communication, a quantitative treatment of the intensities⁷ is still lacking; the present vibrational analyses provide important information toward our understanding of such data.

In previous analyses of the carbonyl absorptions, only vibrations of the principal species, the all-¹²C molecule (95% abundance in $M(CO)_5X$ derivatives), have been utilized. Since there are five force constants to be evaluated in the carbonyl block of the secular equation but only four absorptions observed for the principal species, it has been necessary to make several approximations⁴ in the force field (see Discussion below). With the additional data from the ¹³C-substituted molecules (experimentally verified here through ¹³C enrichment), a full set of five force constants could be calculated without any assumptions about the force field (other than the usual factoring of the carbonyl stretching block from the lower energy vibrations of the molecules). The use of necessary and sufficient vibrational frequencies to match the number of force constants in a molecule has recently been reported by Lewis, Manning, and Miller⁸ for derivatives $L_2Mn_2(CO)_8$

in which the ¹³C vibrations served as a check on the calculations.

One important consequence of such work is that all the bands of the ¹³C-substituted molecules can be assigned, thus resolving, for the pentacarbonyl hydrides⁹ at least, difficulties which had arisen in the assignment of a structure from the carbonyl modes. In addition, the identification of the ¹³C absorptions provides a direct method for following the stereochemistry of CO substitution using ¹³C-enriched CO.

Experimental Section

The compounds $M(CO)_5X$ ($M = Mn, Re$; $X = Cl, Br, I$) were either available in our laboratory from previous work¹⁰ or with one modification were prepared following published methods.^{10,11} $Re(CO)_5Br$ is obtained in high purity by treating $Re_2(CO)_{10}$ with Br_2 in cyclohexane at room temperature. Disappearance of starting carbonyl is monitored by infrared spectrum.

¹³C-Enriched $Mn(CO)_5Br$. Wojcicki and Basolo¹² found through radioactive tracer studies that CO readily exchanges in solution with $Mn(CO)_5Br$. ¹³C-Enriched $Mn(CO)_5Br$ was thus prepared in our laboratories by exchange with 50% ¹³C-enriched CO (Merck Sharpe and Dohme, Ltd., Canada). In a typical exchange experiment 4.5 mg of $Mn(CO)_5Br$ was dissolved in cyclohexane (3 ml) in a small reaction flask fitted with two stopcocks. The total contained volume of the vessel including the stems up to the stopcocks was about 5 ml. One of the stopcock arms was covered with a rubber syringe cap for later withdrawing samples for infrared spectra. The other stopcock was connected to a vacuum line. The solution was thoroughly degassed (through several cycles of cooling to -196°, pumping, and thawing), and finally at room temperature the 50% ¹³C-enriched CO was introduced to a pressure of about 1 atm by mercury displacement from a storage bulb. During the exchange, spectroscopic samples (each 0.3 ml) were removed by syringe through the rubber cap and stopcock. The samples were then flushed free of CO by bubbling purified nitrogen through the liquid for a few minutes (dissolved ¹³C will continue to exchange during the slow, high-resolution infrared scan, distorting the relative intensities of the peaks). After exchange was completed, the ¹³C-depleted gas was separated from cyclohexane and carbonyl derivative and recovered for other uses by means of a Toepler pump and distillation train on the vacuum line.

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Table I. Observed Carbonyl Stretching Frequencies for $M(\text{CO})_5\text{X}$ Molecules. Cyclohexane Solution

$M(\text{CO})_5\text{X}$		Frequency, $^{\circ}\text{cm}^{-1}$							
M	X	a	b	c	d	e	f	g	h
Mn	Cl	2139.1	2131.8	(2083.6) ^b	2077.3	2055.1	2023.5	1998.9	~1956
Mn	Br	2134.0	2126.8	2079.0 ^a	2073.4	2050.0	2020.1	2000.8	1958.8
Mn	I	2125.0	2118.3	2072.1 ^d	2065.7	2043.3	2014.9	2003.2	1960.8
Mn	CH_3	2109.9	2103.3	(2039.3) ^b	2033.4	2011.4	1976.1	1990.0	1948.7
Re	Cl	2154.6	2146.4	(2084.8) ^b	2076.4	2046.3	2017.8	1983.4	1939.5
Re	Br	2151.0	2143.2	(2080.3) ^b	2073.4	2043.8	2015.3	1985.3	1942.1
Re	I	2144.6	2137.7	2077.7	2070.0	2041.2	2012.7	1989.0	1945.5

^a To allow future checks on our calculations, frequencies are given to a precision of one significant figure beyond our experimental accuracy ($\pm 1 \text{ cm}^{-1}$, see text). A typical spectrum is shown in Figure 1, part I. ^b Not observed; calculated from best fit of force constants. ^c Observed in Raman spectrum at 2079.5. ^d Observed in Raman spectrum at 2072.0.

Spectra showing the original solution of $\text{Mn}(\text{CO})_5\text{Br}$ and subsequent ^{13}CO enrichment through exchange are given in Figure 1.

Infrared Spectra. Carbonyl Stretching Region. The infrared spectra of the region 1800 to 2200 cm^{-1} were recorded using a Beckman IR-4 spectrophotometer equipped with a LiF prism. For

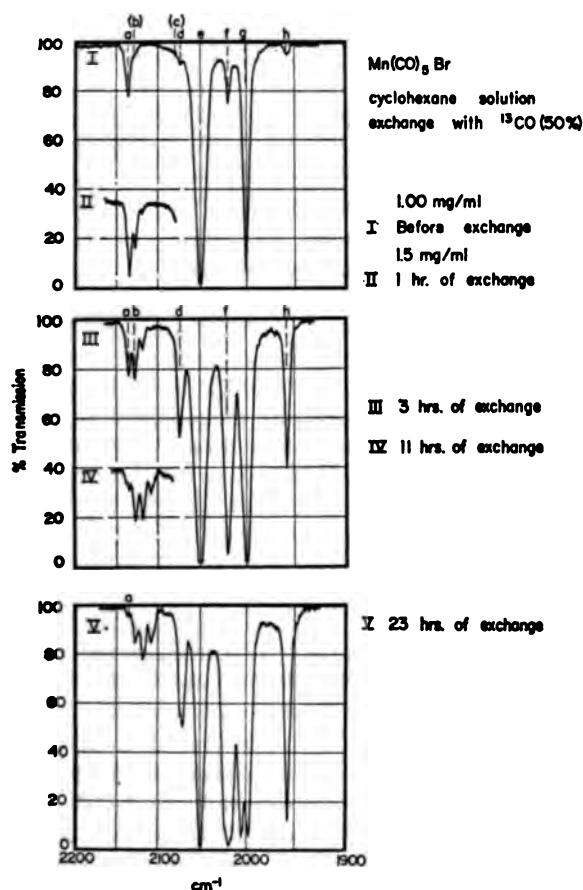


Figure 1. High-resolution infrared spectra in the carbonyl stretching region of $\text{Mn}(\text{CO})_5\text{Br}$ before and after exchange with ^{13}CO (50%).

reasons stated in the Discussion below, it was of the utmost importance to obtain the best possible accuracy within each of the observed spectra. These were determined to $\pm 0.3 \text{ cm}^{-1}$ while the absolute accuracies were about ± 1 or 2 cm^{-1} .

The instrument was run at a scan speed of $0.025 \mu/\text{min}$ with an expansion of $6 \text{ in.}/\mu$ on a chart lined every 0.02μ . Spectra were calibrated against the 5.029μ line of H_2O vapor in the air, with the instrument on single beam. Calibration by this method gave reproducibility of about $\pm 0.001 \mu$, or 0.5 cm^{-1} , for each measurement. As two measurements are involved in each frequency, i.e., the frequency itself and the calibration peak, the accuracy is thus roughly $\pm 1 \text{ cm}^{-1}$. The spectrum of each compound was measured several times, and the average value of up to six spectra is presented

here. The measurement of peak differences for several spectra gave a reproducibility to about $\pm 0.3 \text{ cm}^{-1}$. The data are presented in Table I.

Samples were dissolved in cyclohexane (for the optimum resolution), and spectra were taken at various concentrations, including solutions supersaturated by warming to bring out the ^{13}CO absorptions in natural abundance; CaF_2 sample cells were used of 1-mm thickness, the maximum possible path length without having solvent absorptions destroy instrument response. With warmed solutions, the sample cells had to be heated also, to prevent recrystallization in the cell. This was most conveniently accomplished by placing the cells in the beam of the instrument for about an hour before they were used. Heating causes decomposition of most of the derivatives studied, and it was necessary to subtract the peaks due to decomposition products (essentially the tetracarbonyl halide dimers). Such peaks have been accurately measured before¹³ and are identified both by their position on calibrated spectra as well as their behavior after different periods of heating.

Raman Spectra. Carbonyl Stretching Region. Raman spectra for several of these derivatives were attempted on the laser-source Cary 81, made available to us at the Applied Physics Corp. (now Cary Instruments, a Varian subsidiary) in Monrovia, Calif. The most intense band is the Raman-active B_1 mode, for $\text{Mn}(\text{CO})_5\text{Br}$ at 2079.5 and $\text{Mn}(\text{CO})_5\text{I}$ at 2072 cm^{-1} . Several other weaker Raman shifts were also seen, corresponding to the Raman-infrared active modes which had previously been measured in the infrared so these provided no new information. In addition, Raman shifts attributable to decomposition products were also seen.

Overtone and Combination Region. The infrared spectra in the region 3800 to 4300 cm^{-1} were measured for one representative $M(\text{CO})_5\text{X}$ derivative, namely $\text{Mn}(\text{CO})_5\text{Br}$, for which a more extensive vibrational analysis was carried out. The data were collected on a Cary 14 spectrophotometer; the overtone and combination absorptions are an order of magnitude weaker than the fundamentals. Carbon tetrachloride was used as a solvent because of its transparency in this region. The sample was warmed to give a supersaturated solution, which was placed in 10-cm path length quartz cells which had been prewarmed and left wet with solvent. Decomposition bands, if any, were identified as described above. The spectrum, typical of the $M(\text{CO})_5\text{X}$ derivatives, is shown in Figure 2. The maxima identified for this work are indicated by

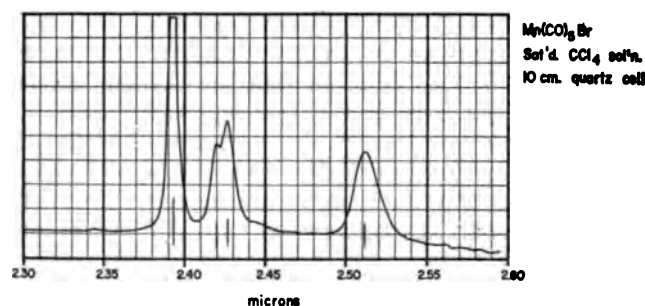


Figure 2. Overtone and combination spectrum, $\text{Mn}(\text{CO})_5\text{Br}$. The vertical lines below the maxima indicate our assignments; these are intended also to reflect somewhat the relative intensities of the bands.

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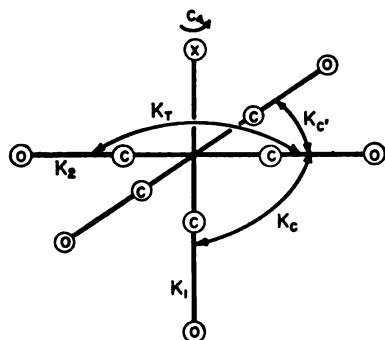


Figure 3. Idealized geometry of $M(CO)_5X$ molecules showing force constants.

small vertical lines below the spectrum and are converted to the following values (in units of cm^{-1}): 4266.2 (w), 4178.3 (s), 4132.1 (m), 4128.8 (m), 4093 (w) 4053 (broad w), 3981.5 (m).

Calculations. Force constants and "normal" modes were calculated using an iterative computer program supplied by Dr. R. Wing (University of California, Riverside, Calif.). The program, based on the work of the Minnesota groups^{14a-c} and also developed by Schachtschneider and Snyder,^{14d} adjusts a set of force constants common to a group of related molecules to give simultaneously a least-squares fit between observed and calculated frequencies for all the molecules. Calculations were performed on the IBM 7094 at the UCLA Computation Center.

Discussion

Assignment of Modes in All- ^{12}C $M(CO)_5X$. The idealized geometry and definition of force constants in the $M(CO)_5X$ derivatives are shown in Figure 3. A structure is thus far available only for the pentacarbonyl hydrides,¹⁵ in which the four radial carbonyl groups are not normal to, but form an angle of approximately 97° with, the axial carbonyl group. The geometry of the pentacarbonyl halides is almost certainly closely related. The five CO groups in the $M(CO)_5X$ molecules give rise to five fundamental CO stretching vibrations separated into the symmetry classes of the C_{4v} point group to which they belong: A_1 (radial), A_1 (axial), B_1 (radial), E (radial, two vibrations, degenerate). The symmetry coordinates for these are conveniently given in terms of the internal bond-stretching coordinates of the molecule in Figure 4. The separation of the two A_1 vibrations into pure radial and pure axial is a convenient fiction at the start of the problem. Any linear combination of the two A_1 vibrations shown would be equally acceptable. Through the calculation of the force constants, the exact form of the vibration, i.e., the mixing of the purely axial and purely radial A_1 modes, will be determined.

Since the two E vibrations are degenerate, only four absorptions are expected, three of which (A_1 , A_1 , and E) are infrared active, while all four are Raman active. The uppermost trace in Figure 1 shows the carbonyl stretching infrared absorptions for a typical $M(CO)_5X$ derivative, namely $Mn(CO)_5Br$. Bands a, e, and g have been assigned to the symmetry coordinates A_1 (radial), E_1 , and A_1 (axial), respectively, by Orgel,² El-Sayed and Kaesz,³ and Cotton and Kraihanzel.⁴ This assignment has been accepted on the basis of the relative

(14) (a) W. T. King, Dissertation, University of Minnesota, Sept 1956; (b) E. C. Curtis, Dissertation, University of Minnesota, May 1959; (c) J. Overend and J. R. Scherer, *J. Chem. Phys.*, **32**, 1289, 1296 (1960); (d) J. H. Schachtschneider and R. G. Snyder, *Spectrochim. Acta*, **19**, 85, 117 (1963).

(15) S. J. La Placa, W. C. Hamilton, and J. A. Ibers, *Inorg. Chem.*, **3**, 1491 (1964).

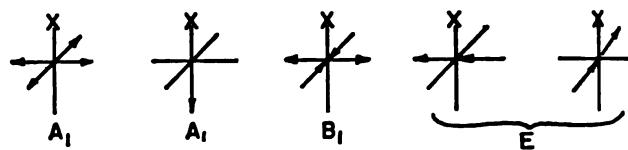


Figure 4. Symmetry coordinates for all- ^{12}C $M(CO)_5X$ molecules.

intensities of the bands and also on the grounds that a reasonable set of approximate force constants was calculated by means of the simplified secular equations.⁴

The choice of the most intense band as the E mode has recently received experimental verification. Wilford¹⁶ and Stone have studied a series of $M(CO)_5X$ derivatives where X is an asymmetric group (such as HCFClCF_2 or HCCl_2CF_2) which has the effect of lowering the over-all symmetry of the molecule. This has led to observable splitting (in gas-phase spectra) of the most intense band usually assigned as the E mode. The splitting (anywhere from 3 to 12 cm^{-1}) is observed because the motions corresponding to the E mode of the related C_{4v} derivatives are no longer degenerate.

Another confirmation for the assignments is achieved through the overtone and combination region spectra. The consistency of the assignment can thus be checked. Table II gives the expected allowed overtones and

Table II. Expected and Observed Overtone Frequencies for $Mn(^{12}\text{CO})_5Br$

	A_1 2134	A_1 2001	B_1 2080	E 2050
A_1	4268 calcd	4135 calcd	Not	4184 calcd
2134	4266 w	4132 m	allowed	4178 s
A_1		4002 calcd	Not	4051 calcd
2001		3982 mbr ^a	allowed	~4053 vw
B_1			4160 calcd	4130 calcd
2080			Not obsd ^b	4128 m
E				4100 calcd
2050				4093 vw

^a We have observed this large difference (anharmonicity) to be typical for the lowest energy combination of a large number of carbonyl derivatives. This effect will be discussed in a future publication. ^b Allowed, but expected to be weak as it is derived from the infrared-forbidden B_1 .

combinations as well as the observed frequencies in cm^{-1} . The calculated and observed frequencies are not expected to coincide because of anharmonicity, and the rather close fit observed for this molecule is an indication that the carbonyl vibrations are not too anharmonic. It would be desirable to determine anharmonicity corrections for these molecules, but this task is beyond the scope of the present work. To date, a detailed determination of anharmonic corrections has been made for only one type of metal carbonyl, the group VI $M(CO)_6$ molecules,¹⁷ where the high symmetry reduces the anharmonic corrections to a workable number.

Assignment of Modes in Mono- ^{13}C -Substituted $M(CO)_5X$. With ^{13}C in 1.1% natural abundance, 1.1% of the molecules $M(CO)_5X$ will be axially substituted with ^{13}C , and 4.4% will be monosubstituted in the radial position. These give rise to their own ab-

(16) J. B. Wilford and F. G. A. Stone, *ibid.*, **4**, 389 (1965).

(17) J. M. Smith and L. H. Jones, *J. Mol. Spectry.*, **20**, 248 (1966).

ons in proportion to the abundance of the individual species and the extinction coefficients of the bands, some of which (but not all) will be distinguishable from the spectrum of the parent all- ^{12}C molecule.

^{13}C substitution in the axial position, the symmetry of the resultant molecule is the same as that of the parent all- ^{12}C molecule (since the position of substitution lies on all elements of symmetry for the molecule). Therefore the symmetry coordinates are the same for these two molecular species. A lower frequency is expected for any vibration involving motion of the heavier ^{13}C , and no shift in frequency is expected for the modes that do not involve ^{13}C . Thus the B_1 modes will be the same for the parent and axial-substituted molecules. Also, if the two A_1 modes were pure radial and pure axial vibrations, only the axial A_1 mode would be shifted. However, they are not, and both are observed to shift but not necessarily by the same amount. The sum of these shifts very nearly equals the expected 45 cm^{-1} for isotopic mass shift. The amount of shift of each mode will be proportional to the amount of axial CO motion in the modes. For the present we are satisfied to assign only band h to this mode, as the A_1 (axial) vibration.

For radial ^{13}C substitution, the symmetry is lowered, and the symmetry coordinates must be written differently as shown in Figure 5. In this case one of the vibrations, the A'' , corresponds to one of the parent molecule vibrations, the E mode. Four vibrations belong to the same symmetry class, and these are expected to be mixed; any or all of our A' vibrations are expected to occur at frequencies different from the vibrations of the parent C_4v molecule, with the expected full ^{13}C isotopic shift of 45 cm^{-1} distributed among the shifts of the four according to the Teller-Redlich product rule (neglecting, of course, the modes outside the carbonyl group). To a first approximation, therefore, vibrations are expected to occur at frequencies slightly lower than any corresponding vibrations in the parent molecule.

Also one might guess at this point that the shift of the A' vibration of the C_4v molecule corresponding to the axial A_1 mode of the parent molecule will be fairly small.

Because of its position relative to the E mode (band f of the parent molecule, band f is assigned as an A' mode of the radial mono- ^{13}C molecule. The most probable one of the four possible A' modes to assign a frequency to (guided by the symmetry coordinates) is the third highest A' vibration of the C_4v molecule, corresponding in relative motions of CO groups to the mode in the all- ^{12}C derivative.

Band b could be assigned either to the radial A_1 mode of the C_{4v} ^{13}C -substituted molecule or to the axial A_1 of the C_4v molecule. The latter assignment is preferred on the basis that its intensity is nearly 10% of the parent radial A_1 vibration. It is expected that the axial A_1 vibration of the C_{4v} mono- ^{13}C molecule will be about 1% the intensity of the parent radial A_1 vibration while A' of the C_4v -substituted molecule would be expected to gain intensity due to its probable asymmetry about the former C_4 axis. This assignment is supported by the fact that no other vibration is observed below the parent radial A_1 which might correspond to the A' of the C_{4v} ^{13}C axial-substituted molecule.

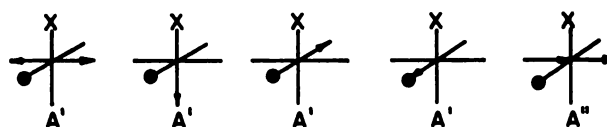


Figure 5. Symmetry coordinates for mono- ^{13}C (radial) $\text{M}(\text{CO})_5\text{X}$.

The assignment of the remaining two frequencies, bands c and d, are not obvious. These will be determined through calculation of force constants which will also provide a check for the previously mentioned assignments.

Confirmation and Completion of the Assignments through Calculation of Force Constants. The above assignments and a set of approximate starting force constants are adjusted by an iterative computer program (see Experimental Section) to fit the frequencies of the all- ^{12}C and the mono- ^{13}C axial and radial substituted $\text{M}(\text{CO})_5\text{X}$ for a given M and X. For a given derivative (i.e., given M and X), we expect that the force constants for the ^{13}C -substituted molecules will essentially be the same as for the all- ^{12}C derivative. This has been shown to be true for the isotopic substitution of deuterium for hydrogen, involving a 100% increase in weight, and will certainly hold for the ^{13}C - ^{12}C substitution. The additional information supplied by the ^{13}C frequencies appears as new frequency parameters (λ 's) in the secular equation $|GF - \lambda E| = 0$.

Because not all of the observed frequencies are independent, the calculations require a greater number of input frequencies than there are force constants to be determined. There are eight observed frequencies, a-h (see Figure 1 and Table I), from which six frequencies are needed to determine the five force constants in the carbonyl stretching block. The bands a, e, g, h, f, and b (in order of their appearance in the discussion of band assignments above) were selected as input data, and, also, a set of starting force constants is supplied to the computer program. In the present case, it is found that the approximate force constants of Cotton and Kraihanzel⁴ (K_1 , K_2 , and K_3 which is equal to K_e and $K_{e'}$ and $1/2 K_t$) provide a suitable starting point since they are quite close to the final values. Even in those cases where starting force constants are not close to the final values, the program is able, through a larger number of iterations, to arrive at the optimum answers.

The optimum calculated force constants and the associated frequencies for all the modes are shown in Table III for a model compound, $\text{Mn}(\text{CO})_5\text{Br}$. The calculated frequencies for bands a, e, g, h, f, and b fit to within 0.1 cm^{-1} of the values used as input. This is a good sign that the input frequencies were placed in their proper assigned positions. The calculation of the two remaining observed frequencies, not used as input, also serves as an independent check on the correctness of the assignments. Bands c and d are predicted within 3 cm^{-1} , the range of expected error derived from using frequencies uncorrected for anharmonicity. A different set of six input frequencies, using either one or both of bands c and d, but dropping one or two of the previous input frequencies, would produce calculated force constants to within 0.02 mdyne/\AA of these reported values, and again predict the remaining two frequencies within the same range of error (3 cm^{-1}).

Table III. Calculation of Force Constants to Assign Bands c and d in $\text{Mn}(\text{CO})_5\text{Br}$

Molecule (symmetry)	Vibr	Input, cm^{-1}	Calcd, cm^{-1}	Obsd, cm^{-1}	Band designation
$\text{Mn}(\text{CO})_5\text{Br}$ (C_{4v})	A_1	2134.0	2133.9	2134.0	a
	A_1	2000.8	2000.8	2000.8	g
	B_1	...	2082.5	2079.0	c ^a
	E	2050.0	2050.0	2050.0	e
Mono- ^{13}CO , axially substituted (C_{4v})	A_1	...	2131.1	...	b
	A_1	1958.8	1958.8	1958.8	h
	B_1	...	2082.5	...	c
	E	...	2050.0	...	d
Mono- ^{13}CO , radially substituted (C_s)	A'	2126.8	2126.9	2126.8	b
	A'	...	2075.7	2073.4	d
	A'	2020.1	2020.1	2020.1	f
	A''	...	1998.3	...	e
Force constants, mdyne/A	K_1	16.35	$K_2 = 0.186$	$K_3 = 0.432$	
	K_2	17.41	$K_3 = 0.305$		

^a Observed in Raman at 2079.5 (strong); very weak in the infrared.
^b Buried beneath 2134.0 (band a). ^c Coincides with B_1 of $\text{Mn}(\text{CO})_5\text{Br}$.
^d Coincides with E of $\text{Mn}(\text{CO})_5\text{Br}$. ^e Buried beneath 2000.8 (band g).

It should be noted that the B_1 vibration is expected in the Raman spectrum although a very weak band in the infrared spectrum (band c) is observed in the calculated position. With the laser Raman, the strongly active B_1 was observed for $\text{Mn}(\text{CO})_5\text{Br}$, the value coinciding with the weak infrared band c. At the high concentrations needed to see all the minor isotopic peaks, we expect to see some weak absorptions not normally predicted in the infrared, which effect has been observed for solutions of $\text{Mo}(\text{CO})_6$ in CCl_4 .¹⁸

Not all of the vibrations predicted for the ^{13}C molecules can be separately observed in the mixture occurring in natural abundance. The presence of an axial mono- ^{13}CO derivative (C_{4v} symmetry) is detected by only one nonoverlapping band, h. As indicated in Table III and in the previous discussion, the B_1 and E bands of this derivative are expected to coincide with the corresponding modes of the all- ^{12}CO molecule and therefore are masked by its more intense absorptions. Similarly, the high-energy A_1 mode through its coupling with the axial mode of the same symmetry is slightly shifted from the high-energy A_1 mode of all- ^{12}CO derivative, but apparently not enough to allow resolution of this peak, more difficult due to its lower relative intensity. The radial mono- ^{13}CO derivative (C_s symmetry) on the other hand shows three separate bands through which it may be characterized, all from the A' block. The A'' of this derivative is expected to coincide with the E mode of the all- ^{12}CO molecule. These characteristic bands for the mono- ^{13}CO substituted molecules will be useful later in following stereochemistry of ^{13}CO substitution in enrichment experiments, through which these ^{13}CO assignments have also been confirmed (see below).

The assignments and calculated force constants may conveniently be summarized by energy-splitting diagrams shown in Figure 6. Through such a graphic representation, formally analogous to spin-spin splitting diagrams in nuclear magnetic resonance analyses, it

(18) L. H. Jones, *J. Chem. Phys.*, **36**, 2375 (1962).

is possible at a glance to understand several features of the vibrational analysis.

In the first row of each of the three frames in the figure (one for each of the compounds illustrated), the energy of the hypothetically isolated internal coordinate is represented by a vertical dashed line. This is the position obtained from the calculated force constants, K_1 and K_2 , by the equation $\nu_1^2 = (5.888 \times 10^{-7})K_1/\mu$ (where μ is the reduced mass of the carbonyl group in atomic weight units $(16.00 + 12.01)/(16.00 \times 12.01) = 0.14583$.) The energy (in cm^{-1}) is plotted on the horizontal axis.

The second row represents symmetry coordinates which are constructed from the internal coordinates.¹⁹ The energies of these are calculated from the interaction constants according to the secular equations for each symmetry coordinate. The third row represents the "normal" coordinates which are the final results of the iterative computation. In these, the positions of the E and B_1 or A'' modes are unchanged from the second line. However, the positions of the A_1 or A' coordinates are altered in proportion to the mixing between the symmetry coordinates. The final observed spectrum of $\text{Mn}(\text{CO})_5\text{Br}$ with ^{13}C isotopically substituted molecules in natural abundance is composed of the sum of the third lines from each of the frames, at a relative intensity determined by the absolute intensity of the band multiplied by its isotopic abundance.

The force constants calculated for the other members of the $\text{M}(\text{CO})_5\text{X}$ series are given in Table IV. These proceed entirely analogously to the assignments and calculations discussed in detail for $\text{Mn}(\text{CO})_5\text{Br}$.

Table IV. Calculated Carbonyl Force Constants for $\text{M}(\text{CO})_5\text{X}$ Molecules^a

M	X	mdyne/A				
		K_1	K_2	K_3	K_4	K_5
Mn	Cl	16.24	17.51	0.231	0.213	0.452
Mn	Br	16.35	17.41	0.305	0.186	0.432
Mn	I	16.38	17.29	0.286	0.181	0.418
Mn	CH_3	16.22	16.81	0.310	0.243	0.474
Re	Cl	15.98	17.52	0.250	0.281	0.586
Re	Br	16.06	17.45	0.306	0.266	0.567
Re	I	16.11	17.39	0.292	0.254	0.551

^a For the possible absolute accuracy of these force constants see the Discussion in the text.

Physical Significance and Trends in the Calculated Force Constants. The possible accuracy of the force constants derived from the energy-factored vibrational analysis has been discussed previously.^{8,20} A full normal coordinate analysis would require the imposition of some force field on the molecule as less data are now available than force constants to be evaluated. As such, this would provide no real check on the energy-factored force constants. Any differences observed between those two sets of force constants would reflect the differences between the assumed force field and the procedure

(19) For derivatives of C_{4v} symmetry, the positions are given by the equations: $\nu_{A_1}^2$ (radial) = $5.888 \times 10^{-7}(K_2 + 2K_3 + K_4)/\mu$; $\nu_{A_1}^2$ = $5.888 \times 10^{-7}(K_2 - 2K_3 + K_4)/\mu$; ν_{E}^2 = $5.888 \times 10^{-7}(K_2 - K_4)/\mu$. For derivatives of different symmetry, these equations may be written following standard procedures; see E. B. Wilson, J. C. Decius, and P. C. Cross "Molecular Vibrations," McGraw-Hill Book Co., Inc., New York, N. Y., 1955.

(20) F. A. Cotton, *Inorg. Chem.*, **3**, 702 (1964).

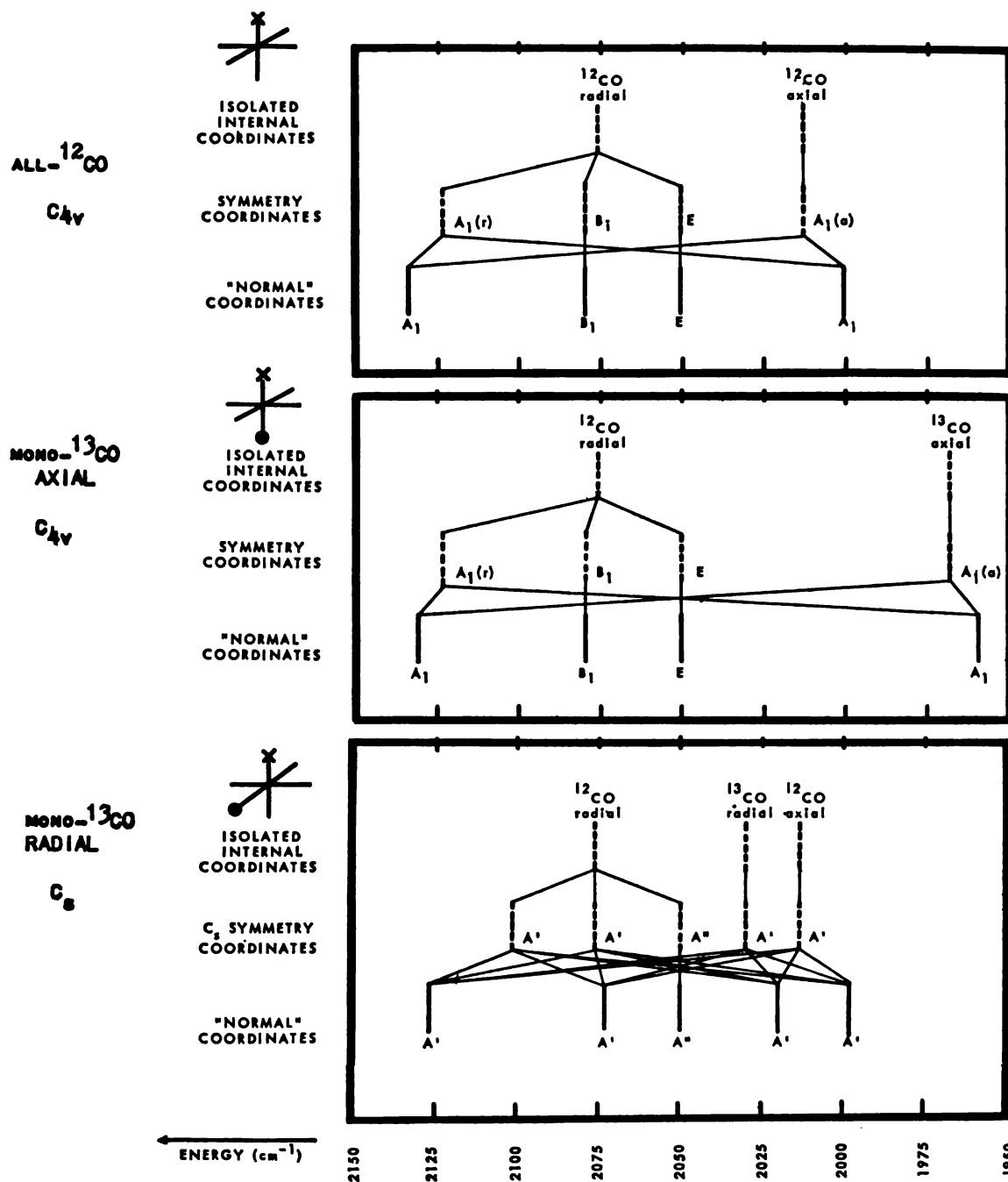


Figure 6. Energy-splitting diagrams for $\text{Mn}(\text{CO})_5\text{Br}$, all- ^{12}CO (95% natural abundance), and the principal monoisotopic specie $\text{Mn}(^{13}\text{CO})_4(^{12}\text{CO})\text{Br}$, (4% ^{13}CO -cis and 1% ^{13}CO -trans to Br).

of energy factoring (which in itself is a force field of one kind).

The match to the ^{13}CO vibrations observed in the present and the previous work⁸ provides one measure of confidence in the procedure of energy factoring. Previous normal coordinate analyses of carbon derivatives^{21,22} further show (from the potential energy distribution) that the CO stretching modes are relatively unmixed. An additional test of the energy-factoring procedure was possible in the pentacarbonyl hydrides.⁹ In these derivatives, the carbonyl stretching force constants were calculated both omitting and including the metal-hydrogen stretching frequencies lying nearby

(ca. 1800 cm^{-1}). Only small changes were produced in the force constants, giving us some additional measure of confidence that changes brought about by inclusion of the next-nearest vibrations (metal-carbon stretching and metal-carbonyl deformation modes, near 600 cm^{-1}) would be even smaller (assuming that the coupling constants in these vibrations with the carbonyl stretching modes are of the same order of magnitude as those for the metal-hydrogen stretching modes with these vibrations).

The present force constants show that the valence force field proposed by Jones^{18,22} (namely that $K_c = K_c' = \frac{1}{2}K_t$ is approximately correct. However, a further degree of refinement is now available which will be useful in any future attempts at a full normal coordinate analysis.

(21) R. S. McDowell, W. D. Horrocks, and J. T. Yates, *J. Chem. Phys.*, **34**, 530 (1961).

(22) L. H. Jones, *J. Mol. Spectry.*, **8**, 105 (1962).

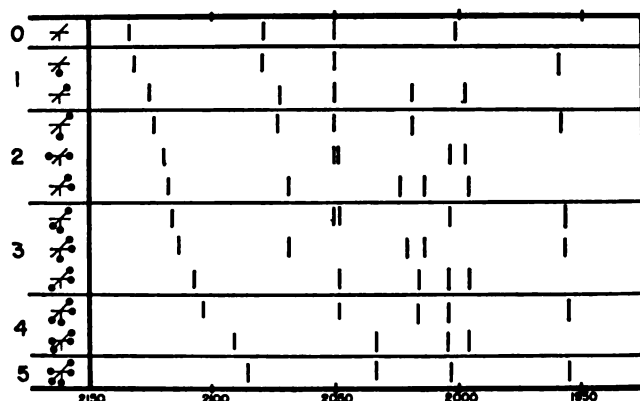


Figure 7. Calculated frequencies for all possible ^{13}CO -substituted $\text{Mn}(\text{CO})_5\text{Br}$. The position of ^{13}CO substitution on the $\text{M}(\text{CO})_5$ skeleton is indicated by a heavy black dot.

Some interesting trends might be pointed out in these force constants (Table IV). Generally the interaction force constants between carbonyl groups are the largest for the least electronegative and least π -electron-withdrawing substituent ($\text{X} = \text{CH}_3$). The interaction force constants should be closely related to the electron density around the metal in the π -electron model for the coupling of carbonyl modes. Other trends are observed, but these fall within about 10 or 15% of the absolute values of these force constants. We refrain from drawing any conclusions about these more refined variations until we feel sure these are due to inherent properties of the molecules in question rather than possible artifacts of the analytical procedure used here.

Mixing of the A_1 Symmetry Coordinates in the A_1 Modes and Correlation with Intensities. The distribution of the A_1 symmetry coordinates (radial and axial) in the high-energy A_1 absorption of all- ^{13}CO and the mono- ^{13}CO axial derivatives is given in Table V. The

Table V. Distribution of Potential Energy of A_1 Carbonyl Stretching Vibrations of the All- ^{13}CO and Mono- ^{13}CO Axial $\text{M}(\text{CO})_5\text{X}$ Derivatives

X		Q (A_1 high energy) ^a			
		All- ^{13}CO		Mono- ^{13}CO axial	
		A_1 (axial)	A_1 (radial)	A_1 (axial)	A_1 (radial)
M = Mn	Cl	0.040	0.960	0.022	0.978
	Br	0.082	0.918	0.044	0.956
	I	0.086	0.914	0.045	0.955
	CH_3	0.109	0.891	0.056	0.944
	D	0.122	0.878	0.061	0.939
M = Re	Cl	0.031	0.969	0.019	0.981
	Br	0.051	0.949	0.030	0.970
	I	0.053	0.947	0.030	0.970
	D	0.107	0.893	0.058	0.942

^a This mode is often referred to as the A_1 (radial). For the coefficients of the low-energy A_1 mode (A_1 (axial)), reverse the coefficients under the headings.

coefficients for the pentacarbonyl hydrides (discussed in the subsequent paper)⁹ are also included here for comparison. It is seen that the high-energy A_1 mode is by and large a mode of the radial carbonyls, as has been deduced in previous qualitative analyses. Increased contributions of axial motion is observed in the series $\text{Cl} < \text{Br} < \text{I} < \text{CH}_3$ and D. Within the halogen derivatives, this follows observed increased relative intensity for the high-energy A_1 mode. However, the

position of $\text{M}(\text{CO})_5\text{D}$ is quite anomalous. These derivatives (and the corresponding hydrides) show the relatively weakest high-energy A_1 absorption. Clearly some effect must be largely responsible for the intensity of the high-energy A_1 mode other than mixing of radial and axial modes. This is currently under study.^{7b}

^{13}CO Enrichment. The assignment of bands discussed above makes it possible to distinguish between molecules which have ^{13}CO located in axial or radial positions. The infrared spectrum is thus a powerful method for following the stereochemical course of reactions involving addition or substitution using ^{13}C -enriched CO. Stereospecific ^{13}CO labeling of $\text{Re}_2(\text{CO})_{10}$ has thus been recently reported.²³

The exchange of radioactive (^{14}C) labeled CO with pentacarbonyl halide molecules has been studied by Wojcicki and Basolo¹² and Hieber and Wollmann.¹⁴ The kinetic data indicated that four CO groups (the radial CO's) exchanged faster than the fifth group (the axial CO). Wojcicki and Basolo assumed that after exchange of the four labile CO groups was essentially complete (in toluene, in the dark, at 32°), the fifth CO equilibrated in about 3 hr at 50° . The results of our exchange reactions are shown in Figure 1. After 3 hr, at room temperature, we observed the trace shown in the middle of the figure (light was not excluded from these samples). It is clear that bands f and h, characteristic of the radial and axial mono- ^{13}CO -substituted species, correspondingly, are enhanced at approximately the same rate, as near as we can tell from the present only qualitative knowledge of the extinction coefficients of these two bands. Therefore, it is clear that if the exchange reactions can be interpreted in terms of preferential substitution first into the radial position, this preference appears very minor.

A difference in the solvents used exists, but it is doubtful whether this has any great influence (cyclohexane in our experiments, used to obtain optimum resolution of the infrared bands, while the previous workers used benzene or toluene).

In other experiments, for which the spectra are not shown here, we took special precautions to exclude stray light in our exchange reactions since the previous work was carried out in the dark. Our exchange reactions were also run in the dark, and special precautions were taken during the infrared scan to minimize exposure to radiation. The infrared cell containing the sample was placed *inside* the infrared instrument just before the exit slits, so that only the infrared radiation which had been monochromated through the prism was allowed to pass through the sample. The instrument was run on single beam, and the spectrum was analyzed by subtracting out the weak solvent absorptions in this region. Dark reactions produced the same enrichment as observed in the previously described runs.

With time, more than one ^{13}CO are expected to exchange into the molecule, and the infrared spectrum will eventually show peaks from molecules with two and more ^{13}CO 's (lower traces, Figure 1). The calculated force constants for the parent molecule enable us to calculate the expected frequencies for all possible ^{13}CO substitution products. The results of this calculation

(23) R. W. Harrill and H. D. Kacsz, *Inorg. Nucl. Chem. Letters*, **1**, 69 (1966).

(24) W. Hieber and K. Wollmann, *Chem. Ber.*, **95**, 1552 (1962).

are shown in Figure 7. The progressive shifts with increasing ^{13}CO substitution are evident, eventually resulting in a spectrum resembling in every way that of the all- ^{12}CO molecule, but completely shifted to lower energy for the all- ^{13}CO molecule. The 100% ^{13}CO -substituted molecule was not achieved in this work to any significant extent due to availability of only 50% ^{13}C -enriched CO. The spectra of intermediate species show some regions of overlap of peaks but at least some peaks which are essentially unobscured and may be used as

characteristic absorptions for the identification of the particular species in question.

Acknowledgment. We wish to thank the Applied Physics Corporation (now Cary Instruments, a Varian subsidiary) in Monrovia, Calif., for making available to us the laser-source Cary 18 Raman spectrophotometer. We also acknowledge the UCLA Computation Facility for making available intramurally supported computer time, and Miss Karen Mehner for preparation of the figures.

Spectroscopic Studies of Isotopically Substituted Metal Carbonyls. II. Assignment of Carbonyl Stretching Absorptions and Their Interaction with Metal-Hydrogen Stretching Modes in Pentacarbonyl Hydrides¹

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Abstract: The infrared absorptions for $\text{Mn}(\text{CO})_5\text{H}$, $\text{Mn}(\text{CO})_5\text{D}$, $\text{Re}(\text{CO})_5\text{H}$, and $\text{Re}(\text{CO})_5\text{D}$ have been recorded in the region 1900–2200 cm^{-1} . All of the observed maxima are accounted for through assignment to the carbonyl stretching modes of the major constituent, $\text{HM}(^{12}\text{CO})_5$, and of the principal isotopic species in natural abundance, $\text{HM}(^{12}\text{CO})_4(^{13}\text{CO})$, 4% ^{13}CO *cis*, and 1% ^{13}CO *trans* to hydrogen. Calculations of force constants in the energy-factored carbonyl stretching block of the (FG^{-1}) matrix support these assignments. The ^{13}CO absorptions have been experimentally verified through enrichment; axial and radial CO groups are observed to be approximately equally enhanced by ^{13}CO exchange, in agreement with previous radiocarbon tracer studies. A shift in some of the CO absorptions in going from $\text{HRe}(\text{CO})_5$ to $\text{DRe}(\text{CO})_5$ has been observed. This is due to coupling between Re–H and *trans*-CO group stretching vibrations. An interaction force constant has been calculated by including the Re–H stretching vibration in the energy-factored (FG^{-1}) matrix. These calculations also provide an interesting check on the method of energy-factored vibrational analysis.

Early spectroscopic studies of the pentacarbonyl hydrides of manganese² and rhenium³ were based on the assumption (derived from earlier electron diffraction work)^{4a} that the hydrogen in these compounds did not occupy a position on the coordination sphere of the metal. Subsequent structural determinations on more stable molecular hydrides such as $\text{HPtBr}(\text{PPh}_3)_4$ ^{4b} and $\text{HOsBr}(\text{CO})(\text{PPh}_3)_4$ ^{4c} revealed that the hydrogen must in fact be counted into the coordination number of the metal like other ligands. At this time, the spectra of the pentacarbonyl halides, especially the extremely low intensity of one of the fundamentals, A_1 (radial), was under study in these laboratories.⁵ The realization that the halides and the hydrides might possess related geometry suggested a similar approach to the assignment of spectra in these two series of molecules.^{6a}

We concluded that the spectra of the hydrides were consistent with an octahedral model in which hydrogen occupied a coordination position around the metal in the hydrides^{6a,b} like the halogens in the halides. This was formally proposed^{6a} shortly before the crystal structure of $\text{HMn}(\text{CO})_5$ was reported.^{7a}

We now wish to report complete assignment of carbonyl modes of all the principal species occurring in natural abundance in the pentacarbonyl hydrides: 95% all- ^{12}CO , 4% mono- ^{13}CO radial, 1% mono- ^{13}CO axial. All the absorptions in the spectra of the pentacarbonyl hydrides are thus accounted for, which had confused the earlier infrared structure assignments for these derivatives. The ^{13}CO modes have been experimentally verified through exchange with ^{13}C -enriched CO.

To confirm the previously assigned metal-hydrogen stretching absorptions,^{2a,3} we have also repeated the spectra of $\text{DMn}(\text{CO})_5$ and $\text{DRe}(\text{CO})_5$. In addition to the large shift in the M–H stretching absorptions, we

(1) (a) Work supported by Grant GP 4175 from the National Science Foundation; (b) for part I of this series, see H. D. Kaesz, R. Bau, D. Hendrickson, and J. M. Smith, *J. Am. Chem. Soc.*, **89**, 2844 (1967).

(2) (a) W. E. Wilson, *Z. Naturforsch.*, **13b**, 349 (1958); (b) F. A. Cotton, J. L. Down, and G. Wilkinson, *J. Chem. Soc.*, 833 (1959).

(3) W. Beck, W. Hieber, and G. Braun, *Z. Anorg. Allgem. Chem.*, **308**, 23 (1961).

(4) (a) See references cited by J. A. Ibers, *Ann. Rev. Phys. Chem.*, **16**, 389 (1965); (b) P. G. Owston, J. M. Partridge, and J. M. Rowe, *Acta Cryst.*, **13**, 246 (1960); (c) P. L. Orioli and L. Vaska, *Proc. Chem. Soc.*, 333 (1962).

(5) M. A. El-Sayed and H. D. Kaesz, *J. Mol. Spectry.*, **9**, 310 (1962).

(6) (a) Dissertation, D. K. Huggins, University of California at Los Angeles, Oct 1963, pp 48–68; (b) D. K. Huggins and H. D. Kaesz, *J. Am. Chem. Soc.*, **86**, 2734 (1964).

(7) (a) Reported by J. A. Ibers, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, Paper No. 50; (b) cf. S. J. La Placa, J. A. Ibers, and W. C. Hamilton, *J. Am. Chem. Soc.*, **86**, 2288 (1964).

Table I. Infrared Absorptions (cm^{-1}) of Pentacarbonyl Hydrides and Deuterides^a

	a	b	c	d	e	f	g	h
$\text{HMn}(\text{CO})_5$	2116.7	2109.8	$\sim 2042.0^b$	2035.4	2014.5	2006.7	1981.8	1965.4
$\text{DMn}(\text{CO})_5$	2117.0	2109.8	~ 2044.0	2036.5	2014.7	2005.4	1981.5	1964.4
$\text{HRe}(\text{CO})_5$	2131.1	2123.1	2053.2 ^b	2042.5	2014.5	2005.3	1982.3	1966.9
$\text{DRe}(\text{CO})_5$	2130.8	2122.9	2051.2	2042.8	2014.5	1999.6	1982.1	1958.2

^a See Figure 1 for identification of these bands according to designated letters. To allow future checks on our calculations, frequencies are given to a precision of one significant figure beyond our actual experimental accuracy ($\pm 1 \text{ cm}^{-1}$). ^b This band is assigned as the Raman-active B_1 band; it appears as a weak band in only the most concentrated solutions; it has been observed directly by laser-excitation Raman of the neat liquids by A. Davison and J. W. Faller, Massachusetts Institute of Technology, private communication: $\text{HMn}(\text{CO})_5$, 2047, and $\text{HRe}(\text{CO})_5$, 2055 cm^{-1} .

observed for $\text{DRe}(\text{CO})_5$ for the first time^{8,9} distinct shifts in at least two of the absorptions in the carbonyl stretching region which were not reported by previous workers. These shifts permit unambiguous assignment of these carbonyl bands to A_1 modes, the same symmetry species as the M-H stretching vibrations with which these have apparently become mixed.

Experimental Section

Preparation. The pentacarbonyl hydrides and deuterides were prepared by methods previously reported for these derivatives.¹⁰ Some additional details only need be mentioned here. The parent carbonyls, $\text{Mn}(\text{CO})_5$ and $\text{Re}(\text{CO})_5$, were purchased from Alfa Inorganics, Beverly, Mass. After reduction of the carbonyls by sodium amalgam in tetrahydrofuran, we found, as others did before, that it is exceedingly difficult to obtain the dry salts necessary in

order to get spectroscopically pure hydride derivatives in the acidification step. The impurities in the sticky solids remaining after reduction and 2 days of pumping under high vacuum up to 50° are extracted with cyclohexane which leaves, after drying under reduced pressure, a slightly colored powder as the pentacarbonyl salt.

The salt is treated under high vacuum with phosphoric acid which has previously been purged with purified nitrogen for several days and then degassed. The volatile products from the acidification are distilled into a trap containing P_2O_5 and cooled to -196° . After completion of the reaction, cyclohexane is distilled into the trap and further purification of the hydride is accomplished by distilling the solution onto fresh quantities of P_2O_5 until complete dryness is attained.

The deuterides are prepared using D_2PO_4 in the acidification step. However, care must be taken with the vacuum line as the hydrides will exchange rapidly with any protonic sites on the glassware not removed even by pumping at 10^{-4} mm for prolonged periods. Such equipment may be properly conditioned for this work by exposure to D_2O vapor before exposure to any deuteriometal pentacarbonyls.

The yields of $\text{HRe}(\text{CO})_5$ (about 30%) are much lower than for $\text{HMn}(\text{CO})_5$ (about 85%). For preparation of hydride sufficient to give the infrared spectra reported here, it was necessary to start with 2.0 g of $\text{NaRe}(\text{CO})_5$ but only with 0.5 g of $\text{NaMn}(\text{CO})_5$.

A great deal of the rhenium may be found in the product mixture in the form of polynuclear carbonyl hydrides of low volatility, described elsewhere.^{8,11}

Exchange Reactions and Infrared Spectra. The procedures have been described in the accompanying publication.^{1b} The spectra for $\text{HRe}(\text{CO})_5$ at two concentrations are shown in upper spectrum of Figure 1. The absorptions after 24-hr exchange with ^{13}C -enriched CO are shown on the lower spectrum. The positions of the maxima as labeled in the figure are given in Table I.

The spectrum of $\text{DRe}(\text{CO})_5$ in the region $1900\text{--}2200 \text{ cm}^{-1}$ is shown in Figure 2. The vertical dashed lines indicate the position of band f and its ^{13}CO satellite band h in $\text{HRe}(\text{CO})_5$, some of which is present in the sample due to imperfect isotopic conversion. The shifts for the two bands f and h are the only perceptible changes in the carbonyl stretching region on going from $\text{HRe}(\text{CO})_5$ to $\text{DRe}(\text{CO})_5$. No such observable shifts are found for the manganese derivatives. These shifts, if any, must be within the range of experimental error which is 1 cm^{-1} under our present method of operation. The presence of some residual amount of $\text{HRe}(\text{CO})_5$ in the $\text{DRe}(\text{CO})_5$, shown in Figure 2, is due to exchange of deuteride with traces of water in the apparatus which was used to handle the cyclohexane solution of $\text{DRe}(\text{CO})_5$. The last traces of $\text{HRe}(\text{CO})_5$ may be removed by shaking the cyclohexane solution with oxygen-free D_2O . Conversely, the $\text{HRe}(\text{CO})_5$ may be regenerated simply by shaking the cyclohexane solution with oxygen-free H_2O . Exchange even in such a heterogeneous system is remarkably rapid.

The metal-hydrogen stretching frequencies, although previously reported,^{8,9} have been checked for internal consistency with our present data. The most concentrated solutions of the appropriate derivatives in cyclohexane were scanned with Perkin-Elmer 421 (grating) spectrophotometer. The observed frequencies were found to be as follows: $\nu_{\text{MnH}} 1775$, $\nu_{\text{MnD}} 1285$, $\nu_{\text{ReH}} 1882$, $\nu_{\text{ReD}} 1313 \text{ cm}^{-1}$.

Calculations. Force constants and "normal" modes were calculated using the iterative computer program of Schachtschneider and Snyder¹² described in the accompanying communication.^{1b} Calcu-

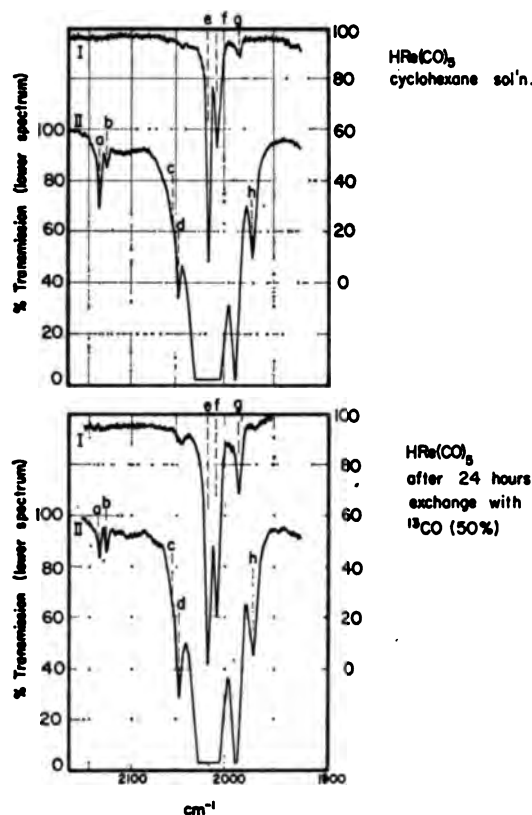


Figure 1. High-resolution infrared absorptions in the carbonyl stretching region for $\text{HRe}(\text{CO})_5$ before and after 24-hr exchange with 50% ^{13}C -enriched CO; cyclohexane solution and LiF prism.

(8) D. K. Huggins, W. Fellmann, J. M. Smith, and H. D. Kaesz, *J. Am. Chem. Soc.*, **86**, 4841 (1964).

(9) L. Vaska, *ibid.*, **88**, 4100 (1966).

(10) (a) R. B. King and F. G. A. Stone, *Inorg. Syn.*, **7**, 198 (1963); (b) "Organometallic Syntheses," Vol 1, J. J. Eisch and R. B. King, Ed., Academic Press Inc., New York, N. Y., 1965, pp 158-160.

(11) W. Fellmann and H. D. Kaesz, *Inorg. Nucl. Chem. Letters*, **2**, 63 (1966).

(12) J. H. Schachtschneider and R. G. Snyder, *Spectrochim. Acta*, **19**, 117 (1963).

were performed on the IBM 7094 at the UCLA Computation Center.

Assignment

Assignment of Absorptions. The three fundamentals A_1 , E for $\text{HM}(\text{}^{12}\text{CO})_5$ are chosen according to the bands described in the previous work on the pentacarbonyl halides.^{1b} The most intense band, e, will not be the E mode. For the two A_1 modes we choose the weak band at highest energy, a, and a band of medium intensity at lower energy, band f. The assignment of band f as an A_1 species is supported by its odd shift upon deuteration in $\text{DRe}(\text{CO})_5$.⁸ Only a band of the same symmetry species as the metal-oxygen stretching modes (which must be of A_1 symmetry) could be affected upon deuteration. No perceptible shift in the position of band a is observed in $\text{Re}(\text{CO})_5$, presumably because this band is less mixed with the Re-H stretching absorption than is band f. The discrimination in the interactions of metal deuterium with certain carbonyl stretching modes has been reported by Vaska.⁹

There are indications that the weak band at ~ 2044 cm⁻¹, band c in $\text{HMn}(\text{CO})_5$, might be the Raman-active mode for the C_{4v} molecule. A previous calculation^{1a} using the approximate secular equations of Wilson and Kraihanzel indicated that the B_1 mode of the derivative might be expected somewhere in this region (calculated position, 2046 cm⁻¹). This band gains intensity in the infrared from some breaking of the C_{4v} symmetry in solution by asymmetric binding of molecules, as suggested by earlier workers in a similar situation for $\text{Mo}(\text{CO})_6$.^{13b} The calculations indicate that the best fit is obtained when this band is indeed attributed to the Raman mode which is finally proved by the failure of this band to gain intensity during ^{13}CO enrichment (see below).

The remaining weak bands may be assigned to either of the two isotopically substituted species in natural abundance containing one ^{13}CO group, similar to methylenetetrahydrothiophene previously.^{1b} For the axially ^{13}CO -substituted molecule, the E and B_1 but not the A_1 modes are identical with those for the all- ^{12}CO molecule. Assign band h as the A_1 (axial) ^{13}CO mode, which is shifted by 38 cm⁻¹ to lower energy from the corresponding ^{12}CO band (f). This is less than the full isotopic shift of 45 cm⁻¹ (or more for frequencies uncorrected for anharmonicity).¹⁴ We may thus infer that this band is mixed with one (or more) other mode of the same symmetry (A_1). The most likely are the A_1 (axial) carbonyl and the A_1 M-H stretching modes. We therefore expect a band slightly shifted to lower energy from band a (the A_1 (radial) band of the all- ^{12}CO molecule). It is tempting to assign band b as the A_1 (axial) mode for the ^{13}CO -substituted C_{4v} derivative, in fact, such a trial assignment gave a poorer fit to the computer in favor of a band even closer to band a than band b (as discussed below). Such a band has not been resolved by us. It must be pointed out

(a) J. B. Wilford and F. G. A. Stone, *Inorg. Chem.*, **4**, 389 (1965); (b) Jones, *J. Chem. Phys.*, **36**, 2375 (1962). Shifts greater than the calculated amount are usually observed for molecules possessing unique CO or NO (using frequencies uncorrected for anharmonicity); see (a) D. P. Tate, J. M. Augl, W. M. Ritchey, B. J. and J. G. Grasselli, *J. Am. Chem. Soc.*, **86**, 3261 (1964); (b) R. J. Howell, W. D. Horrocks, and J. T. Yates, *J. Chem. Phys.*, **34**, 61.

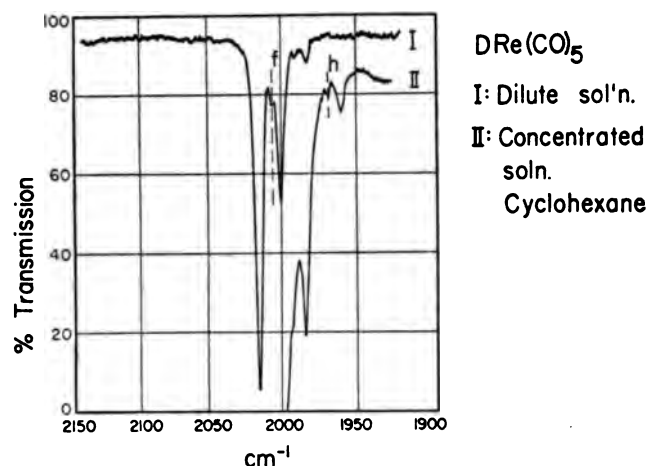


Figure 2. High-resolution infrared absorptions in the carbonyl stretching region for $\text{DRe}(\text{CO})_5$ with some $\text{HRe}(\text{CO})_5$ present in small quantity as impurity (distinguishing peaks marked with dashed vertical lines).

that such a band, belonging to a very weak absorption of a molecule present only in 1% concentration, is probably too weak to be resolved between the already existing bands a and b without specific isotopic substitution. Assignment of the remaining bands is settled through the calculation of force constants.

Calculations. As described above, we feel rather confident about the assignment of bands a, e, f, g, and h. The uncertainty arises for band b (a choice between the A_1 mode for the C_{4v} or for the C_s isotopically substituted molecules) and bands c and d. We may decide the best assignment for these by comparing the calculated values with those observed (which of course are therefore not used as input). The best result is shown in Table II.

Table II. Comparison of Calculated with Observed Frequencies (cm⁻¹) for $\text{DRe}(\text{CO})_5$

	Vibr species	Input	Calcd	Obsd	Band	Force constants, mdynes/A
All- ^{12}CO (C_{4v})	A_1	2130.8	2130.7	2130.8	a	
	A_1	1999.6	1999.5	1999.6	f	
	B_1	2051.0	2051.0	2051.0	c ^a	
	E	2014.5	2014.4	2014.6	e	
Mono- ^{13}CO (C_{4v})	A_1		2127.1	...		$K_1 = 16.37$
	A_1	1958.2	1958.3	1958.2	h	$K_2 = 16.98$
	B_1		2051.0	...		$K_3 = 0.281$
	E		2014.4	...		$K_4 = 0.330$
Mono- ^{13}CO (C_s)	A'	2122.9	2123.0	2123.1	b	
	A'		2044.1	~ 2043	d	
	A'		2000.7	...		
	A'	1982.1	1982.2	1982.1	g	
	A''		2014.4	...		

^a Seen only in very concentrated solutions as a very weak peak; has been measured by laser Raman (at 2055 cm⁻¹) for $\text{HRe}(\text{CO})_5$ by A. Davison and J. W. Faller, Massachusetts Institute of Technology, private communication. ^b Probably too weak to be observed between bands a and b. ^c Degenerate with corresponding mode of all- ^{12}CO molecule. ^d Obscured by intense absorption of band e.

Similar calculations were carried out for the other molecules studied here and the results are summarized in Table III.

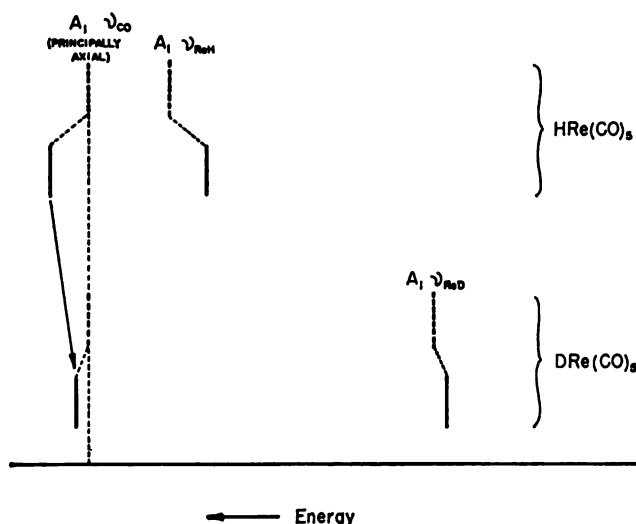


Figure 3. Representation of observed shift (diagonal arrow) of A_1 (principally axial) carbonyl stretching absorption when H is replaced by D in going from $HRe(CO)_5$ to $DRe(CO)_5$. The vertical dashed lines represent the symmetry coordinates before mixing of ν_{CO} with either ν_{ReH} or ν_{ReD} . The solid vertical lines represent the positions of the observed bands.

Interaction of Metal-Hydrogen and Carbonyl Stretching Vibrations. A shift in carbonyl frequencies was first observed by Huggins, Fellmann, Smith, and Kaesz in the pair of derivatives, $H_2Re_3(CO)_{12}$ and $D_3Re_3(CO)_{12}$.⁸ This implied a coupling between metal-hydrogen and carbonyl stretching modes, not previously

Table III. Summary of Force Constants (mdynes/A)^{a,b} for the Best Assignment of Carbonyl Modes in Metal Pentacarbonyl Hydrides and Deuterides

	K_1	K_2	K_3'	K_4	K_5
$HMn(CO)_5$	16.46	16.88	0.266	0.299	0.480
$DMn(CO)_5$	16.47	16.88	0.257	0.304	0.485
$HRe(CO)_5$	16.60	16.95	0.247	0.391	0.550
$DRe(CO)_5^c$	16.34	16.96	0.282	0.328	0.583
$DRe(CO)_5$	16.37	16.98	0.281	0.330	0.582

^a These force constants are relatively significant only to the first four (K_1 , K_2) or three figures (K_3 , K_3' , K_4). For the possible accuracy of these constants see the discussion in the text of the accompanying publication.^{1b} ^b For definition of force constants, see Figure 3 of ref 1b. ^c With ν_{ReH} included. This calculation also yielded the following values: $K_{ReH} = 1.984$, $K_{H-co(cis)} = 0.0006$, $K_{H-co(trans)} = 0.225$ mdynes/A.

reported for known carbonyl hydrides such as $HMn(CO)_5$ whose deuterium derivatives had also been studied.^{2a,3} In our bands, upon repeating this work, we indeed found a shift in the carbonyl frequencies in the pair of compounds $HRe(CO)_5$ - $DRe(CO)_5$ (see Experimental Section). No shifts within the limits of our experimental error were noticed for the analogous manganese derivatives, however. Calculations with the rhenium derivatives therefore were carried out in which the metal-hydrogen stretching frequency was included in the energy-factored (FG^{-1}) matrix. In this case, all of the available carbonyl absorptions were placed in their assigned positions (determined by previous successful calculations carried out on the carbonyl modes alone). The results of this calculation are also shown in Table III (fourth row of numbers).

Several points should be noted. The mixing of ν_{ReH} with the carbonyl stretching modes provides a satisfactory explanation for the observed shift to lower energy of the axial carbonyl band upon deuteration. This is illustrated in Figure 3. In $HRe(CO)_5$, the A_1 purely carbonyl symmetry coordinate (mainly axial) and the A_1 purely ReH symmetry coordinate (vertical dotted lines, top row of figure) will mix and produce observed bands at higher and lower energies (vertical solid lines, second row of Figure 3).

In $DRe(CO)_5$, however, the A_1 purely carbonyl symmetry coordinate is separated by a large amount from A_1 ReD symmetry coordinate. Their mixing will be much decreased, and the observed bands (solid vertical lines, last row of figure) will suffer smaller energy shifts from the positions of the unmixed coordinates. Therefore, the carbonyl band assigned as A_1 (axial) is observed to shift to lower energy (diagonal arrow) when ν_{ReH} is replaced by ν_{ReD} in going from $HRe(CO)_5$ to $DRe(CO)_5$. The absence of similar effects in the spectra of the pentacarbonyl hydride and deuteride of manganese results no doubt from a smaller interaction in these derivatives between the ν_{CO} and ν_{MnH} . The shift, if any, on going to $DMn(CO)_5$ must be below the limits of error of observation of these bands.

The observed shift on deuteration only for the A_1 axial modes is reflected in the calculated interaction force constants between ν_{ReH} and ν_{CO} . The coupling of ν_{ReH} with *trans* ν_{CO} (about 0.22 mdynes/A) is about 400 times greater than the interaction between ν_{ReH} and *cis* ν_{CO} (0.0006 mdynes/A). This provides a quantitative measure of the *trans*-coupling effects of metal hydrides and carbonyl stretching modes observed in this work and also recently reported by Vaska for a number of other derivatives.⁹

The small changes in calculated force constants brought about by inclusion of ν_{ReH} in the calculations (fourth row, Table III) gives us some added confidence in the procedure of energy factoring. If the changes resulting from such a relatively close-lying vibration (at 1822 cm^{-1}) are small, it is expected that those which would result from the other nearest vibrations (metal-carbon stretching and metal-carbonyl bending) around 600 cm^{-1} would be even smaller still (assuming the coupling constants are of about the same order of magnitude) and can justifiably be left out when lack of data requires this. This makes it possible to carry out a vibrational analysis on an isolated portion of the spectrum such as the carbonyl stretching region.

Exchange Reaction. Confirmation of the ^{13}C assignments was accomplished by exchange with ^{13}C -enriched CO.

Both $HMn(CO)_5$ and $HRe(CO)_5$ exchange with ^{13}CO ; the manganese compound exchanges at a much faster rate. The lower spectrum of Figure 1 shows $HRe(CO)_5$ after 24 hr exchange with 50% ^{13}C -enriched CO. Comparison with the normal spectrum of $HRe(CO)_5$ (upper spectrum) shows very definite changes. Peak b has grown almost equal in intensity to a, one of the fundamentals of the all- ^{13}C molecule. The intensity of a has decreased as well since the total concentration of the all ^{13}C -molecule has been reduced. Comparison of spectra shows that g is much more intense in the labeled hydride and that peaks d and h have both increased. These changes confirm our

assignment of these bands as ^{13}C -carbonyl modes and, since all the ^{13}CO peaks increase, indicate that both radial and axial carbonyls exchange. At no time in the exchange reaction does there appear to be a preference for radial or axial positions other than the increased probability of radial exchange since there are four radial to one axial carbonyls (assuming equal exchange rates for both groups). This is in agreement with Basolo, Braült, and Poë¹⁵ who have found for

(15) F. Basolo, A. T. Braült, and A. J. Poë, *J. Chem. Soc.*, 676 (1964).

$\text{HMn}(\text{CO})_6$ from radiocarbon studies that all five CO's exchange at the same rate. The carbonyl spectrum after extensive exchange shows peaks characteristic of multiple ^{13}CO -substituted molecules.

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A Nuclear Magnetic Resonance Study of σ -Cyclopentadienyl(triethylphosphine)copper(I)¹

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Abstract: The nmr spectrum of cyclopentadienyl(triethylphosphine)copper(I) has been examined as a function of temperature between 0 and -70° . The high-temperature spectrum of the cyclopentadienyl group consists of a single line; the corresponding low-temperature spectrum is composed of three lines having relative areas 2:2:1. The latter spectrum requires that the organometallic compound exist in solution as a copper σ -cyclopentadienide. Analysis of the spectral line shapes in the exchange-broadened region indicates that the averaging of chemical shifts observed at high temperatures must occur by either a sequence of 1,2 or 1,3 shifts of the metal atom around the cyclopentadienyl ring, and that it cannot take place by a sequence of random shifts. Chemical shift data are tentatively interpreted to support the 1,3-shift mechanism for the averaging.

Compounds containing a σ bond connecting carbon and copper(I) usually show a low order of thermal stability.² Details of the factors responsible for the thermal lability of this class of organometallic compounds are not well understood: the stability of the incipient radical formed during homolytic cleavage of the carbon-metal bond,³ the ionic character of the bond,⁴ and the magnitude of the energy separating the highest filled and lowest unfilled σ molecular orbitals⁵ have been variously proposed to determine the stability of these and other transition metal alkyls.

As part of an investigation of the structural features influencing the rate of decomposition of several organocopper(I) reagents, we have had opportunity to examine some of the properties of cyclopentadienyl(triethylphosphine)copper(I).⁶ Wilkinson and Piper have formulated this compound as a σ -cyclopentadienide, rather than a π -cyclopentadienide, on the basis of

spectral evidence.⁶ However, the thermal stability of this material is unexpectedly greater than that of other simple alkylcopper(I) compounds; moreover, its room-temperature nmr spectrum shows only a single sharp peak for the protons on the cyclopentadienyl ring.^{6b} The possibility that cyclopentadienyl(triethylphosphine)copper is a member of the group of metal σ -cyclopentadienides characterized by rapid migration of the metal atom between carbon atoms in the cyclopentadienyl ring^{6b-e} has led us to examine the temperature dependence of its nmr spectrum, in hope of learning more about its structure and the reasons for its unexpected thermal stability. In this paper we wish to report evidence which confirms the structure suggested by Piper and Wilkinson, and which sheds some light on the process which averages the chemical shifts of the cyclopentadienyl protons.

Results

The nmr spectrum of the cyclopentadienyl protons of cyclopentadienyl(triethylphosphine)copper in sulfur dioxide solution at 0° consists of a sharp line at 6.30 ppm downfield from internal tetramethylsilane (Figure 1); resonances due to triethylphosphine occur at higher field and are omitted from this figure. As the temperature of the sample is lowered, the cyclopentadienyl proton resonance broadens and splits into three lines

(1) This research was supported by the National Science Foundation through Grant GP 2018. Calculations were carried out in part at the Massachusetts Institute of Technology Computation Center, Cambridge, Mass.

(2) For examples, see G. M. Whitesides and C. P. Casey, *J. Am. Chem. Soc.*, **88**, 4541 (1966); H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); C. E. H. Bawn and R. Johnson, *J. Chem. Soc.*, 4162 (1960); G. Costa, G. Pellizer, and F. Rubessa, *J. Inorg. Nucl. Chem.*, **26**, 961 (1964); H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952); H. Hashimoto and T. Nakano, *ibid.*, **31**, 891 (1966).

(3) F. Glockling and D. Kingston, *J. Chem. Soc.*, 3001 (1959).

(4) H. H. Jaffé and G. O. Doak, *J. Chem. Phys.*, **21**, 196 (1953); H. H. Jaffé, *ibid.*, **22**, 1462 (1954).

(5) J. Chatt and B. L. Shaw, *J. Chem. Soc.*, 705 (1959).

(6) (a) G. Wilkinson and T. S. Piper, *J. Inorg. Nucl. Chem.*, **2**, 32 (1956); (b) T. S. Piper and G. Wilkinson, *ibid.*, **3**, 104 (1956).

(7) H. P. Fritz and C. G. Kreiter, *J. Organometal. Chem. (Amsterdam)*, **4**, 313 (1965).

(8) M. J. Bennett, Jr., F. A. Cotton, A. Davison, J. W. Falter, S. L. Lippard, and S. M. Morehouse, *J. Am. Chem. Soc.*, **88**, 4371 (1966).

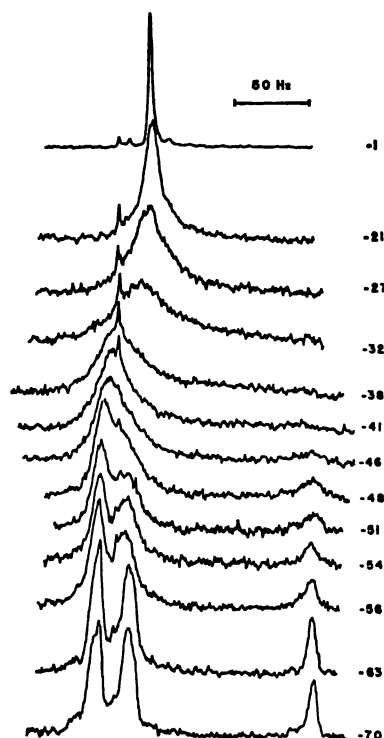


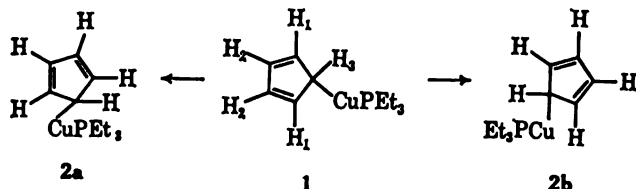
Figure 1. Nmr spectra of the cyclopentadienyl protons of σ -cyclopentadienyl(triethylphosphine)copper(I) in sulfur dioxide solution as a function of temperature. The three peaks in the low-temperature spectrum occur at 6.95, 6.57, and 4.46 ppm from internal tetramethylsilane.

1,2 shifts
 $I(\omega) \propto$

$$\text{Re} \left[(2,2,1) \begin{pmatrix} -i(\omega_1 - \omega) - 1/T_2^1 - 1/\tau & 0.5/\tau & 0 \\ 0.5/\tau & -i(\omega_2 - \omega) - 1/T_2^2 - 0.5/\tau & 0 \\ 1/\tau & 0 & -i(\omega_3 - \omega) - 1/T_2^3 - 1/\tau \end{pmatrix}^{-1} \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} \right] \quad (1)$$

at 6.95, 6.57, and 4.46 ppm, having relative areas approximately 2:2:1. Solutions of cyclopentadienyl-(triethylphosphine)copper, in the concentration range used in these studies, crystallize at temperatures below approximately -40° if allowed to stand. In consequence, spectra taken in the exchange-broadened region of the spectrum were obtained on supersaturated solutions. Attempts to lower the temperature of the sample below -70° to examine spin coupling in the true slow-exchange limit were thwarted by crystallization of the organometallic compound from solution.

The observation of three distinct signals for the cyclopentadienyl protons in the low-temperature spectrum of cyclopentadienyl(triethylphosphine)copper immediately establishes that this compound should be formulated as a copper(I) alkyl (1) containing a carbon-copper σ bond, rather than as a copper(I)-olefin π complex.



The highest field peak in the observed spectrum, having relative area 1, can be safely assigned to the CHCu proton; the two lower field peaks are due to the two nonequivalent types of vinylic protons. Unfortunately,

it is not presently possible to assign chemical shifts to these protons unambiguously. In the discussions which follow, we make the assumption that the resonance occurring at lowest field can be assigned to the protons in site 1 of 1. Some justification for this assumption will be offered below.

The single line observed in the high-temperature spectrum of this compound is most easily rationalized on the basis of rapid hopping of the copper atom between carbon atoms in the cyclopentadienyl ring. In principle, this hopping of the metal atom might take place by any one of three distinct paths: each exchange might shift the copper atom only between adjacent carbon atoms (for example, $1 \rightarrow 2a$); the exchange might shift the copper atom specifically in a 1,3 manner ($1 \rightarrow 2b$); or exchange might occur indiscriminantly by a random mixture of 1,2 and 1,3 shifts.

The unsymmetrical collapse of the resonance due to the vinyl protons observed in the exchange-broadened region offers a method of distinguishing between these alternatives. By following the method developed by Kubo^{9a} and by Sack,^{9b} theoretical line shapes can be calculated for each of these possible exchange schemes. In particular, for a sequence of 1,2 hops, the full line-shape function $I(\omega)$, giving the relative intensity of absorption in the spectrum at frequency ω , is given by eq 1. This equation applies to the labeling of the cyclopentadienyl protons indicated in 1. Here, for example, ω_1 is the chemical shift of the protons at site 1, T_2^1 is the relaxation time for the protons at this site in the

absence of exchange, and τ is the mean time the copper atom spends at each carbon atom between exchanges. Re indicates that only the real part of the expression inside the brackets is considered. The appropriate kinetic transfer matrices K for a 1,3-hopping scheme and for random exchange are given by eq 2 and 3. The corresponding line-shape functions are obtained by substituting these matrices for the exchange terms in eq 1.

1,3 shifts

$$K = \begin{pmatrix} -0.5/\tau & 0.5/\tau & 0 \\ 0.5/\tau & -1/\tau & 0.5/\tau \\ 0 & 1/\tau & -1/\tau \end{pmatrix} \quad (2)$$

Random shifts

$$K = \begin{pmatrix} -0.75/\tau & 0.5/\tau & 0.25/\tau \\ 0.5/\tau & -0.75/\tau & 0.25/\tau \\ 0.5/\tau & 0.5/\tau & -1/\tau \end{pmatrix} \quad (3)$$

Line shapes calculated using eq 1-3 for several values of the pre-exchange lifetime τ are given in Figures 2-4. In these calculations, no attempt was made to take into consideration spin-spin coupling in the slow-exchange

(9) (a) R. Kubo, *Nuovo Cimento Suppl.*, **6**, 1063 (1957); (b) R. A. Sack, *Mol. Phys.*, **1**, 163 (1958); (c) A. Abragam, "The Principles of Nuclear Magnetism," The Clarendon Press, Oxford, 1961, Chapter 10; (d) C. S. Johnson, Jr., *Advan. Magnetic Resonance*, **1**, 33 (1965); (e) H. S. Gutowsky, R. L. Vold, and E. J. Wells, *J. Chem. Phys.*, **43**, 4107 (1965).

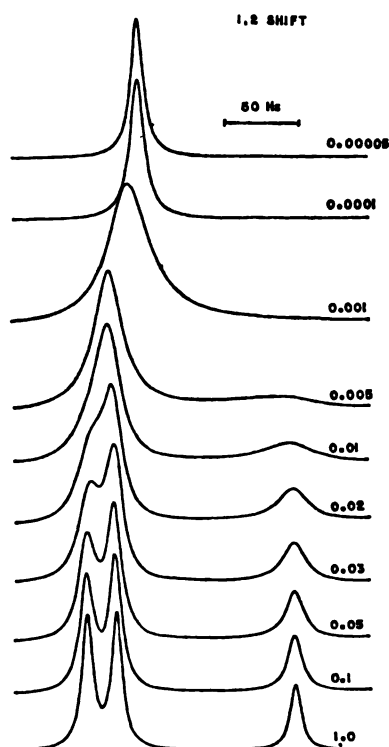


Figure 2. Calculated line shapes for the cyclopentadienyl protons as a function of the mean preexchange lifetime τ (in sec) between successive 1,2 hops. These spectra are based on the assumption the resonance at lowest field can be assigned to the protons in 1.

ra. Indeed, T_2 (here set equal to 0.034 sec for all sites) was adjusted to give line widths at slow exchange which approximated those of the vinylic protons in the observed spectra. Since this value includes contributions to the line shape from both relaxation and from spin-spin coupling, the calculated width in the fast exchange limit is appreciably greater than the observed line width. Nonetheless, qualitative features of these calculated spectra are reliable, and, in particular, the unsymmetrical exchange broadening calculated for the vinyl proton protons in the 1,2- and 1,3-hopping schemes is significant.

The asymmetry in the calculated spectra is physically reasonable if it is remembered that in these schemes exchange changes the precession frequencies of two kinds of vinyl protons by different amounts. For example, for successive 1,2 shifts, the precession frequency of each of the protons labeled H_1 in 1 changes with equal probability by either ~ 100 Hz (if exchange transfers the proton considered to the $CHCu$ site) or 0 Hz (if it is transferred to the second vinylic site). Similarly, the corresponding changes in the precession frequency of each of the protons labeled H_2 are either ± 100 Hz or 0 Hz. Since the relative line broadening for the two types of protons is related to the relative "uncertainty" in their precessional frequencies, the resonance of the proton experiencing the larger changes in frequency per unit time would be expected to broaden more rapidly on increasing the rate of exchange.¹⁰ Comparison of the calculated and observed spectra in the region of exchange broadening indicates that the

For a more detailed presentation of this argument, see S. Meizer, *Elektrochem.*, **64**, 50 (1960); see also ref 8.

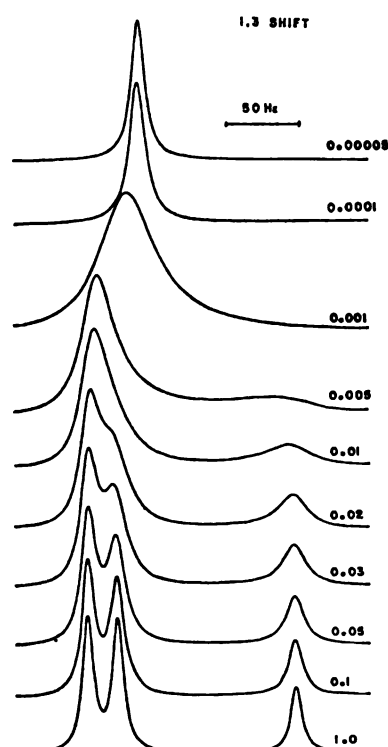


Figure 3. Calculated line shapes for the cyclopentadienyl protons as a function of τ for successive 1,3 hops.

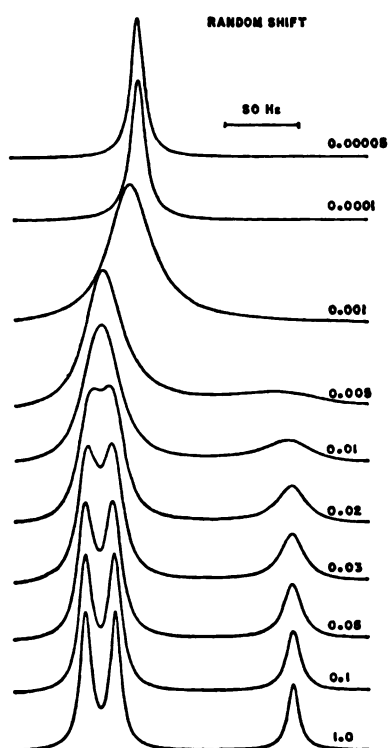


Figure 4. Calculated line shapes for the cyclopentadienyl protons as a function of τ for random hops.

averaging of the chemical shifts of the cyclopentadienyl protons occurs by a sequence of 1,3 hops of the metal atom around the ring, provided that the assignment of relative chemical shifts to the two kinds of vinylic protons is correct.¹¹ If this assignment is

(11) Similar calculations have been applied to a number of related problems: see, for examples, C. MacLean and E. L. Macdon, *Discussions*

reversed, the spectra calculated for the random exchange scheme are unaffected, but the spectra calculated for 1,2- and 1,3-hopping schemes must be interchanged. In this circumstance, comparison of calculated and observed spectra would indicate that averaging occurred by a 1,2-hopping process.

The temperature dependences observed for the spectrum of this organometallic compound in propionitrile and petroleum ether solutions were qualitatively similar to that observed in sulfur dioxide, although the chemical shift of the $CHCu$ proton was appreciably solvent dependent. Further, the copper compound could be recovered from sulfur dioxide solution without apparent change. These observations exclude the possibility that the compound whose spectrum was observed in sulfur dioxide was actually an adduct of the organo-copper compound with sulfur dioxide.¹² Spectra taken in triethylamine or triethylphosphine solutions showed only a single line for the cyclopentadienyl protons at temperatures as low as -70° . Spectra taken in solutions consisting of mixtures of sulfur dioxide and triethylamine or triethylphosphine showed qualitatively the same changes in line shapes as were observed in pure sulfur dioxide; in particular, the same asymmetry was observed in the vinyl proton signals in the exchange-broadened region. However, lower temperatures were required to produce exchange broadening in the mixed solvents than in sulfur dioxide alone.

No direct evidence is available on the extent of association of cyclopentadienyl(triethylphosphine)copper in solution. However, the observations that this compound sublimes readily, and that its mass spectrum shows a clearly defined parent ion (m/e 247 and 249) but no evidence of dimeric or more highly aggregated species, suggest that it is probably unassociated in the vapor phase, and that by inference it is probably also unassociated in a hydrocarbon solvent.¹³ It is of some further interest that the only other relatively abundant ions in the spectrum which clearly contain copper correspond to $(C_5H_5)_2PCu^+$ (m/e 181 and 183). The absence of a strong peak corresponding to $C_5H_5Cu^+$ lends further support to a formulation of this compound as a σ -cyclopentadienide.¹⁴

Discussion

Comparison of the observed and calculated temperature dependence for the spectra of σ -cyclopentadienyl(triethylphosphine)copper(I) permits the conclusion that the averaging of chemical shifts observed at high

Faraday Soc., **34**, 165 (1962); M. Saunders, P. von R. Schleyer, and G. A. Olah, *J. Am. Chem. Soc.*, **86**, 5680 (1964); A. Allerhand and H. S. Gutowsky, *ibid.*, **87**, 4092 (1965), and references therein; C. S. Johnson, Jr., and J. C. Tully, *J. Chem. Phys.*, **40**, 1744 (1964).

(12) Insertion of sulfur dioxide into carbon-metal bonds is well known in the chemistry of other transition metal alkyls: J. P. Bibler and A. Wojcicki, *J. Am. Chem. Soc.*, **88**, 4862 (1966), and references therein.

(13) Other copper(I) and silver(I) organometallic compounds are probably associated both in solution in the crystalline state: P. W. R. Corfield and H. M. M. Shearer, *Acta Cryst.*, **16**, A71 (1963); **20**, 502 (1966); A. F. Wells, *Z. Krist.*, **94**, 447 (1936); F. G. Mann, D. Purdie, and A. F. Wells, *J. Chem. Soc.*, 1503 (1936); D. Blake, G. Calvin, and G. E. Coates, *Proc. Chem. Soc.*, 396 (1959); G. E. Coates and C. Parkin, *J. Inorg. Nucl. Chem.*, **22**, 59 (1961).

(14) π -Cyclopentadienylmetal compounds ordinarily show prominent peaks corresponding to $C_5H_5M^+$.¹⁵ Although the presence of an ion, $C_5H_5Cu^+$ (m/e 128 and 130), cannot be excluded in the spectrum, it certainly does not provide a major pathway for fragmentation.

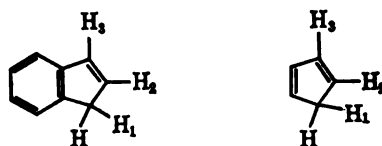
(15) For example, see R. G. Denning and R. A. D. Wentworth, *J. Am. Chem. Soc.*, **88**, 4619 (1966).

temperatures is not the result of *random* hopping of the metal atom between carbon atoms; however, the question of whether the averaging reflects a sequence of successive 1,2 or 1,3 shifts can be answered unambiguously only by correctly assigning chemical shifts to the two kinds of olefinic protons. This assignment cannot at present be made with great assurance.

The relative magnitudes of the coupling constants between the $CHCu$ proton and the two vinyl protons cannot easily be used in assigning chemical shifts, both because the poor resolution in the spectra at the lowest temperatures utilized makes detailed spectral analysis impractical, and because analogous coupling constants in the few model compounds which have been examined suggest that these two coupling constants have approximately the same magnitude.¹⁶ An assignment based on chemical-shift correlations suffers from the scarcity of data from model compounds. Nonetheless, the spectra of cyclopentadienyltrimethylsilane⁷ and -trimethylgermane,⁷ π -cyclopentadienyliron dicarbonyl σ -cyclopentadienide,⁸ and cyclopentadienyl(triethylphosphine)copper share in common the feature that the resonance of at least one of the two kinds of vinylic protons of the cyclopentadienyl group of each compound occurs near 6.6 ppm. If it is assumed that the chemical shift of the vinylic protons which are four bonds removed from the metal atom will be relatively insensitive to the nature of the metal and its ligands,¹⁹ the 6.57-ppm resonance in the copper organometallic compound can be tentatively assigned to H_2 of 1, and consequently, the 6.95-ppm resonance can be assigned to H_1 . Provided these assignments are correct, the high-temperature averaging of the chemical shifts must take place *via* 1,3 shifts of the copper atom.²⁰ However, this conclusion must obviously remain tentative until further experimental work on related compounds is available.

Details of the mechanism of the metal atom shift might be examined by determining the influence of appropriate solution variables on the rate of this reaction. Unfortunately, the spin-spin splitting present in the slow exchange limit severely limits the accuracy

(16) Manatt and Elleman have observed $J_{12} = +2.02$ Hz and $J_{13} = -1.98$ Hz for indene,¹⁷ and $J_{12} = +1.3$ Hz and $J_{13} = -1.5$ Hz for cyclopentadiene.¹⁸ However, both three- and four-bond couplings are



strongly dependent on the geometry of the molecular fragment concerned. In consequence, coupling constants in these hydrocarbons may not provide reliable model parameters for the corresponding coupling constants in the organometallic compounds. For reviews of theoretical and experimental evidence pertinent to the geometrical dependence of these couplings, see M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964); A. A. Bothner-By, *Advan. Magnetic Resonance*, **1**, 195 (1965); E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **86**, 5561 (1964).

(17) D. D. Elleman and S. L. Manatt, *J. Chem. Phys.*, **36**, 2346 (1962).

(18) S. L. Manatt, personal communication.

(19) The chemical shifts observed for the methyl and methylene protons of ethyl-substituted organometallic compounds offers some support for this assumption: A. Davison, J. A. McCleverty, and G. Wilkinson, *J. Chem. Soc.*, 1133 (1963); M. L. Maddox, S. L. Stafford, and H. D. Kaesz, *Advan. Organometal. Chem.*, **3**, 1 (1965).

(20) This type of equilibration is known in allylic organometallic compounds: G. M. Whitesides, J. E. Nordlander, and J. D. Roberts, *Discussions Faraday Soc.*, **34**, 185 (1962); K. C. Ramey and G. L. Statton, *J. Am. Chem. Soc.*, **88**, 4387 (1966), and references therein.

tailed kinetic analysis.²¹ Qualitatively, the significant rate increase observed on adding σ -donor ligands to the sample suggests that, in going to the transition state for the metal atom shift, the compound dissociates to an appreciable extent along the path of dissociated cyclopentadienide anion and metal atom, and that the added ligand serves to increase the rate by stabilizing the increased partial positive charge on the metal atom during the shift. However, the existence of the unsymmetrical mode of collapse of the signals in the presence of added donor ligands indicates that even under these circumstances dissociation does not become complete.

It is of some interest that the temperature dependence of the nmr spectrum of π -cyclopentadienyliron dicarbonyl σ -cyclopentadienide has been interpreted as indicating that the metal atom in this compound shifts out of the cyclopentadienyl ring by a sequence of 1,2 shifts.¹⁷ If both this interpretation and that proposed by the organocopper reagent are correct, the difference between these compounds poses an interesting problem. However, the assignment of the vinylic proton chemical shift in the iron organometallic compound was based on the assumption that the magnitude of the three-bond coupling between the $CHFe$ proton and the vicinal proton was greater than that of the corresponding two-bond coupling, and the ambiguity in this type of assignment has already been indicated.¹⁸ In consequence, comparison of the two compounds is most appropriately deferred until the stereochemistry of the metal shift in each has been more clearly defined.

A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *Chem. Soc.*, **88**, 3185 (1966).

Experimental Section²²

σ -Cyclopentadienyl(triethylphosphine)copper was prepared using a modification of Wilkinson and Piper's method.²³ Commercial cuprous oxide (3.6 g), 10 ml of freshly distilled cyclopentadiene, 7 ml of triethylphosphine, and 20 ml of petroleum ether (bp 30–60°) were refluxed under a nitrogen atmosphere with magnetic stirring for 2 hr and then allowed to stir at ambient temperature for 6 hr. The solvent was removed under reduced pressure, and the resulting brown-black syrup was transferred in a nitrogen-filled glove bag directly to a sublimation apparatus. The product was obtained as hard white or pale yellow-green crystals by slow sublimation at 60° and 0.1 mm. The crystals were moderately stable in the absence of oxygen; solutions of the organometallic were much less stable.

Nmr samples were prepared by transferring a suitable quantity of the freshly sublimed material to a flame-dried nmr tube under nitrogen. The tube was capped with a serum stopper and cooled to the temperature of a Dry Ice-acetone bath, at which temperature, sulfur dioxide was condensed into the tube. The sample was warmed briefly to approximately –35°, to allow the organocopper reagent to dissolve, and then inserted into the precooled (–40°) probe of the nmr spectrometer. If the sample was permitted to warm to temperatures above –40° for more than approximately 5 min, decomposition of the sample introduced significant absorption due to impurities in the olefin absorption region.

Acknowledgments. We wish to express our thanks to Dr. Robert Siekman for his help in obtaining mass spectra, and to Drs. S. L. Manatt and D. D. Elleman for permission to use their data prior to publication.

(22) Nmr spectra were taken at 60 MHz using a Varian A-60 spectrometer equipped with a V-6040 variable-temperature probe and controller. Sweep widths were calibrated using a Krohn-Hite Model 450 oscillator and a Hewlett-Packard Model 524 electronic counter. Calibration of the temperature controller was accomplished by measuring peak separations in a methanol sample. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6D spectrometer. Spectral calculations were carried out using an IBM 7094 computer, and spectra were plotted by a Calcomp plotter.

Mixed Ligand Chelates of Uranium(IV)^{1,2}

G. H. Carey and A. E. Martell³

Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois. Received December 14, 1966

Abstract: Potentiometric studies are described for mixed ligand U(IV) chelate formation with ethylenediamine-tetraacetic acid (EDTA) and nitrilotriacetic acid (NTA) as primary ligands. Secondary ligands studied are salicylic acid (SA), 5-sulfosalicylic acid (SSA), disodium 1,2-dihydroxybenzene-3,5-disulfonate (Tiron), pyrocatechol (PY), 5-sulfo-8-hydroxyquinoline (HQS), disodium 1,8-dihydroxynaphthalene-3,6-disulfonate (CS), *o*-phthalate (Ph), and iminodiacetic acid (IMDA). For the mixed ligand chelate systems containing EDTA, combination with the primary ligand is complete before combination with the secondary ligand takes place. For the less stable NTA systems, overlapping of reactions of the primary and secondary ligands is much more extensive. The relative magnitudes of the equilibrium constants for combination of secondary ligands with the U(IV)-EDTA chelate are $CS > Tiron > PY > SSA > HQS > IMDA \gg Ph$. The mixed ligand chelates of U(IV) are more stable than those of Th(IV) by 1–3 log K units.

Uranium(IV) and thorium(IV) ions are generally considered to have coordination numbers of about 12 in solution and probably form dodecahedral complexes.

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plexes similar to the structures of the crystalline Th(IV) complexes determined by Hoard.⁴ In the case of the 1:1 complexes of Th(IV) and U(IV) with the N,N,N',N'-ethylenediaminetetraacetate anion, the ligand can fill no more than six of the eight coordination sites of the metal ion, leaving two coordinating sites free for hydrolysis, polymerization, or coligation reactions. A

(4) J. L. Hoard and J. V. Silverton, *Inorg. Chem.*, **2**, 235 (1963).

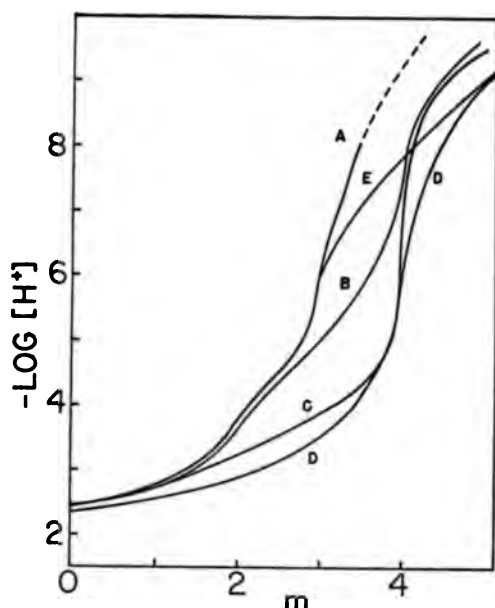


Figure 1. Potentiometric titrations of mixed ligand chelate systems of U(IV) and EDTA; all solutions are $2.0 \times 10^{-3} M$ in U(IV) and adjusted to $\mu = 0.10$ with KCl at the start of the titration; m = moles of base added per mole of metal ion: (A) 1:1 U(IV)-EDTA; (B) 1:1:1 U(IV)-EDTA-PY; (C) 1:1:1 U(IV)-EDTA-Tiron; (D) 1:1:1 U(IV)-EDTA-IMDA; (E) composite curve for the 1:1:1 U(IV)-EDTA-Tiron system; - - - indicates drifting of $-\log [H^+]$ readings; EDTA was introduced as the disodium salt.

bidentate ligand could therefore fill these two vacant sites to give a mixed ligand chelate. In the case of a 1:1 complex formed between U(IV) and a quadridentate ligand such as NTA (nitrilotriacetic acid), there are four coordination sites left upon for hydrolysis and olation reactions which, because of their complexity, would be almost impossible to characterize. However, on the addition of two bidentate groups to complete the coordination sphere of the U(IV), a stable mixed ligand complex, resistant to hydrolysis, might conceivably be formed.

In this study, various bidentate ligands are combined with aqueous EDTA and NTA chelates of U(IV), in order to completely fill the coordination sphere of the metal. Although no data have been previously reported on mixed ligand chelates of U(IV), studies of mixed ligand complexes involving thorium(IV),⁵ zirconium(IV),⁶ the rare earths,⁷ and other metals⁸ have been published. Comparison of mixed ligand chelate formation of U(IV) with that of Th(IV), and of other metal ions, would yield useful information about the nature of the aqueous complex chemistry of these metal ions.

Experimental Section

Materials. Uranium(IV) Solution. The preparation, storage, and standardization of the unique U(IV)-U(III) stock solution are described in detail in a previous paper.⁹ The final solution is approximately 0.026 M in UCl_4 and 0.050 M in excess HCl.

Ligands. Fisher certified samples of the disodium salt of N,N,N',N' -ethylenediaminetetraacetic acid (EDTA) and potassium

acid phthalate (Ph) were used. The 5-sulfosalicylic acid (SSA), salicylic acid (SA), chromotropic salt (disodium 1,8-dihydroxynaphthalene-3,6-sulfonate (CS)), pyrocatechol (PY), and 8-hydroxy-5-quinolinesulfonic acid (HQS) were purchased from the Eastman Kodak Co., while the nitrilotriacetic acid (NTA) and iminodiacetic acid (IMDA) were obtained through the courtesy of the Dow Chemical Co. Tiron (disodium 1,2-dihydroxybenzene-3,5-disulfonate) was obtained from the La Motte Chemical Products Co.

All ligands used were of reagent grade of the highest available purity and were recrystallized whenever necessary. In the case of the water-soluble ligands, a stock solution 0.020 M in the ligand was prepared and standardized potentiometrically with a standard solution of NaOH. With relatively insoluble ligands as well as ligands whose aqueous solutions are susceptible to oxidation or to some other form of decomposition, the purity of the sample was determined and the ligand was introduced into the experimental solution as an accurately weighed solid.

Apparatus and Procedure. A Beckman Model G pH meter was used to determine hydrogen ion concentrations. Potentiometric measurements were carried out in a magnetically stirred, jacketed titration cell of 70-ml capacity fitted with nitrogen inlet and outlet tubes, microburet delivery tube, and glass and saturated calomel extension electrodes. Measurements were made at a temperature of 25.3°. The ionic strength was maintained at 0.10 M by the addition of potassium chloride to the experimental solution. Purified nitrogen was bubbled through the solution in order to exclude carbon dioxide. The electrode system was calibrated with acetic acid, HCl, and NaOH to give $-\log [H^+]$ values directly.

A measured quantity of the uranium(IV) chloride stock solution was run from the inert atmosphere buret directly into the titration cell already containing a solution of potassium chloride and the appropriate amount of the acid form of the ligands. Oxygen was then run through the solution for 3 min to oxidize the U(III) present back to U(IV), and the nitrogen was bubbled through the solution to purge the system of oxygen. Nitrogen was kept flowing continuously throughout the rest of the potentiometric determination to preclude the possibility of any oxygen coming into contact with the uranium(IV) solution. The potentiometric titration was then carried out in the usual manner.

Calculations. Stability constants of mixed ligand chelates were calculated in favorable cases for the combination of the 1:1 EDTA chelates with a second ligand with methods similar to those employed by Thompson and Loraas.⁷

Results

U(IV)-EDTA-Tiron, U(IV)-EDTA-CS, U(IV)-EDTA-PY. The 1:1:1 U(IV)-EDTA-Tiron solution yields a potentiometric curve (Figure 1, curve C) exhibiting a long low buffer region with an extremely sharp inflection at $m = 4.00$. The 1:1 U(IV)-EDTA chelate is completely formed at the start of the titration since the initial hydrogen ion concentration shows that there are two free hydrogen ions present in solution per U(IV) ion. The part of the buffer region from $m = 0$ to $m \cong 2.0$ consists of the titration of the two free hydrogen ions from the 1:1 U(IV)-EDTA chelates. This can be verified by the perfect match of the 1:1 U(IV)-EDTA curve (Figure 1, curve A) with the mixed ligand curve up to an m value of about 1.5.

From $m \cong 1.5$ to $m = 4.00$ the two hydroxyl groups on the Tiron become bound to the 1:1 chelate to form the 1:1:1 mixed ligand chelate. The buffer region terminates with an extremely sharp inflection at $m = 4.00$ indicating that at this point the mixed ligand chelate is completely formed.

Thus the mixed ligand chelate is formed in two steps. In the first step from $m = 0$ to 2.00 the completely formed 1:1 EDTA-U(IV) species is the only chelate present, while from $m = 2.00$ to 4.00 the Tiron becomes bound to the 1:1 U(IV)-EDTA complex to form the 1:1:1 mixed ligand chelate. This conclusion is strengthened by visual evidence, whereby the solution

(5) G. H. Carey, R. F. Bogucki, and A. E. Martell, *Inorg. Chem.*, **3**, 1288 (1964).

(6) B. J. Intorre and A. E. Martell, *J. Am. Chem. Soc.*, **83**, 3618 (1961).

(7) L. C. Thompson and L. A. Loraas, *Inorg. Chem.*, **2**, 89 (1963).

(8) W. B. Schaap and D. L. McMasters, *J. Am. Chem. Soc.*, **83**, 4699 (1961).

(9) G. H. Carey and A. E. Martell, *ibid.*, in press.

green in color because of the presence of the U(IV)-EDTA chelate up to about $m = 2.50$ gradually yellow between $m = 2.50$ and 4.00, and become completely yellow at $m = 4.00$. This yellow is probably due to the addition of the Tiron to the U(IV)-EDTA chelate to form the mixed ligand

as proof for the existence of the mixed ligand is the comparison of the 1:1:1 U(IV)-EDTA-Tiron curve with the composite curve, E. Curve C shows a difference in slope and a large lowering of the buffer region between $m = 2.00$ and 4.00, relative to the composite, which was calculated on the assumption that no mixed ligand chelate is formed. This difference of increased interaction in the presence of two ligands indicates the formation of a relatively stable mixed ligand chelate.

The 1:1:1 U(IV)-EDTA-CS (where CS = disodium dioxynaphthalene-3,6-sulfonate) curve also exhibits a long low buffer region with an extremely sharp inflection at $m = 4.00$. It is superimposable on the 1:1:1 U(IV)-EDTA-Tiron curve up to $m = 4.00$, after which it is differing slightly from the latter on further addition of Tiron. Here also a color change is noted between $m = 5.00$ and 4.00 and a comparison of the 1:1:1 U(IV)-EDTA-CS experimental curve with the composite curve from the same system yields a difference in the buffer region between $m = 4.00$ and 5.00. Therefore, it is evident that this system must undergo the same reactions as that of the U(IV)-EDTA-Tiron system, with the 1:1 U(IV)-EDTA being present from $m = 0.00$ to 2.00, with the formation of the mixed ligand chelate between $m = 2.00$ and 4.00.

The 1:1:1 U(IV)-EDTA-PY system (where PY = pyrocatechol) furnishes a potentiometric curve (Figure 1, curve A) that has a very poor sloping inflection at $m = 4.00$. A titration of the total $[H^+]$ concentration shows that the 1:1 U(IV)-EDTA complex is completely formed at the start of the titration, and the lower buffer region up to $m = 2.00$ merely represents the titration of the 2 equivalent hydrogen ion from the 1:1 U(IV)-EDTA chelate. The second buffer region between $m = 2.00$ and 4.00 corresponds to the hydroxyl groups on the pyrocatechol becoming available to the 1:1 chelate to form the 1:1:1 U(IV)-EDTA-PY mixed ligand chelate. The green color up to about $m = 2.7$ changes completely to yellow at $m = 4.00$. Comparison of the 1:1:1 U(IV)-EDTA-PY experimental curve with the composite curve calculated for no mixed ligand chelate formation shows a difference in shape and lower buffer region for the real system between $m = 2.00$ and 4.00. These observations indicate the formation of the mixed ligand chelate in the second buffer region. It is also evident that the formation of the 1:1:1 U(IV)-EDTA-PY mixed ligand complex occurs at a much higher pH than that of the U(IV)-EDTA-Tiron mixed ligand complex.

It is of interest to compare the above three mixed ligand systems with the behavior of the simple 1:1 U(IV)-EDTA (Figure 2, curve A) chelate compound. In the latter, hydrolysis occurs in the 4.0-5.5 pH range to give a binuclear chelate. With the 1:1:1 U(IV)-EDTA-Tiron system there is no drifting of $[H^+]$ values, or precipitation, which would denote

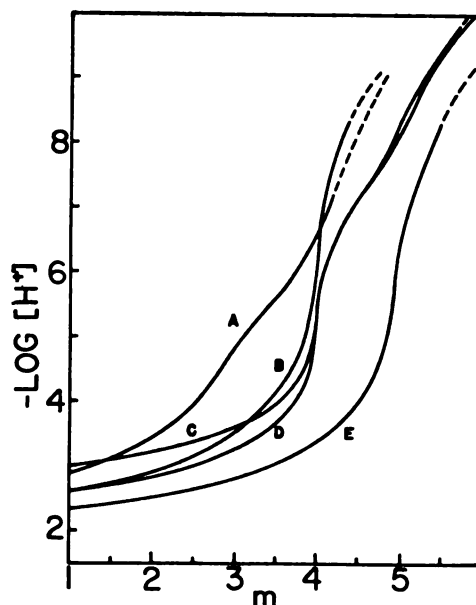


Figure 2. Potentiometric titrations of mixed ligand chelate systems of U(IV) and EDTA; all solutions were adjusted to $\mu = 0.10$ with KCl at the start of the titration; m = moles of base added per mole of metal ion: (A) 1:1:1 U(IV)-EDTA-Ph, $2.0 \times 10^{-3} M$; (B) 1:1:1 U(IV)-EDTA-SA, $2.0 \times 10^{-3} M$; (C) 1:1:1 U(IV)-EDTA-HQS, $7.5 \times 10^{-4} M$; (D) 1:1:1 U(IV)-EDTA-HQS, $2.0 \times 10^{-3} M$; (E) 1:1:1 U(IV)-EDTA-SSA, $2.0 \times 10^{-3} M$; ---- indicates drifting of $-\log [H^+]$ readings; EDTA was introduced as the disodium salt.

a tendency toward hydrolysis and possibly polymerization, while with CS and PY drifting is noted starting around $-\log [H^+] = 9.4$ and 10.6, respectively. Thus it is seen that there is a remarkable difference between the hydrolysis tendencies of the chelate and the mixed ligand chelate and that the addition of a second binuclear ligand effectively hinders hydrolysis and polymerization.

U(IV)-EDTA-SA, U(IV)-EDTA-SSA, U(IV)-EDTA-IMDA, U(IV)-EDTA-Ph. The addition of an equivalent of SA (salicylic acid), SSA (5-sulfosalicylic acid), or IMDA (iminodiacetic acid) to the U(IV)-EDTA chelate produced three mixed ligand systems, each of which yielded analogous potentiometric curves indicating reaction of a similar nature. In the 1:1:1 U(IV)-EDTA-SA system (Figure 2, curve B) and the 1:1:1 U(IV)-EDTA-IMDA system (Figure 1, curve D), the titration curves exhibit a single long buffer region at low $-\log [H^+]$ values which terminates in a fairly sharp inflection at $m = 4.00$, while the 1:1:1 U(IV)-EDTA-SSA curve (Figure 2, curve E) yielded a similar curve with an inflection at $m = 5.00$. The lower part of the buffer region from $m = 0.00$ to 3.00 for the 1:1:1 U(IV)-EDTA-SA and 1:1:1 U(IV)-EDTA-IMDA curves, and from $m = 0.00$ to 4.00 for the 1:1:1 U(IV)-EDTA-SSA curve, corresponds to the titration of the hydrogen ion displaced from the 1:1 U(IV)-EDTA complex, and the acidic hydrogen ions from the secondary ligand (1 equiv in the case of the SA and IMDA and 2 in the case of the SSA). Subsequently, between $m = 3$ and 4 with SA and IMDA and $m = 4$ and 5 for SSA, an additional hydrogen ion is displaced from the ligand, showing the formation of the 1:1:1 mixed ligand chelates U(IV)-EDTA-SA, U(IV)-EDTA-IMDA, and U(IV)-EDTA-SSA, respectively.

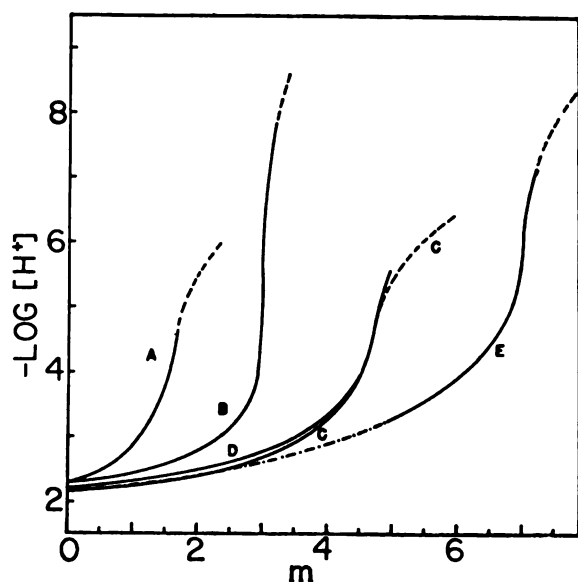


Figure 3. Potentiometric titration of mixed ligand chelate systems of U(IV) and NTA. All solutions were adjusted to $\mu = 0.10$ with KCl at the start of the titration; m = moles of base added per mole of metal ion: (A) 1:4 U(IV)-Tiron, $1.0 \times 10^{-3} M$ in U(IV), also 1:1.5 U(IV)-Tiron, $1.0 \times 10^{-3} M$ in U(IV); (B) 1:2 U(IV)-NTA, $1.0 \times 10^{-3} M$ in U(IV); (C) 1:1:2 U(IV)-NTA-Tiron, $2.0 \times 10^{-3} M$ in U(IV); (D) composite curve derived from A and B; (E) 1:1:2 U(IV)-NTA-HQS, $2.0 \times 10^{-3} M$ in U(IV); - - - indicates drifting of $-\log [H^+]$ readings; - . - . indicates the presence of precipitate in the solution; for curves A and B the actual m values are twice the m values shown.

Hydrolysis is noted above $-\log [H^+] = 8.5$ for SA and SSA, while with IMDA no drifting is noticed even at a $-\log [H^+]$ value of 9.0.

The 1:1:1 U(IV)-EDTA-Ph curve (Figure 2, curve A) (where Ph = potassium acid phthalate) exhibits a buffer region which culminates in a sloping and almost imperceptible inflection around $m = 3.00$. Since the composite curve for this system assuming no mixed ligand chelate formation predicts a slightly higher $-\log [H^+]$ value than the experimental curve between $m = 2.00$ and 3.00 , it is concluded that a mixed ligand chelate is being formed in this region. This mixed ligand chelate once formed undergoes hydrolysis around $-\log [H^+] = 6.50$, above which drifting of the $-\log [H^+]$ value is noted.

U(IV)-EDTA-HQS. The 1:1:1 U(IV)-EDTA-HQS system (HQS = 8-hydroxy-5-quinolinesulfonic acid), $2.0 \times 10^{-3} M$ in U(IV), yields a potentiometric curve (Figure 2, curve D) which has a long buffer region at low $-\log [H^+]$ culminating in a well-defined inflection at $m = 4.00$. Beyond this inflection there is another buffer region which is concentration independent (Figure 2, curves C and D) and which culminates in a sloping inflection around $m = 5.00$. Thus in the lower buffer region a 1:1:1 mixed ligand chelate is formed, while in the second buffer region a distinct monohydroxo mixed ligand chelate is formed, with a calculated $pK_1 = 7.14 \pm 0.01$ for the two different concentrations. Thus the mixed ligand chelate formed in the lower buffer region is not very stable and undergoes hydrolysis to mononuclear monohydroxo mixed ligand chelate around $-\log [H^+] = 7.1$. However, this monohydroxo mixed chelate, once formed, is quite stable since drifting of the pH meter readings indicating further

hydrolysis was noted only at very high $-\log [H^+]$ values above 10.0.

U(IV)-NTA, U(IV)-NTA-HQS. The 1:1 U(IV)-NTA system (not shown) is characterized by a colloidal precipitate and drifting of pH values from the start of the titration. There is a single inflection at $m = 4.75$. Consequently the 1:1 U(IV)-NTA chelate undergoes hydrolysis and ololation reactions, forming an insoluble hydroxo chelate, even at very low $-\log [H^+]$ values.

The potentiometric titration curve of the 1:1:2 U(IV)-NTA-HQS system (Figure 3, curve E) has a long, low pH buffer region from $m = 0$ to 7.0, which terminates in a sloping but fairly well-defined inflection at $m = 7.00$. This system is at first heterogeneous since HQS is only slightly soluble in aqueous solution and remains as a precipitate in strong acid solution. It dissolves slowly as base is added and finally disappears completely at $m = 4.9$ ($-\log [H^+] = 3.3$). Continuation of the potentiometric titration yields a good inflection at 7.00 equiv of base per U(IV) ion. Also, no white colloidal precipitate similar to that of the 1:1 U(IV)-NTA system is noted at any time during the titration. Thus, in the lower buffer region the 1:1:1 mixed ligand chelate which is initially formed is replaced by the 1:1:2 U(IV)-NTA-HQS mixed ligand chelate. Color changes noted in the lower buffer region during the titration are consistent with the formation of these mixed ligand chelate species. The final mixed ligand chelate is stable up to $-\log [H^+] = 7.1$ where a hydroxo complex begins to form, as indicated by a drifting of $-\log [H^+]$ values above 7.1.

U(IV)-NTA-CS, U(IV)-NTA-IMDA, U(IV)-NTA-SSA. The potentiometric curves of systems containing a 1:1:2 molar ratio of U(IV), NTA, and secondary ligand do not provide sufficient information to establish the existence of mixed ligand chelates. In these cases the composite curves formed by the horizontal addition of the 1:1 U(IV)-NTA curve with the free ligand curves closely approximate the experimental curves. Therefore, mixed ligand chelate formation cannot be established from the potentiometric data. Nonformation of mixed ligand chelates in the cases of the 1:1:2 U(IV)-NTA-CS and U(IV)-NTA-IMDA systems is indicated by the fact that a colloidal precipitate of a hydroxo species is present from the start of the titration. This is similar to the precipitate noted in the case of the 1:1 U(IV)-NTA chelate. However, it should be pointed out that weak mixed ligand chelates may be formed during the initial stages of the titration. However, these species are not detectable with the experimental methods employed in the present study.

U(IV)-NTA-Tiron. The mixed ligand potentiometric curve (Figure 3, curve C) for a 1:1:2 molar ratio of U(IV), NTA, and Tiron has a buffer region at low $-\log [H^+]$ values with a poorly defined inflection at $m = 4.50$. Beyond this inflection drifting is noted at and beyond $m = 4.70$ ($-\log [H^+] = 4.3$), showing that hydrolysis and ololation reactions may take place in this region. A similar inflection at $m = 4.50$ was noted previously by Carey, *et al.*,⁵ for the 1:1:2 Th(IV)-NTA-Tiron system and was found to have been caused not by the formation of a mixed ligand chelate, but by the simultaneous formation of two distinct simple chelates $Th(NTA)_2^{2-}$ and $Th_2(Tiron)_4^{4-}$. The

Comparison of Formation Constants of Mixed Ligand Chelates from the 1:1 Chelates and Th(IV) with EDTA (H_4L^{4-}) and 1 Mole of an Additional Ligand (H_nA) [25° , $\mu = 0.10$ (KCl)]

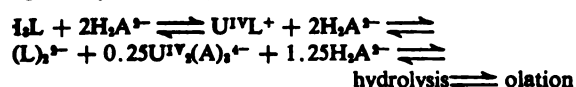
Added ligand	Equilibrium quotient ^a	Formation constant ^b log <i>K</i>	
		1:1 Th-EDTA ^c	1:1 U-EDTA
None	$[ML]/[M^{4+}][L^{4-}]$	23.2 ± 0.1^e	25.8 ± 0.2^d
2-Dihydroxybenzene-3,5-disulfonate anion (A^{2-})	$[MLA^{2-}]/[ML][A^{2-}]$	13.4 ± 0.1^e	15.61 ± 0.05
8-Dihydroxynaphthalene-3,6-disulfonate anion (A^{2-})	$[MLA^{2-}]/[ML][A^{2-}]$	13.66 ± 0.02^e	16.22 ± 0.01
Pyrocatechol anion (A^{2-})	$[MLA^{2-}]/[ML][A^{2-}]$	12.90 ± 0.05^e	14.16 ± 0.5
Sulfosalicylate anion (A^{2-})	$[MLA^{2-}]/[ML][A^{2-}]$	9.29 ± 0.02^e	11.08 ± 0.05
minodiacetic anion (A^{2-})	$[MLA^{2-}]/[ML][A^{2-}]$	6.70 ± 0.02^e	8.2 ± 0.1
Phthalate anion (A^{2-})	$[MLA^{2-}]/[ML][A^{2-}]$	3.09 ± 0.02^e	4.2 ± 0.1
Hydroxyquinoline-5-sulfonate (A^{2-})	$[MLA^{2-}]/[ML][A^{2-}]$	6.98 ± 0.02^e	9.72 ± 0.04
	$[MLA^{2-}]/[MLA(OH)^-][H^+]$	8.02 ± 0.02^f	7.14 ± 0.01

indicates both U(IV) and Th(IV). ^b Numerical values were calculated from many experimental points taken over a wide range of ionic strength. ^c Reference 12. ^d Reference 9. ^e Reference 5. ^f Reference 13.

complex has been described by Murakami and [10, 11]

order to determine if a similar explanation applies to the 1:1:2 U(IV)-NTA-Tiron system, a potentiometric titration curve was run employing the correct stoichiometric amounts of U(IV) and Tiron. The resulting curve yielded a potentiometric titration (Figure 3, C) with a low buffer region and a poor slope at $m = 3.00$. Color changes are also observed, coupled with the inflection at $m = 3.00$, indicating that a 1:1.5 U(IV)-Tiron complex, similar to $U^{IV}_2(Tiron)_3$ complex, is probably formed initially. It has been shown previously⁹ that 1 mole of U(IV) reacts with 2 moles of NTA to give an extremely stable 1:2 U(IV)-NTA complex which yields a curve with an inflection at $m = 6.00$. Thus in the 1:1:2 ligand system half of the U(IV) combines with the NTA present in the solution giving the 1:2 U(IV)-NTA complex, while the other half of the U(IV) combines with the Tiron giving the $U^{IV}_2(Tiron)_3$ complex. Thus at $m = 4.5$, the solution is $1 \times 10^{-3} M$ in the 1:2 U(IV)-NTA complex, $0.5 \times 10^{-3} M$ in the $U^{IV}_2(Tiron)_3$ complex, and $2.50 \times 10^{-3} M$ in excess Tiron.

order to verify this interpretation two additional experiments were measured potentiometrically: a solution $10^{-3} M$ in the 1:2 U(IV)-NTA chelate (Figure 3, B) that gave an inflection at $m = 6.0$, and a 1:4 U(IV)-Tiron solution $1.0 \times 10^{-3} M$ in U(IV) (Figure 3, A) that gave an inflection at $m = 3.00$. The intersection of the ordinates of these two curves yields a value which is superimposable on the actual experimental curve beyond the inflection at $m = 4.5$. This gives convincing evidence that in the lower buffer region what is occurring is the formation of the two species $U^{IV}(NTA)_2^{2-}$ and $U^{IV}_2(Tiron)_3^{4-}$ rather than a mixed ligand chelate. This conclusion is also supported by color changes in the solution during the titration. The general sequence of reactions in this ligand system may be summarized as



where NTA = H_4L and Tiron = H_2A^{2-} . Finally, drifting indicating hydrolysis is noted at and beyond $-\log [H^+] = 4.3$ ($m = 4.6$) for the 1:1:2 system, as expected, since these conditions are the same as those under which hydrolysis occurs for the 1:4 and 1:1.5 U(IV)-Tiron systems.

Equilibrium Constants. The formation constants for the combination of 1 mole of a secondary ligand with the U(IV)-EDTA chelate compound are given in Table I.

Discussion

The present work on mixed ligand U(IV) chelates, as well as the previous study of mixed ligand chelates of Th(IV),⁵ leads to a logical classification of reaction systems containing two different ligands into the following basic types (L represents a "primary" ligand and A represents a "secondary" ligand, and ionic charges are omitted for clarity).

1. Combination of the metal ion with both ligands simultaneously to form a mixed ligand chelate in a single step.



2. Formation of a mixed ligand chelate in two overlapping steps reflecting slight differences in the affinities of the ligands for the metal ion.



3. Formation of a mixed ligand chelate in two distinctly separated steps, reflecting a large difference in the affinity of the ligands for the metal ion.



4. Formation of a mixture of two simple chelate compounds rather than a mixed ligand chelate.



5. A simple complex is formed between one ligand and the metal ion while the other ligand remains unbound in the solution.



All the above five types may be further subdivided according to whether the mixed complex or simple

(12) G. Schwarzenbach, R. Gut, and G. Anderegg, *Helv. Chim. Acta*, **37**, 937 (1954).

(13) G. H. Carey and A. E. Martell, unpublished results.

10. Murakami and A. E. Martell, *J. Am. Chem. Soc.*, **82**, 5605

11. Murakami and A. E. Martell, *Bull. Chem. Soc. Japan*, **39**, 560.

complex once formed is resistant (class A) or susceptible (class B) toward hydrolysis. It should be understood that the above is not intended to be an exhaustive classification system, but merely one which covers the reaction types of various mixed ligand chelate systems that have been observed thus far.

Mixed Ligand Chelates of EDTA. Table II summarizes the evidence for mixed ligand chelate systems of EDTA. It should be noted that the reactions listed may be classified as 2A or 2B, the one exception being the 1:1:1 U(IV)-EDTA-PY system, which is classified as 3B. Mixed ligand complexes are formed by all of the secondary ligands investigated, and the mixed complexes once formed are quite stable. In cases where the secondary ligand contains an aromatic hydroxyl group, the high stabilities of the mixed ligand chelates is evidenced by the lack of hydroxo complex formation in the case of the 1:1:1 U(IV)-EDTA-Tiron chelate, and the high pH at which hydroxo complex formation is observed in the other systems.

Table II. Mixed Ligand Complexes Formed from U(IV)-EDTA (UL) [25°, $\mu = 0.10$ (KCl)]

Ligand added	Inflection ^a	Species formed	Hydroxo complex formation	Reaction type
None	2, 3	UL, ULOH ⁻ (ULOH) ₂ ²⁺	pH > 4.0	..
Tiron (H ₂ A ²⁻)	4	ULA ⁴⁻	None	2A
CS (H ₂ A ²⁻)	4	ULA ⁴⁻	pH > 9.4	2B
PY (H ₂ A)	2, 4	ULA ²⁻	pH > 10.6	3B
HQS (H ₂ A)	4, 5	ULA ²⁻ , ULAOH ²⁻	pH > 7.1	2B
SSA (H ₂ A)	5	ULA ²⁻	pH > 8.5	2B
SA (H ₂ A)	4	ULA ²⁻	pH > 8.5	2B
IMDA (H ₂ A)	4	ULA ²⁻	pH > 9.0	2B
Ph (HA ⁻)	3	ULA ²⁻	pH > 6.5	2B

^a Numbers represent moles of base added per mole of UL.

It is of interest to consider the equilibrium constants for the formation of the mixed ligand chelates, listed in Table I, from the point of view of the constitution of the added ligand. It is seen that CS forms the most stable mixed ligand chelate of all the compounds listed and that the corresponding Tiron complex has nearly the same stability, while the affinity of the catecholate anion for the U(IV)-EDTA chelate is slightly lower. The fact that these stabilities are much higher than any of the other values listed in Table I may be rationalized on the basis that, of the donor groups investigated, the phenoxide groups have the highest affinity for the U(IV) ion. The Tiron and chromotropic salt data are also interesting as an indication that under certain conditions a six-membered chelate ring may be more stable than an analogous five-membered ring.

Two other ligands, HQS and SSA, which provide one phenoxide ion each, form mixed ligand chelates which are somewhat less stable, but nevertheless still appear quite high in the sequence of relative stabilities. In accordance with these observations the least stable mixed ligand chelates are those which are formed from secondary ligands (IMDA and Ph) having primarily carboxylate groups as electron donors.

Table III summarizes the results for mixed ligand chelates of NTA. The first three examples listed are

seen not to involve mixed ligand chelate formation; hence these systems belong to class 5B. It is noted that hydroxo complex formation is first observed in some cases around the same low pH where hydroxo complex formation of the U(IV)-NTA chelate itself occurs. This observation supports the argument that no mixed ligand complex is formed. In the case of HQS, however, the fact that hydroxo complex formation takes place at a higher pH than that at which the 1:1 U(IV)-NTA chelate hydrolyzes is evidence for mixed ligand chelate formation.

Table III. Mixed Ligand Complexes Formed from U(IV)-NTA (UL⁺) [25°, $\mu = 0.10$ (KCl)]

Ligand added	Inflection ^a	Species formed	Hydroxo complex formation
None	~4.75	Hydrolysis product of UL ⁺	pH > 2.5
CS (H ₂ A ²⁻)	~4.8, ~6.75	None	pH > 2.5
SSA (H ₂ A)	~8.75	None	pH > 3.0
IMDA (H ₂ A)	~6.70	None	pH > 2.2
HQS (H ₂ A)	7.00	ULA ⁻ , ULA ₂ ²⁻	pH > 7.1
Tiron (H ₂ A ²⁻)	4.50	UL ₂ ²⁺ , U ₂ A ₃ ⁴⁺	pH > 4.3

^a Numbers indicate moles of base added per mole of UL.

^b Weak mixed ligand complexes may be formed initially.

Finally, as discussed in detail above, the U(IV)-NTA-Tiron system (reaction type 4B) is unique when compared to all the other systems studied. The stabilities of the individual single-ligand chelates are so high that the mixed ligand chelate is not formed to a detectable extent.

Coordination Number of U(IV). It has been noted in the present investigation that in the great majority of the mixed ligand chelates studied, the U(IV) seems to have an effective coordination number of eight. Hence, the resulting U(IV) mixed ligand complexes will probably have dodecahedral arrangements of donor groups similar to that shown by A in Figure 1 for the 1:1:1 U(IV)-EDTA-Tiron complex.

However, the 1:1:1 U(IV)-EDTA-IMDA system indicates the possibility of the expansion of the coordination number of U(IV) from a value of eight to that of nine. Formation of an EDTA-IMDA mixed ligand chelate may be interpreted as involving the displacement of one of the carboxylate groups of EDTA to make way for the three donor groups of IMDA, keeping the total coordination of U(IV) at eight. On the other hand, the relatively high stability constant for the addition of IMDA argues in favor of expansion of the coordination number of U(IV) to nine. In the 1:1:1 U(IV)-EDTA-IMDA mixed ligand chelate, it would probably involve nonacoordination of U(IV) in aqueous solution, as is indicated by Figure 4B. Although no structural data are available for U(IV) coordination in solution, the trigonal prismatic +3 structure suggested¹⁴ seems to offer the most favorable arrangement in mutual repulsions between the negative carboxylate donor groups of the ligand and a reasonable arrangement of the metal chelate rings. The most stable 1:1:1 monohydroxo U(IV)-EDTA-HQS system

(14) A. F. Wells, "Structural Inorganic Chemistry," 3rd ed., Clarendon Press, New York, N. Y., 1962, pp 98-100.

so involve similar nonacoordination of U(IV).

postulated expansion of the coordination number (IV) to nine for the 1:1:1 U(IV)-EDTA-IMDA. The 1:1:1 monohydroxo U(IV)-EDTA-HQS ligand chelate is similar to expansion of the coordination number of Th(IV) from eight to nine in the 1:1:1 Th(IV)-EDTA-IMDA and 1:1:1 Th(IV)-EDTA-NTA mixed ligand chelates postulated by Carey, *et al.*⁵ Also, possible expansion of the U(IV) coordination number from eight to a higher value was previously noted by the present authors⁹ for the monohydroxo 1:1 U(IV)-DTPA chelate and the 1:1 U(IV)-TTHA chelate (where DTPA is diethylenetriaminepentaacetic acid and TTHA is triethylenetetraminepentaacetic acid).

Equilibrium constants for the formation of mixed ligand chelates of U(IV) from the U(IV)-EDTA chelate compared in Table I with those of the analogous Th(IV) chelates previously reported by Carey, *et al.*⁵ In the mixed ligand systems studied there is the expected increase in formation constants when Th(IV) is replaced by U(IV) in the mixed ligand chelate. This increased stability is due to the smaller radius of the U(IV) ion, which results in more favorable ΔH and ΔG effects. The favorable enthalpy effect is due to the greater ionic bond strength of U(IV) complexes.

In addition, there will also be a favorable entropy effect since the smaller U(IV) chelate of the primary ligand will be more strongly hydrated in solution than the corresponding Th(IV) chelate. Consequently, reaction with the secondary ligand to form the 1:1:1 U(IV) mixed ligand chelate results in a greater entropy increase due to displacement of coordinated water molecules compared with the analogous Th(IV) chelate.

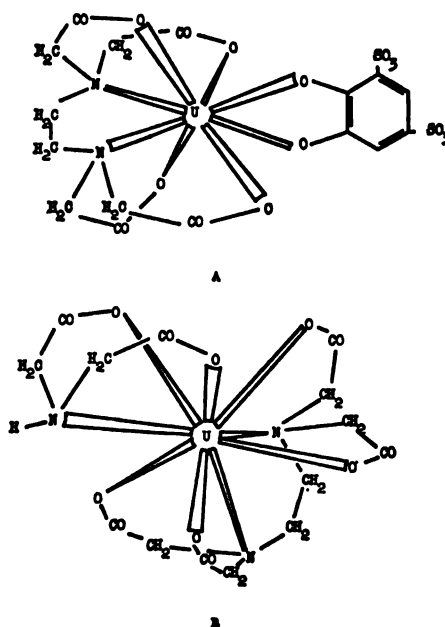


Figure 4. (A) Eight-coordinated 1:1:1 U(IV)-EDTA-Tiron mixed ligand chelate; (B) nine-coordinated 1:1:1 U(IV)-EDTA-IMDA mixed ligand chelate.

Table I also shows that the formation of the monohydroxo mononuclear mixed ligand chelate from the 1:1:1 Th(IV)-EDTA-HQS mixed ligand chelate occurs more readily when the Th(IV) ion is replaced by the U(IV) ion. This may also be considered to be principally a consequence of the smaller radius of the U(IV) ion.

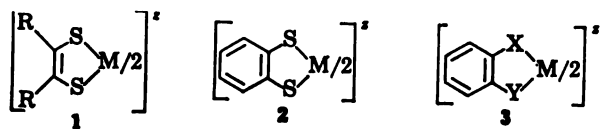
Electron-Transfer Complexes of the $[M-N_2S_2]$ Type. The Existence of Cation-Stabilized Free-Radical Complexes

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Abstract: The propensity to undergo chemical and electrochemical one-electron-transfer reactions, already established in bis-chelate complexes of the general types $[M-S_4]^+$ and $[M-N_4]^+$, has been shown to extend to two groups of $[M-N_2S_2]^+$ complexes. The first group consists of bis-chelate species of presumed *trans* structure and is exemplified by bis(*o*-mercaptoanilido)nickel, $Ni[o-C_6H_4(NH)S]_2$, which undergoes two one-electron reductions in DMSO and dichloromethane solutions and one one-electron oxidation in dichloromethane solution. The mono anion ($z = -1$) of this four-member electron-transfer series has a doublet ground state and displays in glasses a markedly anisotropic g tensor, similar to those of $[Ni-S_4]^-$ and $[Ni-N_4]^-$ species, and, accordingly, is assigned a 2B_1 ground state with an appreciable admixture of metal orbital in the odd-electron wave function. The second group is composed of tetradentate complexes having a necessarily *cis*- N_2S_2 arrangement. Complexes of the types $M(gma)^+$, $M(dtbb)^+$, and $Ni(dbh)^+$ were obtained with $M = Ni, Cu, Zn, Cd$ (gma = glyoxalbis(*o*-mercaptoanil), $dtbb$ = biacetylbis(thiobenzoylhydrazone), dbh = biacetylbis(benzoylhydrazone)). The Ni, Zn , and Cd neutral complexes are electrochemically reducible in nonaqueous media to $z = -1$ and -2 species. The monoanions possess doublet ground states. Their g tensors reveal a barely noticeable but unresolvable anisotropy (Ni) or no observable anisotropy (Zn, Cd). Because the Zn^- and Cd^- species can only be reasonably formulated as cation-stabilized free radicals (csfr), the properties of their g tensors are proposed as reasonable criteria for the appropriateness of csfr formulations, at least in $[M-S_4]^+$, $[M-N_4]^+$, and $[M-N_2S_2]^+$ systems. The epr properties of the *cis*- $[M-N_2S_2]^+$ complexes are interpreted in terms of a simple qualitative molecular orbital model, and probable ground states are assigned to five isoelectronic series of complexes of this general type.

The original demonstration⁴ of the interrelationship of certain bis(*cis*-1,2-disubstituted ethylene-1,2-dithiolato) complexes (1) by electron-transfer reactions has been followed by extensive synthetic and physical investigations of these and related complexes.⁵ Research in this area has taken two general directions. The first relates to the scope of electron-transfer reactions. It has been shown that neither an ethylenic ligand backbone nor an S_4 coordination sphere is a necessary condition for electron-transfer reactions because the complexes 2 (including ring-substituted variants)⁶ and 3, having $X = Y = O$,⁷ $X = Y = NH$,⁸ and $X = O, Y = S$,⁹ undergo one or more such reactions. The presence of a five-membered delocalized chelate ring does appear to be required, however.¹⁰



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(3) (a) University of California; (b) National Institutes of Health Predoctoral Fellow.

(4) A. Davison, N. Edelstein, R. H. Holm, and A. H. Maki, *J. Am. Chem. Soc.*, **85**, 2029 (1963).

(5) For one version of developments in this field through 1964, cf. H. B. Gray, *Transition Metal Chem.*, **1**, 239 (1965).

(6) (a) R. Williams, E. Billig, J. H. Waters, and H. B. Gray, *J. Am. Chem. Soc.*, **88**, 43 (1966); (b) M. J. Baker-Hawkes, E. Billig, and H. B. Gray, *ibid.*, **88**, 4870 (1966).

(7) F. Röhrscheid, A. L. Balch, and R. H. Holm, *Inorg. Chem.*, **5**, 1542 (1966).

(8) A. L. Balch and R. H. Holm, *J. Am. Chem. Soc.*, **88**, 5201 (1966).

(9) A. L. Balch, F. Röhrscheid, and R. H. Holm, *ibid.*, **87**, 2301 (1965).

(10) B. G. Warden, E. Billig, and H. B. Gray, *Inorg. Chem.*, **5**, 78 (1966); J. P. Fackler, Jr., and D. Coucouvanis, *J. Am. Chem. Soc.*, **88**, 3913 (1966).

The second research direction has been toward an elucidation of the ground- (and excited-) state descriptions of these complexes. Nearly all investigations have centered about the $[NiS_4C_4R_4]^-$ species, which have rich electronic spectra and doublet ground states. Their paramagnetic resonance spectra are readily observable in both fluid and glassy media, thereby permitting measurements of the isotropic g value and the principal components of the g tensor.

Among the essential features of any ground-state description in current molecular orbital theory are (i) specification of the symmetry of the highest occupied MO and, therewith, the possible metal and ligand orbitals admixed; and (ii) an estimate of the composition of this MO in terms of metal and ligand contributions. Of all nickel monoanions, $Ni(mnt)_2^-$ (1, $R = CN$) has been the most thoroughly studied.^{11,12} Measurement of the spin-Hamiltonian parameters of this ion enriched in ^{61}Ni in an oriented, magnetically dilute, single crystal has led to the conclusion that the most probable ground-state configuration is $\dots b_{2g}^{-1}b_{1g}^{-1}$ and that the b_{2g} MO¹³ has, very roughly, 50% metal character.^{11,15} Application of semiempirical

(11) A. H. Maki, N. Edelstein, A. Davison, and R. H. Holm, *ibid.*, **86**, 4580 (1964).

(12) S. I. Shupack, E. Billig, R. J. H. Clark, R. Williams, and H. B. Gray, *ibid.*, **86**, 4594 (1964).

(13) Note that the defined x and y axes in D_{2h} symmetry are interchanged in ref 11 compared to ref 12 and 14; we refer to the axis system of ref 11 in which the origin is at the metal, the xy plane is that of the complex, and the y axis bisects the chelate rings. Thus the d_{xy} orbital has b_{2g} symmetry.

(14) G. N. Schrauzer and V. P. Mayweg, *J. Am. Chem. Soc.*, **87**, 3585 (1965).

(15) The most probable ground state was deduced by the best fit of the measured principal components of the g and $A(^{61}Ni)$ tensors to theoretical expressions for these quantities calculated using perturbation theory and a basis set of pure metal 3d functions.¹¹ The use of this basis set has been criticized and the statement made that the epr results

ory has led to two different ground states for $[\text{Ni}(\text{mnt})_2]^-$. Shupack, *et al.*,¹² claim a $^2A_{1g}(\dots)$ state and 26% metal character for the $a_{1g}[\text{Ni}(\text{mnt})_2]^-$. It is difficult to reconcile this state with the observed spin-Hamiltonian parameters.¹¹ Schrauzer and Mayweg¹⁴ report calculation for the magnetically similar ion, $[\text{NiS}_4\text{C}_4\text{H}_4]^-$, to a likely $^2B_{3g}(\dots b_{3g}^1 b_{1g}^0)$ ground state and metal character in the b_{3g} MO. Because spin-orbital parameters are the most demanding properties of metal complexes to be reconciled with state electronic properties, we feel that the description of $[\text{Ni}(\text{mnt})_2]^-$ as containing, in a purely formal way, $\text{Ni}(\text{III})$ with the attendant d^7 configuration is reasonable and is the preferred formulation for interpreting epr properties.

Our formulation for $[\text{Ni}(\text{mnt})_2]^-$, in conjunction with A_{1g} ground state, has been put forth.¹² This formulation involves $\text{Ni}(\text{II})$ with the odd electron delocalized on the ligands. Such a complex could be a cation-stabilized free radical (csfr). In covalent complexes such as those considered, a ground-state description in terms of a formal oxidation state of the metal (and, hence, of the ligands) is a designation cannot be precise and must be an approximation, for both represent extreme cases. It is well emphasized by $[\text{Ni}(\text{gma})^-]$, the initial product of glyoxalbis(*o*-mercaptoanil)nickel, (4, $z = 0$). Authentic $[\text{Ni}(\text{gma})^-]$ ¹⁸ exhibits a detectable but rather small g -tensor anisotropy¹⁹ renders either description inadequate. Obviously what is needed is a complete MO description of the ground state for this and the other complexes considered. Because MO theory in its present semiempirical form cannot be considered reliable in predicting unique ground states for species of the complex 1-4, we feel that it is useful to establish criteria for application of the limiting descriptions. Accordingly, we report here our efforts to establish epr or detectable involvement or lack of essential

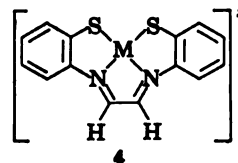
reinterpreted in terms of a complete MO basis set¹⁴ on the basis of the metal-ligand bonding is rather covalent¹² (*vide supra*). This statement is the contention that if a complete basis set is used, the present ground-state description might emerge from the process of using g and A components using precalculated MO's of the complex. We suggest that it is unrealistic to assume that eigenvalues can be calculated so accurately by semiempirical procedures for subsequent use, together with calculated or observed energy levels, can generate g and A values of sufficient validity to finitely more certain ground-state assignment than that made on a limited basis set. Covalency has been introduced in contrast to the use of a limited basis set by reasonable reduction of parameters in fitting measured parameters to theory.¹¹ The use of epr data involves the evaluation of metal-ligand mixtures from measured g and A values (*cf.*, *e.g.*, A. H. Maki and R. E. Berry, *J. Chem. Phys.*, 29, 31 (1958); H. R. Gersmann and R. E. Berry, *ibid.*, 36, 3221 (1962)) rather than the calculation of these parameters from preconstructed MO's of the complex. Finally, either is a formidable task for molecular species of the complexity of 3. In our previous work we have preferred to use the epr data in tractable form.

J. Stiefel, J. H. Waters, E. Billig, and H. B. Gray, *J. Am. Chem. Soc.*, 87, 3016 (1965).

Adamus, Q. Fernando, and H. Freiser, *ibid.*, 86, 3056 (1964). Results already presented,¹⁹ reinforced by more recent work (F. Lalor, M. F. Hawthorne, A. H. Maki, A. Davison, and Z. Dori, and E. I. Stiefel, to be published), have convinced us that the anion with a decidedly anisotropic g tensor produced by borohydride reduction of $[\text{Ni}(\text{gma})^0]$ was incorporated as $[\text{Ni}(\text{gma})^-]$ in ref 16 and that the sodium amalgam product (see Experimental Section) is actually $[\text{Ni}(\text{gma})^-]$, as in ref 19.

A. Maki, T. E. Berry, A. Davison, R. H. Holm, and A. L. Horne, *Chem. Soc.*, 88, 1080 (1966).

involvement of metal orbitals in the wave functions of unpaired electrons in complexes of the types 1-4. As part of this work the electron-transfer properties of complexes of the type $[\text{M}-\text{N}_2\text{S}_2]$ have been investigated. The results augment those already obtained for $[\text{M}-\text{S}_4]$,⁶ $[\text{M}-\text{O}_4]$,⁷ $[\text{M}-\text{N}_4]$,⁸ and $[\text{M}-\text{O}_2\text{S}_2]$ ⁹ systems in which, principally, $\text{M} = \text{Ni}$. Certain of our results on gma complexes have been communicated in preliminary form.¹⁹



Experimental Section

Preparation of Compounds. (a) Glyoxalbis(*o*-mercaptoanil)nickel, $[\text{Ni}(\text{gma})^0]$. $\text{Zn}(\text{gma})$ and $\text{Cd}(\text{gma})$ were prepared according to a published procedure.¹⁷ $\text{Ni}(\text{gma})$ was obtained in an entirely analogous manner as shiny black crystals only sparingly soluble in most organic solvents. A freshly prepared sample was analyzed.

Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{S}_2\text{Ni}$: C, 51.09; H, 3.06; N, 8.51; S, 19.49. Found: C, 51.20; H, 3.27; N, 8.22; S, 19.53.

$[(n\text{-C}_4\text{H}_9)_4\text{N}][\text{Ni}(\text{gma})^-]$. The following operations were performed *in vacuo* or in a nitrogen atmosphere. A suspension of 3.6 g (0.012 mole) of $\text{Ni}(\text{gma})$ in 30 ml of dry, peroxide-free tetrahydrofuran was shaken with a dilute amalgam made from 0.23 g (0.010 g-atom) of sodium and 25 ml of mercury. A rapid reaction with heat evolution ensued to produce an intense red-brown solution, which was separated from the amalgam and filtered to remove unreacted, excess $\text{Ni}(\text{gma})$. The filtrate was treated with a solution of 3.5 g of tetra-*n*-butylammonium bromide in 300 ml of methanol. Agitation of the solution caused the product to separate as small needles during a 2-3-min period. It was collected by filtration and washed with methanol (three 20-ml portions). The product was dried at 25° (10⁻³ mm) for 10 hr and obtained as small, shiny, black crystals, soluble in polar organic solvents to give red-brown solutions. Oxidation of these solutions by air yields immediately $[\text{Ni}(\text{gma})^0]$.

Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{S}_2\text{Ni}$: C, 63.05; H, 8.11; N, 7.35; S, 11.22. Found: C, 61.93, 61.83; H, 7.65, 7.83; N, 7.22, 7.07; S, 11.36, 11.55.

In this preparation it is important to note that a deficiency of sodium was used in the reduction. Excess sodium in the amalgam gives an emerald green solution, which is easily oxidized to a red-brown solution of $[\text{Ni}(\text{gma})^-]$ and which presumably contains $[\text{Ni}(\text{gma})^0]$, whose existence is indicated by polarographic data (*cf.* Table I).

(b) Bis(*o*-mercaptoanilido)nickel. *o*-Mercaptoaniline (5.0 g) and 2.2 g of potassium hydroxide were dissolved in 100 ml of 20% aqueous ethanol. This solution was mixed with one prepared from 4.7 g of nickel chloride hexahydrate and 15 ml of concentrated aqueous ammonia in 75 ml of water. A yellow precipitate of bis(*o*-aminothiophenolato)nickel(II) formed immediately and was filtered off. The precipitate was suspended in 300 ml of water containing 4.0 g of potassium hydroxide; air was passed through the suspension for 5 hr. The deep blue solid which formed was collected by filtration, washed with water, and dried *in vacuo* over P_2O_5 . The final product was obtained by two Soxhlet extractions with diethyl ether, which yielded deep blue crystals. A very similar procedure has been used by Hieber and Brück²⁰ to prepare a blue solid which they claimed to have the composition $[(\text{C}_6\text{H}_4(\text{NH}_2)\text{S})_2\text{Ni}]_x\text{O}_2\text{Ni}_x$.

Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2\text{Ni}$: C, 44.61; H, 3.75; N, 8.67; S, 19.85; Ni, 18.17. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{S}_2\text{Ni}$: C, 47.25; H, 3.30; N, 9.18; S, 21.02; Ni, 19.25. Found: C, 46.79; H, 3.71; N, 9.22; S, 21.02; Ni, 19.06 (total, 99.80).

(c) Bisacetylthiothiobenzoylhydrazones Complexes $[\text{M}(\text{dtbh})]$. The free ligand, H_2dtbh , and the nickel and copper complexes were obtained by the procedures of Bähr and Schleitzer.²¹

(20) W. Hieber and R. Brück, *Z. Anorg. Allgem. Chem.*, 269, 13 (1952).

(21) G. Bähr and G. Schleitzer, *ibid.*, 280, 161 (1955).

Table I. Polarographic Data for $[M-N_2S_2]^+$ and $[Ni-N_2O_2]^+$ Complexes

Complex	Couple $z \rightleftharpoons (z-1) + e^-$	Solvent	$E_{1/2}, v^a$	$i_d/C, \mu A/mmole$
$Ni[o-C_6H_4(NH)S]_2^a$	$-2 \rightleftharpoons -1$	DMSO	-1.04	6.2
	$-1 \rightleftharpoons 0$	DMSO	-0.19	6.4
	$-2 \rightleftharpoons -1$	CH_2Cl_2	-0.93	22
	$-1 \rightleftharpoons 0$	CH_2Cl_2	-0.03	27
	$0 \rightleftharpoons +1$	CH_2Cl_2	1.05	27
$Ni[SC(C_6H_5)NNH]_2^a$	$-2 \rightleftharpoons -1$	DMSO	-1.13	6.4
	$-1 \rightleftharpoons 0$	DMSO	-0.14	6.6
$Ni(dbh)^a$	$-2 \rightleftharpoons -1$	DMSO	-1.67	5.8
	$-1 \rightleftharpoons 0$	DMSO	-0.92	6.1
		CH_3CN	-1.00	32
$Ni(dtbb)^a$		CH_2Cl_2	-0.86	30
	$-2 \rightleftharpoons -1$	DMSO	-1.24	6.9
		CH_3CN	-1.32	23
		CH_2Cl_2	-1.26	23
	$-1 \rightleftharpoons 0$	DMSO	-0.53	7.0
$Cu(dtbb)^{a,b}$		CH_3CN	-0.55	33
		CH_2Cl_2	-0.48	28
	$-1 \rightleftharpoons 0$	DMSO	-0.15	6.3
		CH_3CN	-0.23	29
		CH_2Cl_2	-0.09	26
$Zn(dtbb)^a$	$0 \rightleftharpoons +1$	CH_2Cl_2	1.15	25
	$-2 \rightleftharpoons -1$	DMSO	-1.44	5.3
	$-1 \rightleftharpoons 0$	DMSO	-1.08	6.4
		CH_3CN	-1.10	25
$Cd(dtbb)^a$		CH_2Cl_2	-1.31	23
	$-2 \rightleftharpoons -1$	DMSO	-1.55	5.3
	$-1 \rightleftharpoons 0$	DMSO	-1.13	6.1
$Ni(gma)^a$	$-2 \rightleftharpoons -1$	DMSO	-1.05	6.9
	$-1 \rightleftharpoons 0$	DMSO	-0.30	6.5
$Zn(gma)^a$	$-2 \rightleftharpoons -1$	DMSO	-1.15	5.6
	$-1 \rightleftharpoons 0$	DMSO	-0.75	6.5
$Cd(gma)^a$	$-2 \rightleftharpoons -1$	DMSO	-1.33	5.2
	$-1 \rightleftharpoons 0$	DMSO	-0.79	6.5

^a All potentials not strictly comparable; see Experimental Section. ^b $Cu(dtbb)$ shows poorly resolved wave in CH_2Cl_2 at ~ -0.49 v ($i_d/C \sim 19$)

Zn(dtbb). Biacetylthiobenzoylhydrazide (1.8 g) dissolved in 400 ml of ethanol was added to a solution of 1.1 g of zinc acetate dihydrate in 100 ml of ethanol. The solution volume was reduced to ~ 100 ml whereupon orange crystals separated. These were collected by filtration, recrystallized twice from 1:1 v/v chloroform-ethanol, and dried over P_2O_5 in *vacuo* at 80° . The purified product was isolated as reddish orange crystals.

Anal. Calcd for $C_{18}H_{18}N_4S_2Zn$: C, 51.74; H, 3.86; N, 13.41; S, 15.35. Found: C, 51.40; H, 3.99; N, 13.14; S, 15.05.

Cd(dtbb). A solution of 1.64 g of sodium acetate trihydrate and 3.44 g of cadmium bromide tetrahydrate in 60 ml of ethanol was prepared and filtered to remove sodium bromide. To this solution was added a boiling solution of 3.53 g of biacetylthiobenzoylhydrazide in 200 ml of ethanol. The resultant deep red precipitate was collected and washed with ethanol. Purification was effected by Soxhlet extraction with chloroform followed by drying at 80° in *vacuo*. A brick red microcrystalline product was obtained.

Anal. Calcd for $C_{18}H_{18}N_4S_2Cd$: C, 46.50; H, 3.47; N, 12.05. Found: C, 46.84; H, 3.44; N, 12.44.

(d) Bis(thiobenzoylhydrazido)nickel. A solution of 2.0 g (13 mmole) of thiobenzoylhydrazine²³ in 100 ml of ethanol was added to a solution of 1.6 g (6.7 mmole) of nickel chloride hexahydrate in 100 ml of ethanol. Addition of 80 ml of concentrated aqueous ammonia produced a beige precipitate. The mixture was stirred for 9 hr while air was passed through it. The resulting deep blue solid was collected by filtration, washed with ethanol, and vacuum dried; the yield of the crude product is 2.0 g (80%). One gram of this material was extracted with 150 ml of pure, dry tetrahydrofuran for 8 hr. Cooling of the solution afforded a deep blue, finely crystalline product which was collected and vacuum dried.

Anal. Calcd for $C_{12}H_{12}N_4S_2Ni$: C, 46.82; H, 3.37; N, 15.60; S, 17.86. Found: C, 46.79; H, 3.17; N, 15.41; S, 17.62.

(22) B. Holmberg, *Arkiv Kemi*, **4**, 33 (1951).

(e) Biacetylthiobenzoylhydrazide Complexes, M(dbh). The free ligand, H_2dbh , was prepared by dissolving 14.1 g (0.10 mole) of benzoylhydrazine and 4.4 g (0.05 mole) of biacetyl in 150 ml of 1-propanol, followed by refluxing for 6 hr. The solution was filtered when hot and the white microcrystalline product washed with ethanol and ether, mp $280-290^\circ$ dec; lit.²⁴ 286° .

Ni(dbh). This compound was prepared according to Sacconi's method.²⁴

Cu(dbh). A solution of 3.3 g of biacetylthiobenzoylhydrazide and 0.8 g of sodium hydroxide in 70 ml of ethanol was added with stirring to a solution of 1.7 g of cupric chloride dihydrate in 50 ml of ethanol. The solution was allowed to stand for 1 hr after which brown crystals were isolated by filtration and dried. The crude product was twice recrystallized from 1:1 v/v chloroform-ethanol to yield greenish brown crystals which were dried over P_2O_5 in *vacuo* at 60° .

Anal. Calcd for $C_{18}H_{18}N_4O_2Cu$: C, 56.32; H, 4.20; N, 14.59. Found: C, 55.92; H, 4.31; N, 14.36.

Zn(dbh). This complex was prepared by the same procedure used for the cupric complex with the substitution of zinc acetate for cupric chloride. The final product was obtained as fine yellow crystals.

Anal. Calcd for $C_{18}H_{18}N_4O_2Zn$: C, 56.05; H, 4.18; N, 14.53. Found: C, 55.42; H, 4.28; N, 14.01.

Physical Measurements. Polarographic data were obtained using an ORNL Model 1988 polarograph equipped with a three-electrode configuration. A rotating platinum electrode served as the working electrode. For measurements in acetonitrile and 0.05 M (n -Pr₄N)ClO₄ supporting electrolyte were employed. In dichloromethane solutions the supporting electrolyte was 0.1 M (n -Bu₄N)(PF₆) and potentials were measured vs. a Ag-AgI reference electrode immersed in a 0.05 M (n -Bu₄N)I-0.5 M (n -Bu₄N)PF₆ solution in dichloromethane. The sample and reference compartments were connected by a salt bridge of silica gel impregnated with a dichloromethane solution of the supporting electrolyte. The entire arrangement for measurements in dichloromethane is described in detail elsewhere.⁷ The potentials quoted in Table I were obtained from measurements of solutions prepared from the neutral complexes. Electron paramagnetic resonance measurements were made using a Varian V-4500 spectrometer with 100-kc/sec field modulation. The klystron frequency was measured by means of a transfer oscillator and frequency counter, and the magnetic field was measured with a proton resonance gaussmeter monitored by the same frequency counter.

Results and Discussion

Polarographic and epr results referred to in the following sections are set out in Tables I-III.

Electron-Transfer Properties of $[M-N_2S_2]$ Complexes. The possibility that complexes of this general type have electron-transfer properties was stimulated by the report of Hieber and Brück²⁰ that a deep blue product resulted from the reaction of bis(*o*-aminothiophenolato)nickel(II) with oxygen in basic solution. Earlier, Feigl and Fürth²⁵ had reported a very similar reaction of a nickel salt and *o*-phenylenediamine in aqueous ammoniacal solution which led to a deep blue product now known to have the formulation $Ni[o-C_6H_4(NH)_2]_2$ and to be the central member of a five-membered electron-transfer series.⁸ An entirely analogous series, based on similar reasoning,^{7,8} can be envisaged for the $[Ni-N_2S_2]$ system consisting of the members 5-9. The Hieber-Brück product was claimed by them to have the composition $NiO[C_6H_4(NH_2)S]_2$ and the dimeric μ, μ -dioxo-bridged structure 10; this formulation has been widely quoted in standard texts and references as one of the few Ni(IV) complexes. As communicated earlier,⁷ repetition of this preparation²⁰ leads to a deep blue, diamagnetic compound whose *total* analysis corresponds to the composition $Ni[o-C_6H_4(NH)S]_2$.²⁶ That

(23) H. v. Pechmann and W. Bauer, *Ber.*, **42**, 663 (1909).

(24) L. Sacconi, *Z. Anorg. Allgem. Chem.*, **275**, 249 (1954).

(25) F. Feigl and M. Fürth, *Monatsh.*, **48**, 445 (1927).

Table II. Epr Results for [Ni-S₄]⁻ and [Ni-N₄]⁻ Complexes^a

Complex	Medium	$\langle g \rangle$	g_1	g_2	g_3	Ref
[NiS ₄ C ₄ (CN) ₄] ⁻	DMF-CHCl ₃	2.0633	1.996	2.043	2.140	4
	Single crystal ^b	(2.067) ^c	1.998	2.042	2.160	11
[NiS ₄ C ₄ (CF ₃) ₄] ⁻	DMF-CHCl ₃	2.0618	1.996	2.044	2.137	<i>f</i>
[NiS ₄ C ₄ (C ₆ H ₅) ₄] ⁻	DMSO	2.056	4
[NiS ₄ C ₄ H ₄] ⁻	py-CHCl ₃	2.056 ^d	1.996	2.039	2.126	14
Ni(tdt) ₂ ⁻	DMF-CHCl ₃	2.082	2.016	2.048	2.183	6a
Ni[o-C ₆ H ₄ (NH) ₂] ₂ ⁻	DMF-acetone	2.031 ^e	1.990	2.006	2.102	8

^a $\langle g \rangle$ values are the measured values in solution unless otherwise stated; g_1, g_2, g_3 values obtained from glasses or single crystal. ^b Host crystal (*n*-Bu₄N)(CuS₄C₄(CN)₄). ^c Calculated from anisotropic g values. ^d In pyridine solution. ^e 2.034 observed in DMSO solution.¹⁶

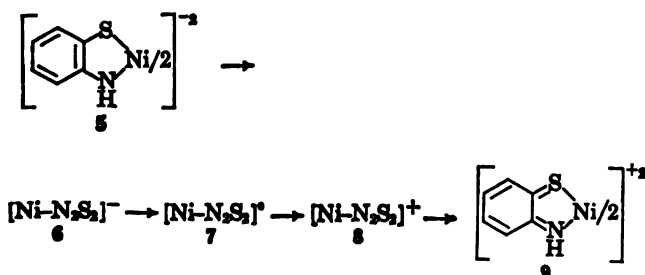
^f A. Davison, N. Edelstein, R. H. Holm, and A. H. Maki, *Inorg. Chem.*, **3**, 814 (1964).

Table III. Esr Results for [M-N₂S₂]^z and [M-N₂O₂]^z Complexes (M = Ni, Cd, Zn, $z = -1$; M = Cu, $z = 0$)

Initial Complex ^a	Medium ^b	Method of reduction ^c	$\langle g \rangle$ ^d	Glass, ~85°K.		
				g_1	g_2	g_3
Ni[o-C ₆ H ₄ (NH)S] ₂	2-MeTHF	Na(Hg)	2.0533	2.005	2.028	2.126
Ni[SO(C ₆ H ₄)NNH] ₂	2-MeTHF	Na(Hg)	2.0435	2.006	2.025	2.094
Ni(gma) (→ Ni-(H ₂ gma) ⁻) ^e	DMF-CHCl ₃	BH ₄ ⁻	2.051	2.009	2.027	2.119
Ni(gma)	DMSO-CHCl ₃	cpe	(2.003)	1.978	2.005	2.026
	DMF	cpe	2.0041
	2-MeTHF	Na(Hg)	(2.004)	1.979	2.006	2.028
	DMSO-CHCl ₃	...	2.0041	1.980	2.004	2.025
(n-Bu ₄ N)[Ni(gma)]	DMF-CHCl ₃ ^f	...	2.0042	1.975	2.005	2.026
	DMF-CHCl ₃	cpe			2.0027 ^h	
Zn(gma)	2-MeTHF	Na(Hg)			2.0033 ^h	
Cd(gma)	2-MeTHF	Na(Hg)			2.0024 ^h	
Ni(dbh)	CH ₃ CN	cpe	2.0006			
	2-MeTHF	Na(Hg)	2.0009		1.997 ⁱ	
Ni(dtbb)	CH ₃ CN	cpe	1.9973			
	2-MeTHF	Na(Hg)	1.9979			
Cu(dbh) ^j	2-MeTHF	...	2.109	2.230	2.048	
				(g_{11})	(g_{11}) ^o	
Cu(dtbb) ^k	2-MeTHF	...	2.062	
	DMF-CHCl ₃					
Zn(dtbb)	2-MeTHF	Na(Hg)	2.0023		2.0023	
Cd(dtbb)	2-MeTHF	Na(Hg)	2.0015		2.0015	

^a Complex reduced (where appropriate) by method given in column 3. ^b Mixed solvents are 50-50 v/v. ^c cpe, controlled potential electrolysis; Na(Hg), 2% sodium amalgam. ^d Isotropic (solution) values; parentheses indicate value calculated from glass data. ^e Calculated from $\langle g \rangle$ and g_{11} . ^f Fresh solution measured. ^g Reduction with borohydride in THF yields Ni(H₂gma)⁻, data from ref 18. ^h No measurable anisotropy in glass; spectra show additional line and half-field resonance compatible with triplet species. ⁱ Anisotropy not resolvable, measurement made at center of absorption. ^j $\langle a(^{63}\text{Cu}) \rangle = 7.19 \times 10^{-3} \text{ cm}^{-1}$, $\langle a(^{14}\text{N}) \rangle = 1.13 \times 10^{-3} \text{ cm}^{-1}$, $a_{11}(^63\text{Cu}) = 1.68 \times 10^{-3} \text{ cm}^{-1}$, $a_{11}(^14\text{N}) = 1.37 \times 10^{-3} \text{ cm}^{-1}$. ^k $\langle a(^{63}\text{Cu}) \rangle = 8.18 \times 10^{-3} \text{ cm}^{-1}$, $\langle a(^{14}\text{N}) \rangle = 1.38 \times 10^{-3} \text{ cm}^{-1}$.

this compound is the central member 7 of the electron-transfer series 5-9 is evidenced by the two one-electron reductions in DMSO and a (very anodic) one-electron

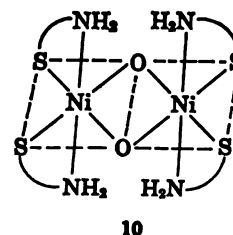


oxidation in dichloromethane. The most oxidized member, 9 has not been detected, probably because of the instability of the *o*-thionequinoneimine structure.

(26) The correct formulation of the Hieber-Brück product has also been recognized in reports^{16,27} appearing shortly after our original communication.⁹ Supporting evidence includes a parent ion peak in the mass spectrum at *m/e* 304¹⁶ and the results of a total analysis including oxygen.²⁷

(27) L. F. Larkworthy, J. M. Murphy, and D. J. Phillips, *J. Am. Chem. Soc.*, **88**, 1570 (1966).

Despite the relative ease with which the neutral complex is reduced to the monoanion by a variety of mild reducing agents, we have been as yet unable to isolate a pure salt of this species.

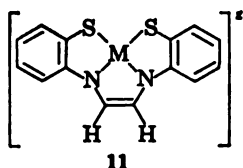


The electron-transfer propensity of Ni(gma) was first demonstrated by Stiefel, *et al.*,¹⁸ who have shown that the series Ni(gma)^z ($z = 0, -1, -2$) exists. The neutral nickel complex¹⁷ as well as neutral complexes of other metals,^{17,28} including zinc and cadmium,¹⁷ have been isolated. We have verified the existence of the three-membered series in DMSO and DMF by polarography and have established by cyclic voltammetry the

(28) E. Bayer, *Angew. Chem.*, **73**, 659 (1961); **76**, 76 (1964).

reversibility of the electrode reactions in DMF.¹⁹ In addition, we have found that Zn(gma) and Cd(gma) in DMF and DMSO can be reduced in two reversible, one-electron steps to the mono- and dianions at potentials significantly more negative than those of the Ni(gma)⁺ system. Reduction of Ni(gma) with sodium amalgam in tetrahydrofuran has afforded the exceedingly oxygen-sensitive monoanion as the crystalline tetra-*n*-butylammonium salt. Because of their extreme oxidative instability, no attempt has been made to isolate the zinc or cadmium mono- and dianions or the nickel dianion.

An electron-transfer series analogous to 5-9 can be visualized for the M(gma)⁺ system. The terminal reduced member could be represented by 11 ($z = -2$) and the intermediate neutral member by 4 or 11 ($z = 0$) or some resonance combination thereof. The gma ligand system provides three five-membered chelate rings, each of which can be to some extent delocalized with concomitant change in formal oxidation state of the metal.²⁹ Obviously related delocalization possibilities exist in the neutral complexes of 1, 2, and 3, thereby underscoring the electronic similarities of the ligand systems known to promote electron-transfer behavior.



We have investigated the generality of electron-transfer reactions in other [M-N₂S₂] complexes by examining species having in principle delocalization properties analogous to those of 7 and 4 (or 11) but with otherwise dissimilar ligand systems. In this connection we have reexamined the work of Jensen and Miguel,³⁰ who have reported that a deep blue product of apparent composition Ni[SC(Ph)NNH]₂ results from the aerobic oxidation of an ammoniacal solution of nickel chloride and thiobenzoylhydrazine. We have obtained this product under similar conditions and confirmed its composition. The oxidation presumably proceeds through the intermediates Ni[SC(Ph)NNH₂]₂Cl₂ and Ni[SC(Ph)NNH]₂, both of which have been isolated.³⁰ The deep blue product can be reduced polarographically in DMSO to the $z = -1$ and -2 species at potentials very similar to those of the Ni[o-C₆H₄(NH)S]₂⁺ system. The structures of the Ni[SC(Ph)NNH]₂⁺ species can be represented by 12 and other appropriate valence-bond representations.³¹

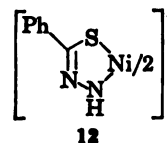
Biacetylbis(thiobenzoylhydrazone) complexes, one representation of which is 13,³² bear the same resem-

(29) No X-ray structural information on gma complexes is available so that the relative contributions of 4 and 11 to the ground state of neutral complexes is unknown. The structure of the related complex biacetylbis(mercaptoethylimine)nickel has been reported (Q. Fernando and P. J. Wheatley, *Inorg. Chem.*, **5**, 1726 (1966)); this species could in principle be considered the neutral parent of a three-membered electron-transfer series with $z = 0, -1, -2$. The large standard deviations of reported distances in the C₂N₂ chelate ring, common to this species and M(gma), preclude conclusions relative to delocalization in this ring.

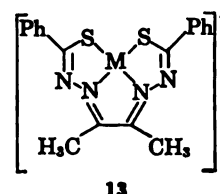
(30) K. A. Jensen and J. F. Miguel, *Acta Chem. Scand.*, **6**, 189 (1952).

(31) Note that valence bond structures can be written for Ni[o-C₆H₄(NH)S]₂⁺ and Ni[SC(Ph)NNH]₂⁺ which are entirely analogous to those for [NiS₄C₄R₄]⁺ (cf. ref 14).

(32) The structure of the related complex, 2-keto-3-ethoxybutyraldehydebis(thiosemicarbazone)copper has been briefly reported (M. R.



blance to Ni[SC(Ph)NNH]₂⁺ as does M(gma)⁺ to Ni[o-C₆H₄(NH)S]₂⁺. Accordingly, these complexes, first prepared by Bähr and Schleitzer,²¹ do undergo electron-transfer reactions. The neutral complexes with M =



Ni, Zn, Cd may be reduced in two one-electron steps to the $z = -1$ and -2 species in DMSO. Because of the apparent instability of Ni(gma)⁻ in at least one solvent medium,^{18,19} we have verified the existence of the $-1 \rightleftharpoons 0$ couple of nickel-, copper-, and zinc-dtbh complexes in three solvents. The M(dtbh)⁻ species are considerably more oxidatively unstable than are the corresponding M(gma)⁻ complexes, and isolation of them has not proven feasible. Cu(dtbh) is particularly easily reduced to a monoanion, but despite a number of attempts we have not been able to isolate a pure salt of this ion.

Several complexes of biacetylbis(benzoylhydrazone) have been prepared. These differ from 13 only in having oxygen in place of sulfur. Ni(dbh) undergoes two one-electron reductions in DMSO where it presumably exists as a paramagnetic, solvated species. Only the first reduction is observed in dichloromethane and acetonitrile, in which the neutral complex is diamagnetic and occurs at potentials significantly more negative than those for Ni(dtbh) in the same solvents. Cu(dbh) and Zn(dbh) do not undergo well-defined one-electron reductions.

Epr Results. (1) [Ni-S₄]⁻ and [Ni-N₄]⁻ Complexes. A collection of *g*-value data for all presently known anions of these types is given in Table II. It is evident that all complexes are markedly anisotropic and that isotropic and anisotropic *g* values of [NiS₄C₄R₄]⁻ species are virtually independent of R. It is concluded that all of these ions, including Ni[o-C₆H₄(NH)S]₂⁻, very probably have the same ground state although the extent of electron delocalization may differ somewhat among the species. On the basis of previous work¹¹ the probable ground state is ²B_g, which generates the following characteristic features in these anions:³³ (i) *g* equal to or in excess of 2.03 and a lower limit of ~2.05 for [Ni-S₄]⁻; (ii) three observable principal *g* values, showing that the effective ligand field is of rhombic, not axial, symmetry. These observations do not support a pure csfr description of the ground state. Although three principal *g* values have been observed

Taylor, E. J. Gabe, J. P. Glusker, J. A. Minkin, and A. L. Patterson, *J. Am. Chem. Soc.*, **88**, 1845 (1966)). The complex is planar and is depicted as having an α-diimine chelate ring; bond angles and distances were not given.

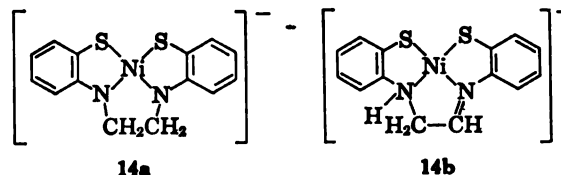
(33) An analogous ground state (²B_g in C_{2h} symmetry) applies for Ni[o-C₆H₄OS]₂⁻ which has *g* = 2.083, *g*₁ = 2.017, *g*₂ = 2.036, *g*₃ = 2.191 (DMF-CHCl₃),⁹ values nearly identical with those of Ni(tdt)₂⁻ in the same medium.^{6a}

zen solutions of sulfur and sulfur-containing s³⁴ and in irradiated single crystals of sulfur-containing compounds,³⁵ the largest anisotropic value is 2.066.³⁶ Furthermore, in radicals where it is probable that the odd electron is essentially on the sulfur atom, $\langle g \rangle$ has not been observed and is 2.03³⁴ and is frequently ~ 2.01 . For example, in the radical anion of 1,8-naphthalene disulfide, 2.0110; extended Hückel calculations predict complete localization of the odd electron on the atoms.³⁷ Likewise, in the species which is applied the 2,4,6-tri-*t*-butylphenylmercapto radical, hyperfine splitting and $\langle g \rangle = 2.0104$ are found.³⁸ We include that the larger *g*-value anisotropies and isotropic *g* values of the complexes in Table II are indications of appreciable admixture of *d* orbitals of the metal in the wave function of the odd electron. We have already remarked, the anisotropic and isotropic *g* of Ni(mnt)₂⁻, as well as the ⁶¹Ni hyperfine *g* tensor, can be quantitatively accounted for by the 3_g ground state and a relatively large degree of ligand covalent bonding.

Bis-Bidentate [M-N₂S₂]⁻ Complexes. Ni[o-(H)S]₂⁻ and Ni[SC(C₆H₅)NNH]₂⁻ were prepared by sodium amalgam reduction in 2-methyltetrahydrofuran but were not isolated. Both ions give strikingly similar epr spectra with the general features i and ii above. Hyperfine splitting was not observed in solution. Because of the close relationship between the *g* values of these complexes and those in II, it is concluded that a ³B_g ground state (as C_{2h} symmetry) is very probable for these [Ni-species].³⁹

M(gma)⁻ Complexes. Ni(gma) has been prepared by controlled potential electrolysis in DMSO-solution and by treatment with sodium amalgam in ethyltetrahydrofuran. Both methods generate complexes with *g* values only slightly above the free-electron value (2.0023) and with a *g* anisotropy markedly less than those of bis-bidentate [M-N₂S₂]⁻ or [M-S₄]⁻ complexes. Further, the analyzed salt (*n*-Bu₄N)[Ni] in DMSO-CHCl₃ solution or in a freshly prepared CHCl₃ solution gives isotropic and anisotropic *g* within experimental error of those obtained by chemical or chemical reduction of Ni(gma). Usually, borohydride reduction of Ni(gma) was found to produce Ni(gma)⁻.¹⁶ This is now known to be the case and the product obtained has been identified as the bridge-hydrogenated species 14a

or 14b,¹⁸ Ni(H₂gma)⁻. The borohydride reduction product is reported¹⁶ to have $\langle g \rangle = 2.051$, $g_1 = 2.009$, $g_2 = 2.027$, $g_3 = 2.119$, values very similar to those of the bisbidentate [Ni-N₂S₂]⁻ species.



Two particular advantages of the gma system over the bidentate ligands in 1-3 are that the zinc and cadmium complexes, if monomeric, are constrained to have a more or less planar structure similar to that which Ni(gma) (diamagnetic) surely possesses, and that they are reducible to monoanions.⁴⁰ Zn(gma)⁻ and Cd(gma)⁻ can only be reasonably formulated to contain Zn(II) and Cd(II) with closed-shell *d*¹⁰ configurations and a coordinated radical-anion ligand and, therefore, should be useful for establishing criteria of metal orbital involvement in the odd-electron wave functions of [M-N₂S₂]⁻ complexes. The *g* tensors of Zn(gma)⁻ and Cd(gma)⁻ are isotropic in glasses to the limit of resolution and have values extremely close to that of a free spin.

(4) M(dtbbh)^{0,-1} Complexes. Sodium amalgam reduction of Zn(dtbbh) and Cd(dtbbh) affords the monoanions whose *g* values are virtually identical with those of the corresponding gma species. Values very near the free-electron value are found and no anisotropy is measurable in glasses of 2-methyltetrahydrofuran. Ni(dtbbh)⁻ prepared by chemical or electrochemical reduction exhibits isotropic *g* values just under the free-electron value and a barely noticeable anisotropy in 2-methyltetrahydrofuran glass which was, however, not sufficiently well resolved to measure. It is apparent that the degree of metal orbital involvement in Ni(dtbbh)⁻ is scarcely detectable by epr measurements and is only slightly greater than that of Zn(dtbbh)⁻ and Cd(dtbbh)⁻, which is not detectable. Cu(dtbbh)⁰ solutions in 2-methyltetrahydrofuran and DMF-CHCl₃ give at room temperature a spectrum characteristic of planar Cu(II) complexes.⁴³ Hyperfine splittings due to ^{63,65}Cu and ¹⁴N are clearly resolved. The spectrum in frozen glasses ($\sim 85^\circ$) is complex and has not been fully interpreted as yet.

(5) M(dbh)^{0,-1} Complexes. Generation of Ni(dbh)⁻ was accomplished by chemical or electrochemical reduction of the neutral complex. The epr properties of this anion are nearly identical with those of Ni(dtbbh)⁻, viz., an isotropic *g* value very near the free-electron value and a barely observable anisotropy in 2-methyltetrahydrofuran glass which is too small to measure. The epr spectrum of Cu(dbh) is entirely usual for a Cu(II) complex with an O₂N₂ coordination sphere.⁴³

(40) The only zinc complexes of the type [Zn-S₄]⁻ which have been reported are Zn(tdt)₂⁻¹ and Zn(mnt)₂⁻¹.⁴¹ No analogous cadmium complexes are known nor are any [M-N₄]⁻ species of either metal. Unlike other M(mnt)₂⁻¹ complexes, Zn(mnt)₂⁻¹ is very probably tetrahedral,⁴² and in acetonitrile or dichloromethane it does not undergo a discrete one-electron oxidation.

(41) W. H. Mills and R. E. D. Clark, *J. Chem. Soc.*, 175 (1936).

(42) E. Billig, R. Williams, I. Bernal, J. H. Waters, and H. B. Gray, *Inorg. Chem.*, 3, 663 (1964).

(43) A. H. Maki and B. R. McGarvey, *J. Chem. Phys.*, 29, 31, 35 (1958); D. Kivelson and R. Neiman, *ibid.*, 35, 149 (1961); A. K. Wiersma and J. J. Windle, *J. Phys. Chem.*, 68, 2316 (1964).

I. G. Hodgson, S. A. Buckler, and G. Peters, *J. Am. Chem. Soc.*, 1963); J. J. Windle, A. K. Wiersma, and A. L. Tappel, *J. Phys.*, 41, 1996 (1964); A. Zweig and W. G. Hodgson, *Proc. Roy. Soc.*, 417 (1964); and references therein.

18. Akasaka, *J. Chem. Phys.*, 45, 90 (1966), and references

in exception to this statement is found with the radical obtained on bombardment of a single crystal of L-cysteine hydrochloride, $g_x = g_y = 1.99$, $g_z = 2.29$; K. Akasaka, *ibid.*, 43, 1182. The large value of g_z is attributed to a near-degeneracy of the 3p_y sulfur orbitals, one of which is occupied by the odd electron. A similar situation should not be present in the complexes under

19. Zweig and A. K. Hoffman, *J. Org. Chem.*, 30, 3997 (1965).

20. Rundel and K. Scheffler, *Angew. Chem.*, 77, 220 (1965).

21. D_{2h} symmetry any of the ground states (³A_g, ³B_{2g}, ³B_{1g}) contra our previous analysis does in principle require a threefold axis of the *g* tensor.¹¹ Our designation of the ³B_g ground state as probable for these [Ni-N₂S₂]⁻ complexes is based only upon isotropies of their *g* tensors, which are about the same as those of [M-S₄]⁻ species.

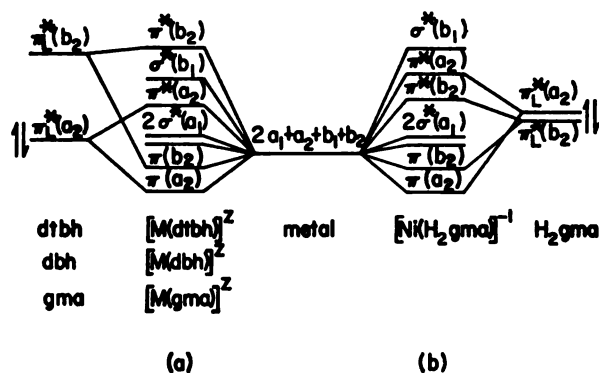


Figure 1. Qualitative molecular orbital diagrams for *cis*-[M-S₂N₂]⁺ complexes: (a) [M(dtbbh)]⁺, [M(dbh)]⁺, [M(gma)]⁺ complexes (see text for comments about variable energy order of $\sigma^*(b_1)$ and $\pi^*(b_2)$); (b) *sym*-Ni(H₂gma)⁻.

Criteria of Metal-Orbital Involvement. We take as models for the paramagnetic dtbh and gma complexes in which there will be minimal metal orbital involvement in the odd-electron wave functions the monoanions of zinc and cadmium. In the neutral complexes both the ligand and metal have closed-shell configurations. The odd electron added in the first reduction step is then described by what must be an essentially ligand-based MO (*vide infra*). The *g* tensors anticipated approach those of an aromatic free radical. The extent to which sulfur atoms will increase the *g* value above the free-electron value by spin-orbit coupling is difficult to predict. On the basis of available results this effect is slight in aromatic radicals.⁴⁴ Accordingly, it is proposed that gma and dtbh complexes having coordinated radical-anion ligands should manifest the following *g*-tensor properties characteristic of aromatic radicals:⁴⁵ (i) isotropic values less than ~ 2.01 , and (ii) slight or unresolvable anisotropy. As pointed out elsewhere,¹⁸ when comparing complexes of the same metal with different ligands, it is especially desirable to have measurement of the anisotropic dipole-dipole contribution to the electron-nucleus hyperfine tensor in addition to the principal components of the *g* tensor. However, such information is available only for Ni(mnt)₂⁻ so conclusions about metal-orbital involvement can be drawn only from properties of the *g* tensors.

Using these criteria the paramagnetic complexes considered in this work are assigned the ground-state descriptions as shown in Table IV. The classification of Ni(gma)⁻ is perhaps least satisfactory. Compared to the [Ni-S₄]⁻ and the [Ni-N₄]⁻ species, this complex has the least metal admixture in the odd-electron orbital, as judged from the smaller *g* anisotropy, such that this orbital is mostly, *but not completely*, ligand-based.

The most striking correlation which is apparent in the classification of the [Ni-S₂N₂]⁻ complexes is the effect of bridge conjugation on the description of the ground state. This effect is well illustrated by the comparison of Ni(H₂gma)⁻ and Ni(gma)⁻, where the *cis* geometry is maintained. Conjugation of the ligands leads to a striking reduction in the *g* tensor (*cf.* Table III), con-

(44) It is significant to note that $\langle g \rangle = 2.03$ and $\Delta g_{\max} = 0.06$ have thus far been observed only in alkylsulfur radicals, where substantial delocalization of the odd spin onto the hydrocarbon portion is unlikely.

(45) For a tabulation and discussion of *g* tensors of oriented π -electron free radicals (not containing sulfur), *cf.* J. R. Morton, *Chem. Rev.*, **64**, 453 (1964).

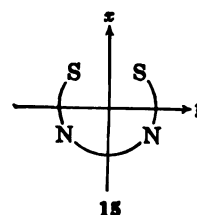
Table IV

² B _g or ² B _g with appreciable metal-orbital admixture	Csfr, Ni(II), d ⁸	Cu(II), d ⁹	Csfr, M(II), d ¹⁰
[NiS ₄ C ₄ R ₄] ⁻	Ni(gma) ⁻	Cu(dtbbh)	Zn(gma) ⁻
Ni(tdt) ₂ ⁻	Ni(dbh) ⁻	Cu(dtbbh)	Zn(dtbbh) ⁻
Ni[o-C ₆ H ₄ (NH) ₂] ₂ ⁻	Ni(dtbbh) ⁻		Cd(gma) ⁻
Ni[o-C ₆ H ₄ (NH)S] ₂ ⁻			Cd(dtbbh) ⁻
Ni[SC(Ph)NNH] ₂ ⁻			
Ni(H ₂ gma) ⁻			

* Assumed *trans* (C_{2h}) structure. ^b Possible ground states: ³A_g (C_{2v}, 14a), ³A_g (C₁, 14b).

sistent with an increase in the ligand character of the half-filled molecular orbital. This correlation has prompted us to deduce from the paramagnetic resonance results a qualitative molecular orbital model for bonding in these complexes.

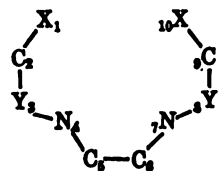
Simplified Bonding Model. *cis*-[M-N₂S₂]⁺ complexes possess the common chelate ring structure (15) of C_{2v} symmetry. The π and σ MO's transform as $a_2 + b_1$



and $a_1 + b_1$, respectively. Symmetries of the metal orbitals are as follows: $a_1 - d_{z^2}, d_{x^2-y^2}, s, p_z$; $a_2 - d_{yz}$; $b_1 - d_{xy}, p_y$; $b_2 - d_{xz}, p_x$. Because of the over-all complexity of these systems, we outline what appears to be the simplest possible model. A partial, qualitative MO diagram for [M(dtbbh)]⁺, [M(dbh)]⁺, and [M(gma)]⁺ complexes is set out in Figure 1a. The orbitals shown are those which presumably will have significant metal character and/or those which will be relevant in ground-state descriptions. The complex metal-ligand orbital mixing allowed by symmetry has been simplified by assuming that, for the purpose of ground-state descriptions, the most important π mixing will involve ligand orbitals which are most nearly non-bonding; these are just those which are the highest filled and lowest vacant orbitals in the dinegative ligand. The energy order, symmetries, and eigenvectors of these orbitals were obtained from a series of Hückel calculations.⁴⁶ The results are given in Table V. The coefficients c_6 - c_{10} (not shown) are obtained for the a_2 and b_2 orbitals by multiplying c_1 - c_5 by -1 and $+1$, respectively. For dtbh, dbh, and gma, the forms of $\pi^*(a_2)$

(46) To assure the reliability of the energy orders and general forms of the eigenvectors, the ordinary Hückel parameters k and h in $\alpha_i = \alpha + h_i\beta$ and $\beta_{ij} = k_{ij}\beta$ were varied over wide ranges in calculations for gma, dtbh, and dbh. Particular attention was given to the sulfur parameters whose suggested values are variant and dependent on the specific system and property under investigation.⁴⁷ Representative results were obtained with $\beta_{CN} = \beta_{NN} = \beta$ and $\alpha_N = \alpha + 0.5\beta$ for the three ligands. Using these parameters and simultaneously varying k_{CS} and h_S over the limits $0.5 \leq k_{CS} \leq 1.5$ and $0 \leq h_S \leq 2$, it is found that for dtbh and gma the energy differences between $\pi^*(a_2)$ and $\pi^*(b_2)$, $\pi^*(a_1)$ and the next most stable MO, and $\pi^*(b_2)$ and the next highest MO are all ~ 0.4 - 0.8β or more.

(47) D. S. Sappenfield and M. M. Kreevoy, *Tetrahedron Suppl.*, **2**, 157 (1963); A. Kuboyama, *J. Am. Chem. Soc.*, **86**, 164 (1964); R. Gardil and E. A. C. Lucken, *ibid.*, **87**, 213 (1965); E. T. Strom and G. A. Russell, *ibid.*, **87**, 3326 (1965). For a discussion of sulfur parameters in HMO theory, *cf.* R. Zahrádnik, *Advan. Heterocyclic Chem.*, **5**, 1 (1965).

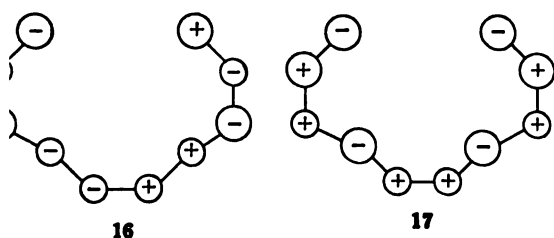
V. Molecular Orbitals of dtbh, dbh, gma, and H₂gma^a

dtbh: X=S, Y=N
 dbh: X=O, Y=N
 gma, H₂gma: X=S, Y=C

MO	$E(\beta)$	c_1	c_2	c_3	c_4	c_5
bh ^{b,c}	$\pi_L^*(a_2)$	0.1031	-0.3697	+0.1467	+0.3962	-0.3040
	$\pi_L^*(b_2)$	-0.4236	-0.3159	+0.2918	+0.0811	-0.3667
dh ^{c,d}	$\pi_L^*(a_2)$	0.1659	-0.2316	+0.2059	+0.4078	-0.3422
	$\pi_L^*(b_2)$	-0.4397	-0.2327	+0.3010	+0.0958	-0.3910
aa ^b	$\pi_L^*(a_2)$	0.1504	-0.4518	+0.1579	+0.2538	-0.2082
	$\pi_L^*(b_2)$	-0.2998	-0.2170	+0.1736	+0.0128	-0.4224
<i>m</i> -H ₂ gma ^b	$\pi_L^*(b_2)$	0.0000	-0.5345	+0.2673	+0.2672	-0.5345
	$\pi_L^*(a_2)$...

^a Results obtained with $\beta_{CN} = \beta_{NN} = \beta$, $\alpha_N = \alpha + 0.5\beta$. ^b $\beta_{CS} = \beta_{CN} = \beta$, $\alpha_S = \alpha + 0.5\beta$. ^c $\beta_{NN} = \beta$, phenyl groups coplanar with molecule. ^d $\alpha_O = \alpha + 1.5\beta$.

and $\pi^*(b_2)$ (17) are shown below in schematic. On the basis of the form of its eigenvector $\pi^*(a_2)$



ected to mix significantly with d_{yz} . On the other, overlap of $\pi^*(b_2)$ with d_{xz} is not large, and probably little mixing occurs. On this basis $\pi^*(b_2)$ pure 1a is heavily ligand in character.

e tetradentate complexes which have been isolated nerated chemically or electrochemically in solution nto the isoelectronic groups I-V below, arranged rder of increasing number of valence electrons. dtbh system offers the broadest base for ground-comparisons because all species in these groups been prepared or generated. In addition to the

I	II	III	IV	V
Ni^0 Cu^+	Ni^- Cu^0	Ni^{-2} Cu^- Zn^0 Cd^0	Zn^- Cd^-	Zn^{-2} Cd^{-2}

lata already discussed, it is noted that Ni^0 , Zn^0 , Cd^0 complexes are diamagnetic. No direct evidence is available relating to the ground states of Cu^+ group I, Ni^{-2} or Cu^- in group III, and Zn^{-2} and Cd^{-2} in group V. Examining first group II complexes, pr data leave little doubt that the ground states of and Ni^- are different. Both $\text{Cu}(\text{dbh})$ and $\text{Cu}(\text{dtbh})$ give characteristic spectra of $\text{Cu}(\text{II})$ complexes ig near-axial symmetry. Referring to Figure 1a, complexes are assigned the configuration... $\pi^*(b_2)$. $\text{Ni}(\text{dtbh})^-$ and $\text{Ni}(\text{dbh})^-$, on the other hand, fect spectra not compatible with this configura-

Their csfr formulations are best accommodated erting the order of $\sigma^*(b_1)$ and $\pi^*(b_2)$, leading to onfiguration ... $\pi^*(b_2)$. A slight admixture of this MO and/or mixing in other configurations by orbit coupling could account for the just noticeable but unresolvable g -tensor anisotropy. All MO's

in group I complexes up to and including $\pi^*(a_2)$ are filled. The configuration of the Ni^0 complexes is presumably ... $\pi^*(b_2)$, $2\sigma^*(a_1)$, $\pi^*(a_2)$. The relative order of these orbitals is not known, but the results on group II complexes strongly indicate that they are of lower energy than $\sigma^*(b_1)$ or $\pi^*(b_2)$. In group III the ... $\sigma^*(b_1)$ configuration for Zn^0 and Cd^0 is assigned. The possibility of triplet ground states, viz., $\sigma^*(b_1)\pi^*(b_2)$, for Cu^- and Ni^{-2} is recognized, but no information is available. The $\pi^*(b_2)$ configuration is believed to apply to the group IV species. Here metal orbital admixture, as reflected by the epr results, is minimal due to the stability of the effective d^{10} configuration of the coordinated metal. The $\pi^*(b_2)$ configuration follows for the species of group V.

Finally, attention is turned to a comparison of $\text{Ni}(\text{gma})^-$ and $\text{Ni}(\text{H}_2\text{gma})^-$, which have markedly different g tensors. For H_2gma in both the symmetrical (14a, *sym*) and unsymmetrical forms (14b, *unsym*), a series of Hückel calculations similar to those for gma was performed⁴⁸ but with $\beta_{CC} = 0$ and one or both β_{CN} values for the bridge taken as zero. Compared to gma , the absence of a conjugated bridge π system in either structure leads, in any calculation, to a much reduced interaction of the two halves of the ligand system. It is just this effect which is believed to account for the difference in magnetic properties of the two complexes. Because the detailed structure of $\text{Ni}(\text{H}_2\text{gma})^-$ is at present unknown, 14a is selected as the model structure for investigating the effect of bridge hydrogenation on ground-state electronic properties. Use of this structure facilitates a direct comparison with the parent ion, $\text{Ni}(\text{gma})^-$, for both have idealized C_{2v} symmetry. In *sym*- $\text{H}_2\text{gma}^{-2}$ the ligand orbitals taken to be most important in π mixing with the metal orbitals are $\pi_L^*(b_2)$ and $\pi_L^*(a_2)$, both of which have a Hückel energy of 0β .⁴⁸ These orbitals have forms similar to 16 and 17 but with no contribution from the bridge carbon atoms (*cf.* Table V). As before, $\pi_L^*(a_2)$ will mix much more strongly with d_{yz} than will $\pi_L^*(b_2)$ with d_{xz} . A qualitative MO diagram for *sym*- $\text{Ni}(\text{H}_2\text{gma})^-$ showing the orbitals of principal interest is given in Figure 1b.

(48) These are the highest occupied and lowest vacant orbitals in the dinegative ligand. Using the parameters in Table V the next most stable and unstable orbital pairs have energies of 0.5656β and -1.1294β , respectively.

Unlike the case of Ni(gma)^- , the differential mixing of $\pi_L^*(a_2)$ and $\pi_L^*(b_2)$ with metal orbitals will depend nearly completely on overlap, rather than on a combination of overlap and relative energy factors. This situation will almost certainly lead to the energy order $\pi^*(a_2) > \pi^*(b_2)$ for $\text{sym-Ni(H}_2\text{gma)}^-$, compared to $\pi^*(b_2) > \pi^*(a_2)$ for Ni(gma)^- . Further, the epr results for the former require $\sigma^*(b_1) > \pi^*(a_2)$ inasmuch as the observed g tensor does not reveal the near-axial symmetry expected from the $\sigma^*(b_1)$ configuration. Therefore, the $\dots \pi^2(b_2), 2\sigma^4(a_1), \pi^{*2}(b_2), \pi^{*1}(a_2)$ ground configuration is assigned to $\text{sym-Ni(H}_2\text{gma)}^-$, with the order of orbitals more stable than $\pi^*(a_2)$ unknown. The proposed appreciable admixture of d_{yz} in this MO results in a situation analogous to the ${}^2B_{3g}$ states of $[\text{Ni-S}_4]^-$ and $[\text{Ni-N}_4]^-$ and to the 2B_g state of $\text{trans-[Ni-S}_2\text{N}_2]^-$, and on this basis could account for the observed g -tensor anisotropy.

Summary

The principal result of this work is the experimental establishment of g -tensor properties for coordinated radical anions. For those complexes assigned the csfr formulation, the measured g tensors suggest the

following order of decreasing metal orbital involvement in the odd-electron wave functions: $\text{Ni(gma)}^- > \text{Ni(dtbh)}^- \sim \text{Ni(dbh)}^- > \text{Zn(gma)}^- \sim \text{Zn(dtbh)}^- \sim \text{Cd(gma)}^- \sim \text{Cd(dtbh)}^-$. The persisting problem is the establishment of the quantitative degree of metal orbital involvement in these series of complexes which possess, in the phraseology of Schrauzer and Mayweg,¹⁴ "delocalized ground states." In an experimental epr sense, all that can be presently done is to measure the departure of the g tensor from its properties in a cation-stabilized free-radical complex toward those expected for a complex in which the electron is essentially metal-localized. At what point the description is changed from ligand free radical to metal-localized radical is currently a subjective matter.¹⁸ As already emphasized, either description is inadequate and neither supplants a complete molecular orbital treatment including configuration interaction and spin-orbit coupling, which produces a ground state demonstrably reconcilable with experiment.

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Theoretical Aspects of the Linear Enthalpy Wavenumber Shift Relation for Hydrogen-Bonded Phenols¹

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Contribution from the William Albert Noyes Laboratory, University of Illinois, Urbana, Illinois, and Salem Hall, Wake Forest College, Winston-Salem, North Carolina. Received November 4, 1966

Abstract: The approximation involved in using the observed OH wavenumber shift of phenol upon hydrogen-bond formation as a measure of the magnitude of the interaction has been examined. The equation $-\Delta H = 0.016\Delta\nu_{\text{O-H}} + 0.63$ has been recast in terms of the change in the OH bond energy of phenol on adduct formation, δE_{OH} , and the energy of formation of the new bond between the donor and the hydrogen E_{HB} . The results of molecular orbital calculations (extended Hückel variety) have been analyzed in terms of the bond-energy relationship for the original bond to hydrogen and the hydrogen to base bond. These results provide theoretical justification for the original relationship. Furthermore, this treatment has yielded a parameter which is a quantitative measure of the response of the OH bond of the acid to perturbation by an approaching lone pair of electrons.

In 1962 an enthalpy-OH wavenumber shift ($\Delta\nu_{\text{OH}}$) relationship² for phenol adducts was presented which involved a wide range of electron-pair donors. The two experimental quantities were related by the equation

$$-\Delta H (\pm 0.5 \text{ kcal mole}^{-1}) = 0.016\Delta\nu_{\text{O-H}} + 0.63 \quad (1)$$

The work verified, at least for phenol adducts, the earlier prediction² of a linear relationship between the enthalpy of hydrogen-bond formation and OH wavenumber shift. Lippencott and Schroeder⁴ several years

ago presented a semiempirical model of the hydrogen bond which also predicted a linear relationship between these two quantities over an enthalpy range of -1 to approximately $-14 \text{ kcal mole}^{-1}$. A very slight curvature near the origin was predicted which implied a nonzero intercept on the enthalpy axis upon extrapolation of the linear portion of the curve.

More recently, other workers^{5,6} have questioned the validity of this linearity. They have studied weak donor systems which apparently do not obey this relationship. In addition it has been stated⁶ that there is no theoretical basis for the existence of such a relationship. This uncertainty has stimulated us to examine the theory of frequency shifts from the point of view

(1) (a) Presented at the 5th National Meeting of the Society for Applied Spectroscopy, Chicago, Ill., 1966; (b) abstracted in part from the doctoral dissertation of K. F. Purcell, University of Illinois, 1965.

(2) M. D. Joesten and R. S. Drago, *J. Am. Chem. Soc.*, **84**, 3817 (1962).

(3) R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 839 (1937).

(4) E. R. Lippencott and R. Schroeder, *ibid.*, **23**, 1099 (1955).

(5) R. West, D. L. Powell, L. S. Whately, M. K. T. Lee, and P. von R. Schleyer, *J. Am. Chem. Soc.*, **84**, 3221 (1962).

(6) D. L. Powell and R. West, *Spectrochim. Acta*, **20**, 983 (1964).

the approximations involved in the vibrational aspects of the problem and also to examine the changes in the molecular orbitals defining the A-H...B hydrogen-bond system as the H...B interaction is altered. By so doing we hoped to find theoretical justification for the large amount of data which is in accord with this relationship.

Calculations

The molecular orbital calculations are lcao-mo calculations of the extended Hückel type⁷ including a procedure for adjusting valence-state ionization energies and orbital exponents for core charge. A calculation relative with respect to a self-consistent set of atom energies.⁸ Off-diagonal H matrix elements were taken

$$H_{ij} = -1.75S_{ij}(H_{ii}H_{jj})^{1/2}$$

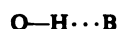
neutral atom valence-state ionization energies are those of Hinze and Jaffé.⁹ Slater atomic functions have been used.

The simple valence force constant calculations were carried out by hand using the GF formulation described by Wilson, *et al.*¹⁰

Results and Discussion

In studying the wavenumber shift-enthalpy relation for hydrogen-bonding acids, one is faced with the question of what does the wavenumber shift actually measure and how is this related to the total enthalpy for the formation of a hydrogen bond. It is certainly true that the change in the force constant of the O-H bond (phenol, for example) is a better measure of the change in the strength of that bond than the wavenumber shift because the frequency assigned as the "O-H stretching vibration" is that determined by at least a three-body-two-force constant oscillating system.

One approximation normally made is that neglect of coupling of the O-H stretching coordinate with other vibrational coordinates within the acid itself is negligible or at least invariant under the conditions of adduct formation. Owing to the high energy of the O-H stretching vibration and the large mass of the oxygen atom, this is a good approximation for C-O, O-H stretching. Phenol, for example, would be considered as a two-body system with the phenyl ring and the oxygen or the oxygen alone acting as a single "atom." A hydrogen-bonded adduct may then be represented



where B represents the donor atom or molecule and O represents the remainder of the acid molecule. A second approximation that has been made is³ to ignore the force constant of the H...B bond and, hence, to treat the hydrogen-bonded adduct as a diatomic molecule. This approximation is significantly poorer than the first because of the small mass of the hydrogen atom but is the one which leads to the use of frequency itself as a measure of the change of OH force constant or strength of the O-H bond.

⁷ R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).

⁸ C. Van Der Voorn, Doctoral Dissertation, University of Illinois, 1965.

⁹ I. Hinze and H. H. Jaffé, *J. Am. Chem. Soc.*, **84**, 540 (1962).

¹⁰ E. B. Wilson, J. C. Decius, and P. C. Cross, "Molecular Vibrations," McGraw-Hill Book Co., Inc., New York, N. Y., 1955.

Recently, data have become available which allow an assessment of this last approximation. Ginn and Wood¹¹ have obtained spectra for carbon tetrachloride solutions of phenol containing trimethylamine, triethylamine, and pyridine in the region 380-80 cm⁻¹. They find vibrations in this region which they attribute to stretching of the H...B bond: trimethylamine at 143 cm⁻¹, triethylamine at 123 cm⁻¹, and pyridine at 134 cm⁻¹.

Using the experimental values of 5.508 sec⁻² for λ_{OH} ² and 0.012 sec⁻² for λ_{HB} ¹¹ in the trimethylamine adduct and 7.681 sec⁻² for the O-H vibration of the phenol monomer,² the vibrational secular equations were solved for the corresponding force constants.

The solutions to these equations are given in Table I. According to these results there is a pronounced decrease in the O-H force constant of phenol upon hydrogen-bond formation with trimethylamine.

Table I

	F_{OH} , mdynes/A	$F_{\text{OH}}^{1/2}$, mdynes/A ^{1/2}
F_{OH}^a	7.660	2.76
F'_{OH}^b	5.026	2.24
F''_{OH}^c	5.493	2.34
F_{HB}	0.478	...

^a F_{OH} is the monomer phenol force constant. ^b F'_{OH} is the "true" adduct phenol force constant. ^c F''_{OH} is the adduct phenol force constant ignoring the H...B bond.

In comparing F'_{OH} and F''_{OH} we find that in ignoring the H...B force constant a 10% error in F_{OH} results and that the error in $F_{\text{OH}}^{1/2}$ is only about 5%. However, the difference between these two calculated changes in O-H force constant is ~20% (for $F_{\text{OH}}^{1/2}$ -0.52 vs. -0.42). The importance of $F_{\text{OH}}^{1/2}$ will be seen shortly. Trimethylamine is one of the strongest bases to have been studied with phenol, and this force constant may be taken as an approximate upper limit for H...B bonds in phenol adducts used in the correlation.

It is interesting to compare this value with the N-B force constant¹² for (CH₃)₃NBH₃ (=2.4 mdynes/A) and with the N-H force constant for (CH₃)₃NH⁺ which will be¹⁰ on the order of 5 mdynes/A.

The relationship between the O-H wavenumber shift or force constant and enthalpy of adduct formation (in a poorly solvating solvent) may now be examined. The enthalpy change for the reaction of phenol with a Lewis base may be thought of as consisting of two contributions: the change in the phenol O-H bond energy, $\delta E_{\text{O-H}}$, and the bond energy of forming the new hydrogen bond to the base, E_{HB} .

$$\Delta H = \delta E_{\text{O-H}} + E_{\text{HB}} \quad (2)$$

Any nonbonded repulsions which occur between the oxygen atom and the base are implicitly absorbed in E_{HB} . This contribution to ΔH will be small but varies with the base and is properly considered as one of the factors affecting the basicity of a lone-pair donor toward a hydrogen-bonding acid. Now a relationship between the change in O-H bond energy and the wavenumber shift or force constant change is needed as well as a

(11) S. G. Ginn and J. L. Wood, *Proc. Chem. Soc.*, 884 (1965).

(12) R. C. Taylor, *Advances in Chemistry Series*, No. 42, American Chemical Society, Washington, D. C., 1964, p. 59.

relationship between E_{HB} and the O-H wavenumber shift. Several authors^{13,14} discuss the relationship between D_0 , the bond dissociation energy, and ω_e (the harmonic oscillator vibrational energy in cm^{-1}) and x_e (the anharmonicity constant for that oscillator) for an anharmonic diatomic oscillator

$$D_0 = D_e(1 - 2x_e) = \frac{\omega_e^2}{4\omega_e x_e}(1 - 2x_e)$$

where D_e equals D_0 plus the zero-point energy. A change in oscillator frequency may then be related to a change in D_0 by

$$\delta D_0 = \frac{\delta \omega_e}{4x_e}(1 - 2x_e)$$

for no change in x_e .¹⁵ Since ω_a (the anharmonic energy in cm^{-1}) is given by

$$\omega_a = \omega_e(1 - 2x_e)$$

δD_0 , in terms of $\delta \omega_a$, is simply

$$\delta D_0 = \frac{\delta \omega_a}{4x_e} \text{ or } \delta E_0 = -\frac{\delta \omega_a}{4x_e} \quad (3)$$

E_0 is meant, here, to be the bond energy, and $\delta \omega_a < 0$ implies that $\delta E_0 > 0$. For δE_0 in kcal mole^{-1} , the above relation is

$$\delta E_0 = -\frac{hcN}{4x_e} \delta \omega_a \quad (4)$$

with Planck's constant in units of $\text{kcal molecule}^{-1} \text{ sec}$. Since ω_e is given by

$$\omega_e = \frac{1}{2\pi c} \sqrt{\frac{k_e}{\mu}}$$

it follows that $\delta \omega_a$ and $\Delta k_e^{1/2}$ are related by

$$\delta \omega_a = \frac{1}{2\pi c} \Delta \sqrt{\frac{k_e}{\mu}} (1 - 2x_e)$$

Rewriting this in terms of an anharmonic force constant, k_a , one obtains

$$\delta \omega_a = \frac{1}{2\pi c \sqrt{\mu}} \Delta(k_a)^{1/2}$$

The last two equations are identical when $x_e = 0$. The relationship for change in E_0 and change in $k_e^{1/2}$ is given by

$$\delta E_0 = -\frac{hcN}{4x_e} \left(\frac{1 - 2x_e}{2\pi c \sqrt{\mu}} \right) \Delta k_e^{1/2}$$

Some experimental justification for the linear relationship between E_0 and ω_a or $k_a^{1/2}$ for a given bond type has been given by Fox and Martin.¹⁶ Our problem lies in evaluating δE_0 for the OH bond in phenol from $\Delta \nu_{\text{obsd}}$ (the observed wavenumber change) which differs from $\delta \omega_a$ by virtue of vibrational coupling of the OH and H...B coordinates in the "OH" normal coordinate.

(13) G. Herzberg, "Spectra of Diatomic Molecules," D. Van Nostrand Co., Inc., New York, N. Y., 1950, p 100.

(14) G. W. King, "Spectroscopy and Molecular Structure," Holt, Rinehart and Winston, New York, N. Y., 1964, p 163.

(15) Unfortunately, we are frustrated by both a lack of proper data and a theoretical means to account for variation in x_e in the adducts.

(16) G. Fox and A. Martin, *Trans. Faraday Soc.*, **36**, 897 (1940); *J. Chem. Soc.*, 884 (1939).

Ideally one would try to observe both ν_{OH} and $\nu_{H...B}$ and carry out a normal coordinate analysis for each adduct as was done for phenol-trimethylamine above. Each analysis would yield k_a (or $k_a^{1/2}$) and allow the calculation of $\delta \omega_a$ and δE_0 directly for the OH bond. As noted earlier, both vibrational energies are generally not available. Until such data become available one is left to approximate $\delta \omega_a$ by $\Delta \nu_{\text{obsd}}$. The seriousness of the ensuing error is judged by the data in Table I which show that the use of ν_{obsd} for the adduct constitutes a 5% error in approximating ω_a in the adduct while the error in using $\Delta \nu_{\text{obsd}}$ (the change in wavenumber) for $\delta \omega_a$ underestimates the latter by ca. 20%.

It is interesting to consider at this point the cumulative errors introduced by the Birge-Sponer relationship as applied here (eq 4) and that introduced by setting $\Delta \nu_{\text{obsd}} = \delta \omega_a$. The Birge-Sponer method of obtaining E_0 is known^{13,14} to overestimate E_0 by ca. 20%. As noted above, $\Delta \nu_{\text{obsd}}$ is ca. 20% smaller than $\delta \omega_a$. The two approximations made here, therefore, will cancel one another to within a few per cent and will, therefore, result in a cumulative error of ca. 5%, say in the value of δE_{OH} calculated using eq 6 below. The error limits in eq 1 range from ~20% for low ΔH to ~5% for the larger ΔH . It is therefore seen that this method of obtaining δE_{OH} from $\Delta \nu_{\text{obsd}}$ is valid to well within the limits of the original empirical relationship.

It appears that if a more accurate determination of $\delta \omega_a$ should be made, it must be accompanied by a more accurate relation between δE_0 and $\delta \omega_a$ (that resulting from the Rydberg potential function, for example) if one wishes to maintain an uncertainty of ~5% in the calculated δE_{OH} .

In order for eq 1 to be theoretically sound there must be a linear relationship between the energy of the base to the hydrogen bond, E_{HB} , and the destabilization of the O-H bond. From the equations, in which Planck's constant has units of kcal sec/molecule

$$\Delta H = -\left(\frac{hcN}{4x_e}\right) \delta \omega_{OH} + E_{HB} \quad (5)$$

and

$$\delta E_{OH} = -\left(\frac{hcN}{4x_e}\right) \delta \omega_{OH} \quad (6)$$

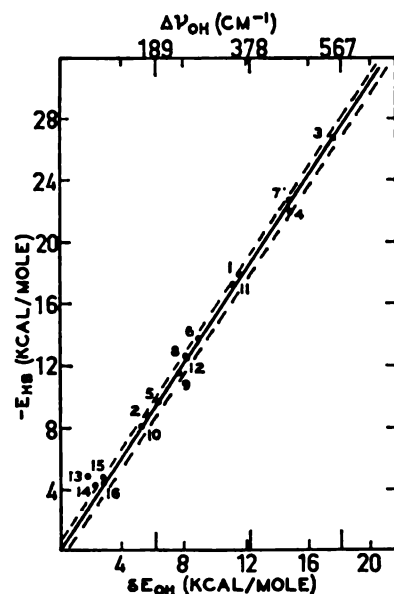
one can determine E_{HB} and δE_{OH} . This has been done¹⁷ for some literature data^{2,5} using $\Delta \nu_{OH}$ for $\delta \omega_{OH}$. The results are shown in Figure 1 and Table II. The dotted lines in the figure are the error limits ($\pm 0.5 \text{ kcal/mole}$) reported² for the 90% confidence level of the $\Delta \nu_{OH}$ - ΔH relationship. It is seen that E_{HB} is linearly related to δE_{OH} , as is required, with a nonzero intercept on the E_{HB} axis of ~-0.6. It is interesting to note also the reasonable magnitudes of the E_{HB} for coordinate bonds.

Equation 1 may now be recast as

$$\Delta H = \left(\frac{1}{k'} - \frac{hcN}{4x_e}\right) \Delta \nu_{OH} + \text{constant}$$

where k' is the slope of the E_{HB} , $\Delta \nu_{OH}$ relationship. In terms of δE_{OH} ($\delta E_{OH} = k E_{HB} + \text{constant}$, $k = (hcN/4x_e k')$) this constant ($k = -0.682$ for phenol) measures the response of the O-H bond to the effect of an ap-

(17) The anharmonicity constant for *p*-chlorophenol was determined in this laboratory to be 0.0229; the value 0.0227 for phenol was calculated from data in ref 6.



1. Energy of the H...B bond as a function of the change in the O-H bond energy of phenol.

ing lone pair of electrons. It is tempting to state a correlation of this quantity with other measures of acidity. The pK_a 's, OH proton chemical shifts, substituent constants of OH acids might be expected to bear a direct relationship to this parameter. This quantity is unique in that it measures a *bond* property. It is a measure of the susceptibility of the O-H bond to distortion by a Lewis base.

I. Data for Figure 1

		δE_{OH}^a	E_{HB}^a	$\Delta \nu_{OH},$ cm^{-1}
1	DMA	10.9	-17.3	345
2	CH_3CN	5.6	-8.8	178
3	Et_3N	17.4	-26.6	553
4	Me_2PO	14.6	-22.0	470
5	Me_2CO	6.1	-9.4	193
6	Et_2O	8.8	-13.8	279
7	H_2N	14.6	-22.6	462
8	Et_3S	7.9	-12.5	250
9	Bu_3Se	7.6	-11.3	240
0	EtOac	5.2	-8.0	154
1	DMSO	11.3	-17.8	359
2	Bu_3S	8.0	-12.3	254
3	$\text{C}_6\text{H}_{11}\text{F}$	1.7	-4.8	53
4	$\text{C}_6\text{H}_{11}\text{Cl}$	2.1	-4.3	66
5	$\text{C}_6\text{H}_{11}\text{Br}$	2.6	-4.6	82
6	$\text{C}_6\text{H}_{11}\text{I}$	2.7	-4.4	86

^a Energies in kcal/mole.

Imaginary data are available¹⁸ for *p*-chlorophenol. A similar calculation for this acid. The ΔH_{OH} plot for this acid has a slope of 0.021, i.e.

$$\Delta H = 0.021 \Delta \nu_{OH}$$

may be interpreted in terms of a larger dipolar contribution to the total enthalpy than with phenol added.

The value of k for this acid is -0.592 (cf. 2 for phenol), a fact which also indicates that the bond energy change is smaller for this more polar or a given E_{HB} than in the case of phenol. This

¹⁸ Henneke, private communication.

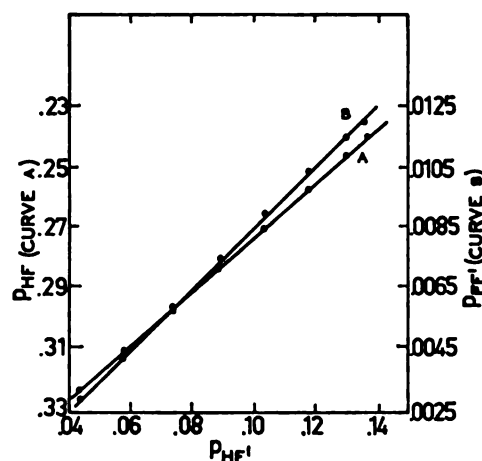


Figure 2. The overlap populations of the H-F bond and the F-F' "bond" as a function of the overlap population of the H...F' bond: (A) H-F vs. H...F', (B) F-F' vs. H...F'.

may be interpreted in the following ways. (1) The OH bond in *p*-chlorophenol is more resistant to distortion by a lone-pair donor. (2) There is a large contribution to E_{HB} from dipolar interaction in the case of *p*-chlorophenol. That is, the greater electron-withdrawing property of the *p*-chlorophenyl group results in a higher positive charge on the proton. Both an increased dipolar interaction with electron-pair donors and a less polarizable or less easily perturbed OH bond results. It is interesting to note that this interpretation is very similar to the currently popular "hard and soft" acid concept in that phenol is the softer more distortable acid in the vicinity of the acid site. It is this ability of " k " to reflect the distortability of the electrons in the bond containing the acid atom that makes it such a useful quantity.

While these results are interesting, the question as to why the energy of the hydrogen bond should be linearly related to the change in the energy of the O-H bond still remains. It was decided to attempt an extended Hückel calculation on the hydrogen-bond system $(\text{HF})^-$ and to examine the effect on the two fluorine to hydrogen bonds of gradually removing one of the fluorines from the other atom.⁵ The use of F^- was felt to be more realistic and representative of actual hydrogen-bonding situations involving alcohols than the use of O^{2-} since the oxygen atoms in alcohols most certainly do not carry a net charge as large as two. The curve derived by Lippencott and Schroeder for $\text{O}-\text{H} \cdots \text{O}$ systems was used to allow for contraction of the HF bond as the second fluorine was removed. The results of our calculations are given graphically in Figures 2, 3, and 4. In Figure 2 we have plotted the overlap population¹⁹ of the short HF bond (ρ_{HF}) against the overlap population of the long HF bond ($\rho_{HF'}$). Also included for comparison is the non-bonded F-F' repulsion ($\rho_{FF'}$) (i.e., the negative FF' overlap population). Over the range of F-F' distances 2.49 to 2.80 Å (a range which covers enthalpies of -1 to -14 kcal/mole on the Lippencott-Schroeder curve), these quantities are linearly related.

According to Mulliken's formulation,¹⁹ ρ_{ij} is proportional to Ω_{ij} ("the overlap energy") and the relation-

(19) R. S. Mulliken, *J. Chem. Phys.*, **23**, 1833, 1841, 2338, 2343 (1955); (b) *ibid.*, **36**, 3428 (1962).

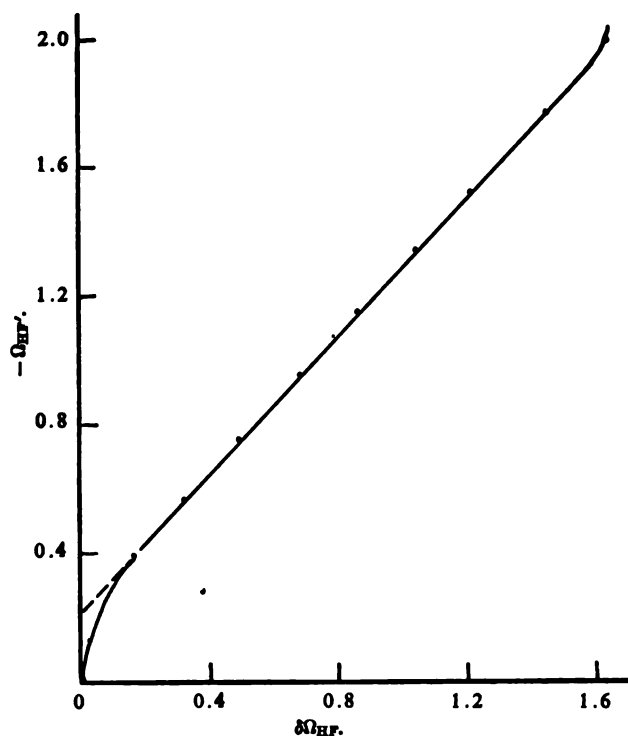


Figure 3. The change in overlap energy of the original hydrogen bond as a function of the overlap energy of the new hydrogen bond.

ship is $\Omega_{ij} = \rho_{ij}\beta_{ij}/S_{ij}$, where $\beta_{ij} = H_{ij} - 1/2 S_{ij}(H_{ii} + H_{jj})$. We can determine the nature of the Ω_{HF} vs. $\Omega_{HF'}$ relationship by calculating the β_{ij}/S_{ij} values from the results of our iterative calculations. Here we use the definitions

$$\Omega_{HF} = \sum_k (\sum_i \Omega_{iH}) k$$

$$\Omega_{HF'} = \sum_k (\sum_j \Omega_{jH'}) k$$

where the summations are over the k -occupied molecular orbitals and the i and j ao's of F and F', respectively. The results of these calculations are presented graphically in Figure 3 as a plot of $\delta\Omega_{HF}$ ($=\Omega_{HF} - \Omega_{HF'}$) vs. $\Omega_{HF'}$. The slope is -0.94 and the dotted lines are drawn at *ca.* $\pm 3\%$ tolerance on $\delta\Omega_{HF}$. Another point of consistency relates to the behavior of the curve near the origin. Figure 3 indicates that a nonzero intercept is expected for the linear portion of the curve in agreement with the experimental data and the Lippencott-Schroeder model.

It appears that the experimentally determined linearity between δE_{OH} and E_{HB} is theoretically sound. The slope calculated for the (FHF)⁻ model is in essential agreement with that for phenol when one recalls that this slope is sensitive to the nature of the AH bond in the acid (*vide supra*). These results are extremely encouraging and do suggest that the original relationship (eq 1) is not just a fortuitous situation. The linear frequency shift-enthalpy relation originally proposed by Badger and Bauer appears to be valid for phenol when sufficient care is taken to obtain accurate enthalpy data for the hydrogen-bonding interaction.

In this treatment we have been thus far concerned only with the covalent contribution to the bond energies and have neglected, in an explicit sense, any ionic contributions to these energies. Such contributions are extremely difficult to determine with any accuracy and, moreover, some ionic bond character has been included

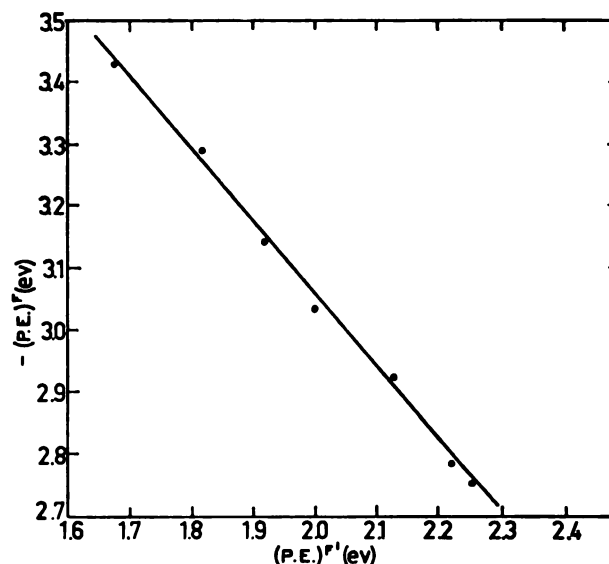
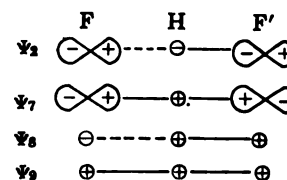


Figure 4. The Coulombic energy relationship of the two fluorine "atoms."

through the lcao-mo treatment itself. However, in an attempt to gain a qualitative estimate of the nature of the relation of the electrostatic potential energy of one fluorine relative to the other during the retraction of a fluorine, we have calculated the Coulombic potential energies for each fluorine atom with the other and the hydrogen atom for each step in the retraction process. The atomic charges used in this calculation were the atomic charges found in mo calculations. When plotted one against the other (Figure 4), the potential energies are found to be very closely linearly related, and the slope of this line is -0.6 , to be compared with the others.

A qualitative description of the occupied σ molecular orbitals in terms of ao's is given below.

∞ represents a fluorine 2p orbital and
 \bigcirc represents an s orbital (2s for F, 1s for H).



The σ mo's are found, on the basis of the eigenvectors²⁰ (see Table III for the eigenvectors for the case

Table III. Eigenvectors for the Case $R_{FF'} = 2.49$ Å

	F _s	F _{pσ}	H _s	F' _s	F' _{pσ}
Ψ_2	0.015	0.587	-0.007	-0.006	0.817
Ψ_7	-0.125	0.728	0.250	-0.096	-0.511
Ψ_8	-0.539	0.004	0.005	0.846	0.003
Ψ_9	0.811	-0.007	0.083	0.508	0.003

$R_{FF'} = 2.49$ Å), to involve primarily either fluorine 2p or 2s orbitals with little "hybridization" of the two in any one mo. A series of dots between two ao's indi-

(20) Recall that the basis set ao's have charge adjusted orbital exponents.

Table IV. One-Electron Orbital Energies (ev) of HF_3^-

	$R_{\text{FF}'} = 2.49 \text{ \AA}$	$R_{\text{FF}'} = 2.79 \text{ \AA}$	ΔE
$E(2)$	-18.97	-18.93	-0.04
$E(7)$	-20.24	-20.26	0.02
$E(8)$	-36.37	-36.31	-0.06
$E(9)$	-36.92	-36.98	0.06
E_{F}	-19.28	-19.43	0.15
$E_{\text{F}'}$	-19.08	-18.93	-0.15

es an "antibonding" interaction of the orbitals; a straight line connecting two ao's represents a bonding interaction. The mo's labeled ψ_7 and ψ_9 are bonding with respect to both H-F and H...F'; ψ_2 and ψ_8 are H...F' bonding and H-F antibonding. The unoccupied fifth mo is not shown. This result is obtained whenever the HF' distance is greater than the HF distance.

It may also be noted (from the magnitudes of the eigenvectors) that ψ_2 and ψ_8 correspond to "nonbonding" orbitals in the sense that there is little hydrogen 1s involvement. This description is misleading, however, since these orbitals contribute significantly to the HF, F' overlap populations and energies.

In Table IV are given the one-electron energies of the mo's for F-F' internuclear distances of 2.49 and 2.79

Å. The effect of shortening the F-F' distance is as follows: ψ_2 is stabilized, ψ_7 is destabilized, ψ_8 is stabilized, ψ_9 is destabilized. The stabilization of the molecule by changes in ψ_2 and ψ_8 is larger than the destabilization of the molecule by ψ_7 and ψ_9 . The change in H-F bond energy must then be less than the change in H...F' bond energy. We note that the formation of the new bond is more important than destabilization of the old bond and this, of course, is the prime reason for stability of the hydrogen-bonded adduct. Note that ψ_7 and ψ_9 include contributions from the new bond as well as the original bond. Contributions from the strength of the new bond in these molecular orbitals are less than the destabilization of the original bond since the net change in energy of both of these molecular orbitals is in a positive direction.

A comment on the nonbonding $2p_z$, $2p_y$ orbitals can be made. The data in Table IV indicate that these filled nonbonding π -type orbitals on F are destabilized to the same extent that these nonbonding orbitals on F' are stabilized (move to lower energy). The directions of the changes are a consequence of the decreasing negative charge on F' and the increasing negative charge on F as $R_{\text{FF}'}$ is decreased.

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Contact-Shift Studies and Delocalization Mechanisms of Nickel(II)-Benzylamine Complexes

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Contribution from the William Albert Noyes Laboratory, University of Illinois, Urbana, Illinois. Received January 14, 1967

Abstract: The proton nmr contact shifts of $[\text{Ni}(\text{bz})_6]^{2+}$ (bz = benzylamine, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$) have been investigated to ascertain whether or not unpaired spin can be delocalized in the phenyl π system when the ligand-metal interaction is essentially σ . The amino, methylene, and aromatic protons are assigned in the nmr spectrum of the complex. The contact shifts and electron spin-nuclear spin coupling constants for these protons are reported. Results obtained from the nmr data show that electron spin is delocalized into the π system of the phenyl group of the ligand. Since the bonding to the ligand is σ , this study shows that contrary to several literature reports one may not assume *a priori* that π delocalization in a phenyl ring is evidence for metal-ligand π -type bonding. A delocalization mechanism which accounts for the observed shifts is presented. The complex with the formula $[\text{Ni}(\text{bz})_6]\text{BF}_4(\text{BF}_4)$ was isolated as a solid. Spectral and conductance data are presented to substantiate that $[\text{Ni}(\text{bz})_6]^{2+}$ is the species present when the previously mentioned complex is dissolved in nitromethane solutions containing an excess of benzylamine.

The general theory and interpretation of nmr contact shifts has been extensively discussed in a previous publication from this laboratory² and should be considered along with the references therein for background information. In this paper, we are specifically concerned with using both the signs and magnitudes of the contact shift for the ligand protons to deduce information about the metal-ligand bonding. The unpaired

spin in most complexes is in a molecular orbital which is essentially a metal d orbital. The extent of mixing of the ligand orbitals with this essentially d metal orbital to form a nonbonding or antibonding mo is taken as an indication of the mixing of the d orbitals with the ligand orbitals in forming the bonding molecular orbital. Hence, by looking at the contact shift, one infers information about the bonding.

Happe and Ward³ have found proton contact shifts indicating a σ mechanism for delocalizing spin onto pyridine. There have been many reports in the literature,

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¹) Abstracted in part from the Ph.D. thesis of R. Fitzgerald, University of Illinois, 1968; National Institutes of Health Predoctoral Fellow, 1966-1967.

²) B. B. Wayland and R. S. Drago, *J. Am. Chem. Soc.*, **87**, 2372 (1965).

for example, the work of Eaton, *et al.*,⁴ on the aminotroponimineates, where unpaired electron density is delocalized into the π orbitals of conjugated ligands. The authors concluded from this study that there was considerable metal-ligand π bonding. Similarly, the magnitude and direction of the phenyl proton shifts were taken to indicate delocalization of spin into the π orbitals of complexed $(C_6H_5)_3P$ in $(R_3P)_3MX_3$ complexes.^{5,6} Similar shifts are found for $[Ni(C_6H_5CN)_6]^{2+}$.⁷ These observations were taken as an indication of metal-ligand $d\pi-d\pi$ bonding in the phosphine complexes and π bonding in the nitrile complexes.

In the above ligands, the unpaired spin in the π orbitals is transmitted from aromatic ring π orbitals to the protons which are orthogonal to these π orbitals by an atomic exchange coupling mechanism.⁸ Levy has proposed⁹ that when a methylene group is attached to an aromatic ring, a linear combination of the atomic $1s$ orbitals of the methylene protons form pseudo- π -type orbitals and interact directly with the ring carbon p_z orbitals. Thus spin is placed directly on the methylene protons through a hyperconjugative-type mechanism. By considering the operation of these mechanisms in reverse, one could place unpaired spin in the π system of the ligand, even though the metal-ligand bond is primarily a σ bond.

In the $(C_6H_5)_3P$ complex, the phenyl π orbitals are not orthogonal to the phosphorus lone pair, and, if spin were placed on phosphorus by a σ interaction with the metal, it could be placed in the π system by a mechanism similar to that discussed for the methylene group above. In the case of the benzonitrile ligand, spin placed on the nitrogen by a σ interaction could enter the π system by an atomic exchange coupling mechanism similar to that discussed above for protons which are orthogonal to aromatic rings. These arguments, in principle, would offer an alternative explanation to the triphenylphosphine and benzonitrile contact shifts in the nickel(II) complexes and would cast doubt upon the previously cited conclusions regarding π -type metal-ligand bonding. It is difficult to sort out the reported interpretations and the alternatives offered here in the above complexes. In an attempt to ascertain whether or not the alternatives we have offered here are operative, we decided to investigate the contact shifts in $[Ni(bz)_6]^{2+}$.

Mixed anion-neutral ligand complexes with benzylamine have been previously reported.¹⁰⁻¹² However, we could find no previous report of the preparation of $[Ni(bz)_6]^{2+}$ which is described here.

Experimental Section

Apparatus. a. **Nmr Spectra.** The nmr spectra were obtained with Varian Models A-60A, A-56-60, and DP-60 spectrometers.

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(11) A. K. Mujumdar, A. K. Mukherjee, and A. K. Mukherjee, *J. Inorg. Nucl. Chem.*, **26**, 2177 (1964).

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All nmr spectra were measured relative to TMS as an internal standard.

b. **Visible and Near-Infrared Spectra.** All near-infrared and visible spectra were determined using a Cary recording spectrophotometer, Model 14.

c. **Conductance Data.** The conductance measurements were made on an Industrial Instruments conductivity bridge, Model RC 16B2.

d. **Magnetic Susceptibility Measurements.** The solution moment was determined by nmr at 28° using a method first reported by Evans.¹³ The measured susceptibilities were corrected for diamagnetism by the use of Pascal's constant.^{14,15}

Reagents and Solutions. Hydrated nickel(II) tetrafluoroborate (Alfa Inorganics), anhydrous reagent grade diethyl ether, and reagent grade methanol were used without further purification.

Matheson benzylamine was distilled from BaO under reduced pressure, a constant-boiling middle fraction being selected for use. Aldrich *p*-methylbenzylamine was purified in a similar manner. The ligands were stored in a desiccator containing P_2O_5 .

Fisher reagent grade nitromethane was dried over Linde 3A Molecular Sieves for at least 24 hr.

All additions of ligand were carried out in a drybox equipped with an automatic continuous air flow drying system. When accurate complex concentrations were necessary the materials were weighed in stoppered volumetric flasks and addition of ligand was accomplished by use of Hamilton microliter syringes.

Preparation of the Complexes. a. $[Ni(bz)_6](BF_4)_2$. Aqueous nickel(II) tetrafluoroborate (7.5 g) was dissolved in 20 ml of methanol and then dehydrated by stirring in 50 ml of 2,2-dimethoxypropane¹⁶ for 2 hr at room temperature. Upon addition of diethyl ether to this solution a green oil was formed, which was then redissolved in a minimal amount of nitromethane and allowed to stir again. Upon further addition of diethyl ether to the solution, a light green complex, $[Ni(MeOH)_4](BF_4)_2$, was precipitated. This compound was filtered in a drybox and dissolved in 30 ml of benzylamine and allowed to stir for 2 hr. Upon addition of diethyl ether to this solution a blue complex was precipitated. This solution was filtered in the drybox and the complex analyzed. *Anal.* Calcd for $[Ni(bz)_6](BF_4)_2$: C, 54.4; H, 5.87; Ni, 7.60. Found: C, 54.2; H, 5.80; Ni, 7.80. Infrared analysis detected no water.

b. $[Ni(p-CH_3bz)_6](BF_4)_2$ (*p*-CH₃bz = *p*-Methylbenzylamine). This compound was prepared by a method analogous to the preceding preparation, retaining the appropriate mole ratios, but substituting *p*-methylbenzylamine in the final step. Here a light blue complex was precipitated. *Anal.* Calcd for $[Ni(p-CH_3bz)_6](BF_4)_2$: C, 57.3; H, 6.61; Ni, 7.00. Found: C, 57.2; H, 6.67; Ni, 6.68. Infrared analysis detected no water.

c. $[Zn(bz)_6](BF_4)_2$. This compound is also prepared in a manner analogous to the nickel(II)-benzylamine complex. A white solid is precipitated here. *Anal.* Calcd for $[Zn(bz)_6](BF_4)_2$: C, 50.4; H, 5.44. Found: C, 49.8; H, 5.43.

Treatment of the Nmr Data. The complexes studied in this work exchange rapidly with excess ligand. In solutions containing excess ligand a single averaged line position for each proton is observed (*i.e.*, separate complexed and free ligand resonances are not detected).

Although we cooled the solution to its freezing point, -47.8° , we were unsuccessful in our attempt to stop exchange and did not see exchange broadening at this temperature. Thus one may conclude that the fast exchange condition, $1/T_c \gg \Delta\nu$, where $1/T_c$ is the rate of chemical exchange and $\Delta\nu$ is the shift relative to the diamagnetic complex, is fulfilled at room temperature. The chemical shift of the complex can then be calculated from a knowledge of the stoichiometry of the complex and the chemical shift of the free ligand according¹⁷ to

$$\nu_{\text{obsd}} = \nu_{\text{complexed}}N_{\text{complexed}} + \nu_{\text{free}}N_{\text{free}} \quad (1)$$

where ν and N represent the resonance frequency and mole fraction, respectively.

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temperature dependence of the contact shift is then given by the Bergh equation¹⁸ (eq 2, modified for the case of protons),

$$\frac{\Delta\nu}{\nu} = -A_n \frac{\gamma_e g \beta S(S+1)}{\gamma_H 3kT} \quad (2)$$

$\gamma_H = 6.58 \times 10^3$, $g = \mu_{eff}/\sqrt{S(S+1)}$, $\beta = 9.27 \times 10^{-21}$. S is the sum of the electron spins, A_n the nuclear spin-spin coupling constant, $\Delta\nu$ the shift relative to the diamagnetic complex, and ν the probe frequency (both in cps), the other having their usual significance.

Nmr Data. The proton spectrum of free benzylamine in nitromethane is found to consist of three

Our values for the chemical shift are consistent with those reported by earlier workers¹⁹ for benzylamine in cyclohexane. The results of the nmr studies are presented in Table I.

Nmr Spectra in CH_3NO_2 ^a

Compound	NH_2	CH_2	<i>ortho</i>	<i>meta</i>	<i>para</i>
CH_3NH_2	-73	-217	-428 ^b	-428 ^b	-428 ^b
$3\text{F}_4\text{N}_2$	-90	-240	-438 ^b	-438 ^b	-438 ^b
$3\text{F}_4\text{N}_2$	+6240	-2300	-350	-523	-345

Chemical shifts are in cps relative to TMS as an internal standard. Temperature is 33°. ^b The *ortho*, *meta*, and *para* protons of an $\text{A}_2\text{B}_2\text{C}$ system and appear as a singlet in our spectra.

Nmr contact shifts, $\Delta\nu$, and the electron spin-spin coupling constants, A , for the octahedral complex of Ni(II) are reported in Table

Nmr Contact Shifts and Electron Spin-Nuclear Coupling Constants for $[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$ in CH_3NO_2

Proton	$\Delta\nu$, ^a cps	$A \times 10^3$, ^b gauss
I_1	+6330	-458
I_2	-2060	149
<i>ortho</i>	+88	-6.31
<i>meta</i>	-85	6.15
<i>para</i>	+93	-6.74

relative to the diamagnetic $\text{Zn}(\text{II})$ complex at 33°. ^b Calculated $\Delta\nu$ at 33° using eq 2 and $g = 2.39$.

Assignment of these peaks is treated in the Discussion. In addition to the benzylamine complex, the nmr spectrum of $[\text{Ni}(\text{p-CH}_3\text{bz})_2]^{2+}$ was studied. Peaks assigned to *ortho* and *meta* protons shifted in the same direction relative to free ligand in this complex as in the benzylamine complex. However, the methyl peaks were shifted downfield in this complex (relative to the free ligand) while the *p*-hydrogen showed an upfield shift in the benzylamine complex. The lower solubility of the *p*-methylbenzylamine complex precludes reporting of accurate contact shifts, but approximate values of $\Delta\nu = +53$, -77 cps were obtained for the *ortho* and *meta* protons and *p*-methyl protons, respectively.

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Takahashi, T. Sone, Y. Matsuki, and G. Hazato, *Bull. Chem. Soc.*, **36**, 108 (1963).

Table III. Conductance Data for $[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$ in CH_3NO_2

Complex	Type	Λ_{molar}	Temp, °C	Concn $\times 10^3$ ^a
$[\text{Ni}(\text{bz})_2(\text{BF}_4)_2] + \text{excess bz}$	2:1	169	26.4	1.08
$[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$	2:1	177	24.6	0.964

^a Concentration in moles/liter of solution.

Table IV. Spectral Data for $[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$

Compound	Solvent	ν_{max} , cm^{-1}	Band assignment
$[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$	CH_3NO_2 ^a	8,909 sh 9,716 16,064	${}^1\text{B}_1 \rightarrow {}^1\text{E}$ ${}^1\text{B}_1 \rightarrow {}^1\text{B}_2$ $\rightarrow {}^1\text{A}_g$
$[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$	$\text{CH}_3\text{NO}_2 + \text{excess bz}$	9,744 16,502	${}^1\text{A}_{1g} \rightarrow {}^1\text{T}_{1g}$ $\rightarrow {}^1\text{T}_{1g}(\text{F})$
$[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$	DMA ^b	9,688 16,271	${}^1\text{B}_1 \rightarrow {}^1\text{E}$ ${}^1\text{B}_1 \rightarrow {}^1\text{B}_2$ $\rightarrow {}^1\text{E}$ $\rightarrow {}^1\text{A}_g$
$[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$	DMA + excess bz	9,746 16,485 27,210	${}^1\text{A}_{1g} \rightarrow {}^1\text{T}_{1g}$ $\rightarrow {}^1\text{T}_{1g}(\text{F})$ $\rightarrow {}^1\text{T}_{1g}(\text{P})$

^a When CH_3NO_2 is the solvent, the high-energy band cannot be detected due to intense solvent absorption. ^b DMA = N,N-dimethylacetamide.

(2) Evidence for the Octahedral Species in Solution. The conductance data presented in Table III are clearly indicative of a 2:1 electrolyte. The spectral data for the complexes are presented in Table IV. The spectrochemical parameters calculated from the data in Table IV are listed in Table V and the magnetic data for the complex in CH_3NO_2 solution are presented in Table VI.

Table V. Calculated Spectrochemical Parameters

Compound	Solvent	Dq	$\nu_{\text{calculated}}$	ν_{observed}
$[\text{Ni}(\text{bz})_2]^{2+}$	CH_3NO_2	974	...	16,502
$[\text{Ni}(\text{bz})_2]^{2+}$	DMA	974	15,971	16,485

Table VI. Magnetic Susceptibility Data for $[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$ ^a

Complex	$\chi_m \times 10^3$	$\chi_{\text{diamagnetic}} \times 10^3$	$\chi_m (\text{cor}) \times 10^3$	μ_{eff} , BM
$[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$	4163	-539	4702	3.38 ± 0.05

^a The moment was determined at 28°.

Discussion

Nature of the Species in Solution. It is essential for our study to demonstrate that the species in solution is the octahedral complex, and further that there is no equilibrium in solution involving appreciable concentrations of other species.

The $[\text{Ni}(\text{bz})_2(\text{BF}_4)_2]$ compound is light blue. When this compound is dissolved in CH_3NO_2 , the solution is green, but when excess benzylamine is added the solution turns a darker blue. On the basis of our conductance studies, both the green and blue solutions are clearly 2:1 electrolytes. An analogous process

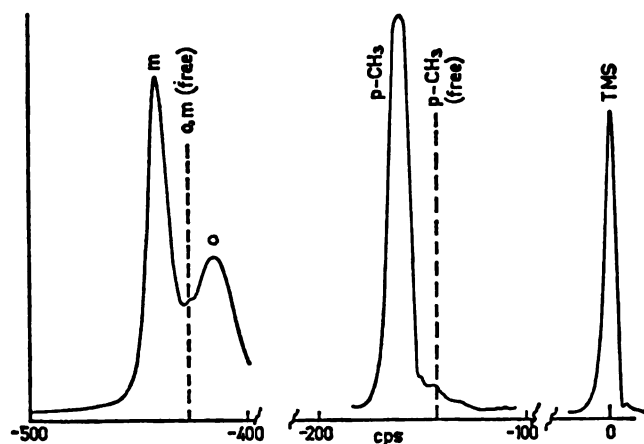


Figure 1. Nmr spectrum of $[\text{Ni}(\text{p-CH}_3\text{bz})_4]^{2+}$ plus excess $\text{p-CH}_3\text{bz}$.

occurs when DMA is the solvent. We propose that two different species are formed in solution according to eq 3, and that the second reaction is essentially complete for a 1:1 mole ratio of complex and excess benzylamine.



Evidence for the octahedral species is provided by the spectral data. Spectra in both CH_3NO_2 and DMA solutions containing excess benzylamine indicate that the same species is present in both solvents. Our conductance data show that BF_4^- cannot be coordinated, and therefore the only species common to both solvents must be $[\text{Ni}(\text{bz})_6]^{2+}$. Furthermore, addition of excess ligand to a solution of $[\text{Ni}(\text{bz})_4\text{BF}_4](\text{BF}_4)$ in a ratio greater than 3:1 does not alter the band positions. The fit of the middle band is somewhat poorer than one might expect for an octahedral complex. However, there is a charge-transfer band on the high-energy side of the ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}(\text{P})$ transition, thus biasing the data in a manner consistent with the error.

Finally plots of ν_{obsd} vs. N_{comp} , where ν_{obsd} is the observed nmr frequency in cps and N_{comp} is the mole fraction of ligand complexed, give straight-line plots for all the protons of benzylamine indicating that only one species is present in solution, in addition to excess ligand.

These observations lead us to conclude that in solutions of the complex with excess benzylamine the complexed species is indeed $[\text{Ni}(\text{bz})_6]^{2+}$.

Interpretation of the Contact Shifts. The contact shifts, $\Delta\nu$ (cps), for all the protons of $[\text{Ni}(\text{bz})_6]^{2+}$ are reported in Table II. The contact shifts are reported relative to the diamagnetic $\text{Zn}(\text{II})$ complex. The electron spin-nuclear spin coupling constants, A , were calculated according to eq 2 and are also listed in Table II. The assignments of the amino and methylene protons in the complex were made by adding excess ligand to the solution of the complex and tracing back to the free ligand value. Because of the line width of the complexed N-H peak, the amino peak can only be detected in solutions containing a large excess of ligand.

Integration of the aromatic proton resonances in the benzylamine complex gave an approximate 3:2 ratio of upfield to downfield peaks. Upon substituting a p-CH_3 for p-H , the p-CH_3 is shifted downfield, i.e.,

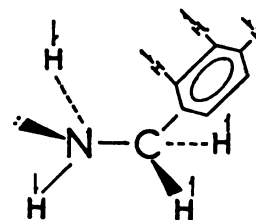


Figure 2. Spin densities on benzylamine protons.

the opposite direction of the p-H . This is an indication of a π -delocalization mechanism²⁰ in the phenyl group and suggests that the upfield peaks be assigned to o - and p -H and the downfield peak to m -H. This assignment is further substantiated by the fact that the peak we have assigned to the *ortho* proton in the p -methylbenzylamine complex (the upfield peak) is the broadest C-H in the spectrum, as can be seen in Figure 1. It is not possible to assign unambiguously the two upfield peaks in the benzylamine complex to the *ortho* and *para* positions because of their substantial overlap. A tentative assignment is presented, and, as will be seen, this assignment does not alter the conclusions to be drawn. Since octahedral nickel(II) complexes are of cubic symmetry and possess a ${}^3\text{A}_{2g}$ ground state, the g tensor should be isotropic and there should be no pseudo-contact interaction.²¹ Even though the "true" point group of these complexes is not O_h , we may assume any pseudo-contact shifts to be extremely small and neglect them. We can then consider the observed contact shifts to be isotropic shifts and interpret them in terms of spin delocalization mechanisms.

Since there are two unpaired electrons in the metal e_g orbitals, which are aligned with the magnetic field, a σ -type metal-ligand bond with the amine would place the unpaired spin in the σ^* antibonding orbital. Thus, positive spin density (spin aligned with the field) is also placed on the nitrogen and on all other ligand atoms making a substantial contribution to the σ^* antibonding orbital. This gives rise to a downfield shift at these atoms. The spin densities on the protons, as indicated by the nmr data, are shown in Figure 2. We have the very interesting result that, in a system where the metal-ligand interaction is essentially σ , the distribution of spin density at the phenyl protons is that expected for the π -delocalization mechanism (i.e., alternation of the sign of the spin densities). Clearly then, this experiment indicates that one cannot use distribution of unpaired spin in the π system of the ligand as an indication of metal-ligand π bonding as has so often been done.⁵⁻⁷ Thus, unpaired spin may be delocalized onto the ligand by a σ mechanism and be placed in the π system by various mechanisms, including one that operates in the reverse of that used by Levy⁸ and Copla and DeBoer²² to explain how spin is transmitted from the phenyl ring to methylene or methyl protons.

Having established the hypothesis this experiment was designed to test, an interpretation of the contact shifts remains. As mentioned previously, the σ -bonding interaction of the ligand with nickel places positive spin density in the σ^* antibonding molecular

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ls that are formed. Thus a positive spin density is placed on the nitrogen.

Since the methylene protons are not orthogonal to the nitrogen orbitals, spin density can be placed on these protons (*i.e.*, the methylene protons contribute directly to the σ^* molecular orbital). This accounts for the observed positive coupling constant. The methylene group in benzylamine must bear the same relationship to the phenyl π system as the methylene groups in pyracene ions.²² As discussed by Rice,²³ a linear combination of methylene protons $\pi_H = N[\phi_{1s}^A - \phi_{1s}^B]$, where π_H is the pseudo- π orbital, N is a normalization constant, and ϕ_{1s}^A and ϕ_{1s}^B are the normalized $1s$ atomic orbitals on the methylene protons) has the correct symmetry to interact directly with the π system of the phenyl ring. Spin in the π system is transmitted directly to the methylene protons through a hyperconjugative-type mechanism. The hyperfine coupling of methylene and methyl protons in many aromatic radicals can be explained on this basis. In benzylamine the methylene protons are part of both the σ^* mo and this extended π system. Consequently, placing a net positive spin density on the methylene protons as described above also places spin density in the phenyl π system. This π delocalization gives rise to positive spin densities at the *o*- and *p*-positions and negative spin density at the *m*-carbon.²⁴ Spin density may then be transmitted to the aromatic protons by the well-known σ - π , C-H spin polarization effect.⁸ Thus, we expect negative spin density at *o*- and *p*-hydrogens and positive spin density at *m*-hydrogen. The lack of attenuation, the alterations of the coupling constants for the aromatic protons, and the opposite signs of the *p*-hydrogen and methyl hydrogen shifts indicate that the electron spin is placed in the π system of the phenyl ring.²⁴ It should be mentioned that a mechanism which involves overlap of the amino and methylene protons and the phenyl π system with the t_{2g} set of nickel orbitals would result in an opposite sign from that observed for the phenyl and methylene protons. Exchange interactions on nickel would place spin down on the

ligand. Also, a direct overlap of t_{2g} nickel orbitals with the ring π orbitals would give rise to signs opposite to those observed for the ring protons because of exchange effects on nickel.

The large upfield shift of the amino protons is surprising when compared to the water²⁵ and methanol²⁶ contact shifts. One might expect that the amino protons would contribute directly to the σ^* mo in the complex and be deshielded by having spin placed directly on them. Instead they are observed to be shielded. The hydroxy protons in $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ and $[\text{Ni}(\text{CH}_3\text{OH})_6]^{2+}$ are both deshielded^{25,26} by this direct mechanism. The direction of the shift for the amino protons is similar to that reported by Wayland and Rice²⁷ for hexaamminenickel(II) complexes. These authors conclude that negative spin density reaches the protons by a spin polarization effect. O'Reilly,²⁸ in discussing spin densities in alkali metal-ammonia solutions, has proposed that the observed negative spin density on the hydrogen results from a node in the wave function of the unpaired electron near hydrogen. Consequently N-H σ - π spin polarization effects, formally analogous to the more familiar C-H spin polarization effects, are reported to dominate these proton shifts. Our results are consistent with those reported by these authors.

These conclusions should not be construed to mean that we believe that metal-ligand "back-bonding" does not exist. In general, several lines of experimental evidence are required to substantiate its existence. For example, we have recently²⁹ reported the existence of back-bonding in some substituted pyridine N-oxide complexes of nickel(II). To draw these conclusions, it was necessary to study the infrared, electronic, and nmr spectra of the nickel complexes and the infrared spectra of some phenol adducts of the ligands.

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The Preparation and Properties of Tetra-, Penta-, Hexa-, Hepta-, and Octaphosphates

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Abstract: Gram quantities of pure polyphosphates containing from four to eight phosphorus atoms per molecule were prepared. The phosphates were hydrolyzed at pH values of 4, 7, and 11 at 30 and 60°. First-order specific rate constants were determined for the over-all degradation of each compound. The rate constants for the end-group clipping to the next lower phosphate and an orthophosphate and the rate constants for the split-out of trimetaphosphate from the chain phosphates were also determined.

The chemistry of pyro-, tri-, trimeta-, and tetrametaphosphate has been the subject of hundreds of scientific articles during the past 100 years. The chemistry of the complex and complicated mixtures of poly- and metaphosphates contained in amorphous phosphate glasses and crystalline very long chain polymers has also been studied extensively. Despite the large volume of information gathered on the systems which have been studied, very little is known of the specific properties of the condensed phosphates containing more than four phosphorus atoms per molecule.¹⁻⁴ The knowledge of the properties of tetraphosphate is not extensive when compared with pyro- and triphosphates, but much valuable information has been gained on this anion during the past 20 years.⁵⁻¹³

Phosphates containing more than four phosphorus atoms and less than ca. 500 phosphorus atoms are not phase-diagram entities, and no simple method has been devised to prepare even gram quantities of the pure phosphates. The one exception is calcium hexaphosphate which can be prepared with relative ease.^{14,15} The compound is very insoluble and cannot yet be used to obtain useful quantities of soluble hexaphosphate salts, however.

The primary objective of this work is to establish a foundation for the comparison of the hydrolysis of polyphosphates as a function of their molecular size. The work is based on more than 20,000 qualitative and quantitative analyses. It is believed to be as reliable as the state of the science allows today without drastically limiting the number of compounds considered.

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Experimental Section

Preparation of the Pure Polyphosphates. Polyphosphoric acid was chosen as a source of polyphosphate anions. The acid was prepared by heating 85% orthophosphoric acid in a gold dish at 400° for 12 hr to yield a polyphosphoric acid with an average chain length near five. The average chain lengths were determined by end-group titrations.¹⁶

A 200-g sample of the phosphoric acid was dissolved in 2 l. of water, and the phosphate was extracted from the aqueous solution into 3400 ml of a 25% solution of *t*-caprylamine dissolved in xylene. The tertiary amine, Alamine 336S, was obtained from the General Mills Co. The two immiscible solvents were shaken together for 1 hr and then allowed to separate. The aqueous phase was discarded. The desired phosphates were stripped from the amine solution with 500-ml portions of 0.1 *N* aqueous ammonium hydroxide; 10 to 12 fractions removed the desired phosphates. The fractions were analyzed by paper chromatography. At this stage of the extraction each fraction contained three major components. About 50 g of polyphosphoric acid was recovered while 150 g was discarded as ortho- and longer chain phosphates, unwanted for this work.

The solutions of phosphates were stored in a refrigerator at 2° until ready to be reextracted. Before the phosphates could be refractionated, it was necessary to convert the ammonium salts back to the corresponding acids. Samples containing similar quantities of the same phosphates were combined and passed through a cation-exchange column containing 4 lb of Dowex 50W-X4 resin in the hydrogen form. The acidic solutions were then mixed with a fresh batch of 33% amine solution at the ratio of 160 g of amine solution to 500 ml of aqueous phosphate solution. The quantities of course depended on the number of phosphate solutions which were combined. The aqueous phase was again discarded after 1 hr of mixing. The phosphate was stripped from the amine solution with 100-ml portions of 0.1 *N* aqueous NH₄. In a typical extraction 20 fractions were obtained and the amine was completely stripped of phosphate. At this stage each fraction contained two major constituents. The extraction procedure was repeated with combined fractions containing similar phosphates. The third and usually final fractionation of the phosphate solutions was made in a similar way except the final extraction was made with 0.1 *N* NH₄NO₃ and the aqueous extract volume was reduced to 10 ml. The fractions contained one major fraction, a smaller quantity of a second phosphate, and traces of longer chain phosphates.

When only two major constituents must be separated, an anion-exchange chromatographic column may be heavily loaded and still give satisfactory separation of the two components. A column 1 cm in diameter with 27-cm bed depth was filled with Dowex 1-X8 resin in the chloride form.¹⁷ The column was treated with 400 ml of 0.30 *N* KCl solution adjusted to pH 5.0 with HCl. Then the column was loaded with 0.5 g of ammonium polyphosphates contained in 50 ml of the solvent extracted from the amine solution. The concentration of the eluting agent used depended upon the phosphates to be separated. If the solution contained tetra- and penta- or penta- and hexaphosphate, the column was eluted with

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N KCl adjusted to pH 5. If hexa- and heptaphosphates were separated, the concentration of KCl was adjusted to 0.35 N; meta- and octaphosphates were to be separated, the KCl concentration was increased to 0.40 N. When the longer chain phosphates (hexa-, hepta-, or octa-) were to be separated, the column was treated with 400 ml of 0.3 N KCl to remove any shorter chain phosphates, and then the concentration was increased to the separation level.

The flow rate of the column was adjusted to 1 ml/min and 20-ml portions were collected with an automatic fraction collector. After the first 90 fractions had been collected, the phosphate was removed by spotting a drop of each fraction on a filter paper and developing the filter paper as though it were a paper chromatogram which had not been subjected to solvent separation.

After the phosphates were located, the midfractions were chromatographed to ensure the purity of the fractions. Like fractions were then combined, and the water was removed from the solution on a thin-film vacuum evaporator connected to a water aspirator. The flask of the evaporator was maintained at approximately 40°. Evaporation was discontinued when the first crystals of KCl appeared in the flask.

Diethyl ether was used to separate the KCl from the phosphate solution.

The saturated solution of KCl was put into a dialysis membrane (0.75 × 10 in.), and then the membrane was suspended in 4 l. of distilled water. The removal of the KCl was rapid and complete. Within 3 hr, with three changes of the outside water, the chloride ion inside the dialysis tube was barely detectable. This method was found to be superior to the various precipitation techniques commonly used on benzidine,^{1,2} because the phosphate suffered no detectable degradation in this process and no foreign ions were added to the phosphate solution. Once the phosphates were concentrated and freed from the KCl, they were stored in a refrigerator at 2° until dried.

These samples of polyphosphates can be preserved much easier than they can be as the amorphous solids which form either a sodium or potassium salt is precipitated. In every attempt the sodium or potassium salts reorganized within a few days or two if the salts were stored as the solids. If the crystalline form of either the guanidinium or acridinium phosphates were used, as by the methods of Quimby⁸ employed to crystallize the tetraphosphate, they were stable if care was taken to make certain that they were dry.

Analysis of the Phosphates. It has been well established that the various polyphosphates do truly exist and can be separated as pure substances by chromatographic techniques.¹⁸ It is not considered necessary to attempt to reestablish this fact. The analytical problems which were confronted were quantitative rather than qualitative.

Qualitative methods¹⁹⁻²⁰ were needed which were reasonably accurate and at the same time reliable if the large number of analyses which were needed in a hydrolysis study were to be handled within required time limits. After several hundred tests with columns, thin-layer papers, and thin-layer chromatograms, the decision was made to employ ascending paper chromatograms on a 10 × 11.5 in. piece of Schleicher and Schuell 589 Orange Ribbon paper. The paper has the advantage of being easily referenced and graphic. Thin-layer chromatograms are also graphic, but quantitative analyses of phosphates were more difficult.

The acidic chromatographic solvent 92-D recommended by Coffey²¹ was used in this work but it was modified in one respect. Separations were obtained with the longer phosphates if solid ammonium carbonate was substituted for the aqueous ammonia solution suggested. For solvents designed to separate hepta-, octa-

and nonaphosphates, 1.4 g of ammonium carbonate was used per 1 l. of solvent solution, while the solvents used to separate the shorter chain phosphates (tetra-, penta-, and hexa-) required 2.5 g of (NH₄)₂CO₃/l. The basic solvent used in the two-dimensional chromatograms was that recommended by Karl-Kruppa.²² The chromatographic chambers were standard 6 × 12 in. cylinders and contained 100 ml of solvent. The chromatographic chambers were thermostated at 17° in a modified commercial deep freezer equipped with a forced air fan. The temperature-sensing element in the refrigerator was replaced with a thermistor and an electronic relay to improve the temperature control of the freezer.

The phosphate solution to be tested (10–20 μl) was placed 1.25 in. from the bottom of the filter paper as a band 0.75 in. long and 1/8 in. wide. Each chromatogram held four spots or two duplicated samples. Attempts were made to store chromatograms at 2° while awaiting a vacant chromatographic chamber, but this technique caused errors if the chromatograms were stored for more than 24 hr because the phosphates degraded on the paper.

Chromatographic papers were allowed to remain in the chromatographic chamber for about 12 hr or until the solvents reached the top of the chromatograms. The chromatograms were then removed from the chambers, air-dried, and then dried for 5 min at 100° in a forced air oven.

The chromatographic sprays used to develop the chromatograms were those recommended by Hanes and Isherwood.²³ At this point the treatment of the chromatogram depended upon its ultimate use. Parts of the chromatograms were quantitatively analyzed for the per cent of the phosphorus in the phosphate in question compared to the remainder of the phosphate on the chromatograms. These chromatograms were analyzed by the method recommended by Smith,^{24,25} using a Spectronic 20 spectrometer manufactured by the Bausch and Lomb Co. The spectrometer was fitted with a digital readout supplied by the same manufacturer.

Other chromatograms were analyzed for the distribution of phosphate species to give a total analysis of the phosphates. These chromatograms were analyzed by the method recommended by Bernhart and Chess,²⁷ and an Analytrol-RB spectrometer manufactured by the Beckman Instrument Co. was employed to perform the analyses. The latter method of analysis was not as accurate as the extraction technique, but a quantitative analysis was obtained for all species present. Hydrolyzing samples of octaphosphate contain as many as nine species, and the time required to obtain an analysis of each phosphate by the extraction technique was prohibitive. The two methods agreed within about 2% per species analyzed except for an occasional analysis when the errors, which we attributed to the authors, resulted in complete disagreement between the two methods. The data were discarded when the errors greater than about 2% per phase were committed.

The Rates of Hydrolysis of Polyphosphates. Nearly 100 papers have been published on the rates of hydrolysis of condensed phosphates yet only three works have been reported for the hydrolysis of individual polyphosphates longer than tetraphosphates.^{1,4,6} Even the hydrolysis of tetraphosphate has received but little attention,^{5,6,8} while only two works have been published on the hydrolysis of higher ring metaphosphates.^{24,28} Pyrophosphate has been studied in great detail.²⁹⁻³¹ The complex glasses, very long chain

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In the work presented here the rates of hydrolysis were determined for tetra- through octaphosphates at pH values of 4.0, 7.0, and 11.0 at 30 and 60°. The concentrations of the polyphosphate solutions were adjusted to allow for a convenient analysis by paper chromatography since there was no obvious reason for adjusting the concentrations to any other values. The concentration of phosphate was adjusted as near to 50 µg of phosphorus per 10 µl of solution as was convenient; however, no differences in the data obtained could be attributed to changes in concentration of the phosphate even if the concentration was increased or decreased by as much as 200%.

Before the phosphates were hydrolyzed, they were converted from the potassium salts to either the sodium or tetramethylammonium salts. The conversion to the sodium salt was accomplished by passing the phosphate over a large excess of Dowex 50 resin which was converted to the sodium form with 0.2 N NaOH and then washed with distilled water until the wash water was no longer basic. The column used was simply a 100-ml buret which had been cut to 20 ml and contained 10 ml of dry resin. A similar technique was used for the tetramethylammonium conversion except the phosphate was first converted to the acid form with the cation-exchange resin, and then the phosphate was neutralized with 3% tetramethylammonium hydroxide. This was done to keep the excess tetramethylammonium ion concentration as low as possible.

Samples of 2 ml were found to be convenient for the hydrolysis studies. The samples were adjusted to the required pH with the aid of a Beckman Model G.S., battery-powered, pH meter. The usual precautions were observed and the pH was adjusted to within 0.01 unit of the required value. No sodium ion corrections were applied. After the pH was adjusted to the proper value the sample was transferred to a 2-dram glass vial, which was then placed in a thermostated water bath. The baths were obtained from the E. H. Sargent Co., but the thermoregulator was replaced by a more sensitive unit obtained from the H and B Instrument Co. The baths were capable of maintaining 30.00 ± 0.01 or $60.00 \pm 0.01^\circ$ for as long as 2 years without readjustment. The pH was maintained by periodic adjustments back to the original value when required.

The time the samples were maintained in the baths and the time at which samples were collected was monitored by two master interval timers. At the start of each hydrolysis experiment the local time was recorded, as well as the time on the master timers. The time was recorded to 0.1 hr in all cases except the very fast reactions where the time was measured in minutes.

A zero-time analysis was made on each sample before it was placed in a thermostat. If any trace of a higher polyphosphate than the one under consideration was found in a sample to be hydrolyzed, the sample was repurified. The shorter chain lengths caused no difficulties in the determination of rate constants. The presence of phosphates with chain lengths greater than the phosphate under consideration could not be accepted because there was no simple way to correct the errors caused by their degradation before their rate constants were known. At prechosen intervals, samples were withdrawn from the vials and analyzed. On the average eight data points were collected for each rate constant. Two types of chromatograms were prepared and each chromatogram was duplicated and placed in reserve in case an analytical result was questionable. The reserves were not maintained for more than 24 hr at 2° or they were considered to be useless. One-dimensional chromatograms were used to establish the per cent phosphorus present as the polyphosphate under study vs. the remainder of the phosphate contained in the sample being studied.

The duplicate half of the same chromatogram was analyzed by the Analytrol to give the percentage phosphorus present as the

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Table I. The Rate Constants for the Hydrolysis of Polyphosphates

Phosphate	pH	Specific rate constants, total reaction, k_t , min ⁻¹		ΔE_{\pm} , total reaction, kcal	Specific rate constants, trimeta split-out, k_m , min ⁻¹		ΔE_{\pm} , trimeta split-out, kcal	Specific rate constants, end-group clipping, k_e , min ⁻¹		ΔE_{\pm} , end- group clipping, kcal
		30°	60°		30°	60°		30°	60°	
odium salts										
Tetra-	4	7.5×10^{-6}	4.6×10^{-4}	27.5				7.5×10^{-6}	4.6×10^{-4}	27.5
	7	4.6×10^{-6}	2.0×10^{-4}	25.2				4.6×10^{-6}	2.0×10^{-4}	25.2
	11	2.0×10^{-6}	8.8×10^{-5}	25.3				2.0×10^{-6}	8.8×10^{-5}	25.3
Penta-	4	2.4×10^{-6}	6.3×10^{-4}	21.8	8.2×10^{-6}	9.8×10^{-6}	16.6	1.6×10^{-6}	5.3×10^{-4}	23.4
	7	1.5×10^{-6}	4.8×10^{-4}	23.2	4.4×10^{-6}	1.7×10^{-4}	24.6	1.4×10^{-6}	3.0×10^{-4}	20.5
	11	4.8×10^{-6}	2.5×10^{-4}	26.4	1.8×10^{-6}	8.4×10^{-5}	25.7	3.0×10^{-6}	1.7×10^{-4}	11.6
Hexa-	4	(3.4×10^{-6})	7.1×10^{-4}	20.3	9.7×10^{-6}	1.1×10^{-4}	16.4	2.4×10^{-6}	6.0×10^{-4}	21.5
	7	3.8×10^{-6}	7.6×10^{-4}	20.0	6.5×10^{-6}	2.5×10^{-4}	24.4	3.4×10^{-6}	4.9×10^{-4}	17.8
	11	8.0×10^{-6}	4.8×10^{-4}	27.4	(6.6×10^{-6})	2.9×10^{-4}	25.3	3.0×10^{-6}	2.0×10^{-4}	12.3
Hepta-	4	4.3×10^{-6}	7.9×10^{-4}	19.5	1.2×10^{-6}	1.3×10^{-4}	16.2	3.2×10^{-6}	6.5×10^{-4}	20.1
	7	7.5×10^{-6}	1.0×10^{-3}	17.3	9.2×10^{-6}	3.5×10^{-4}	24.3	6.6×10^{-6}	6.6×10^{-4}	15.4
	11	1.5×10^{-6}	7.7×10^{-4}	26.3	1.2×10^{-6}	5.8×10^{-4}	25.7	3.0×10^{-6}	1.9×10^{-4}	12.3
Octa-	4		8.5×10^{-4}			1.6×10^{-4}			6.9×10^{-4}	
	7		1.4×10^{-3}							
	11		1.1×10^{-3}			9.8×10^{-4}			1.2×10^{-4}	
tetramethylammonium salts										
Penta-	4	1.4×10^{-6}	4.2×10^{-4}	22.7						
	7	6.9×10^{-6}	9.8×10^{-5}	18.0						
	11	8.6×10^{-7}	2.0×10^{-5}	21.0						
Hexa-	4	1.4×10^{-6}								
	7	9.5×10^{-6}	1.1×10^{-4}	16.3						
	11	4.2×10^{-6}								
Hepta-	7		7.5×10^{-4}							
	11		6.6×10^{-4}							

arious degradation products if it was not needed as a duplicate or the single species analysis. A two-dimensional chromatogram was also set up to determine the percentage trimetaphosphate which formed from the longer chain phosphates. The two-dimensional chromatograms were divided into three parts: the phosphate under study, the trimetaphosphate, and the short-chain phosphates which were degradation products. This selection of samples gave an independent check in the values obtained from the one-dimensional chromatograms.

The analyses of samples are so involved and the possible sources of error are so numerous that no attempt will be made to discuss them. The reader is referred to the literature cited from which the analytical techniques were adopted. An estimate of the errors committed in determining the rate constants was made at the 95% confidence limits. These estimates reflect more the precision of the work than its accuracy. Rather than attempt to assign a more or less meaningless estimate of error to each rate constant, it can be safely stated that the error is less than $\pm 10\%$. Much more effort was expended by the authors to furnish a self-consistent group of data than to attempt to supply highly reliable data with tools that are inherently difficult to control. For this reason the rate constants developed in this work will be reported to only two significant figures. The reader can gain much greater feeling for the errors in the work by comparing the various plots of the rate constants vs. pH or chain length.

No major difficulties were encountered in the analyses of the sodium polyphosphates but the tetramethylammonium polyphosphates were particularly difficult to analyze when the longer phosphates were chromatographed. The major difficulty arises from the fact that the tetramethylammonium hexa-, hepta-, and octaphosphates streak badly in the chromatographic solvents which separate them within 12 to 16 hr. A second difficulty results from the tetramethylammonium ions which impart a blue color to a chromatogram when developed with the ammonium molybdate reagents used in this work. No method was devised to overcome these two sources of error, and the tetramethylammonium phosphate work was limited. The data obtained with the tetramethylammonium phosphates are reported but the errors are twice as large as those for the sodium polyphosphates.

The need for the tetramethylammonium data vs. sodium ion data has been discussed in a previous work.¹⁰ It will be noted that there are several notable differences in the sodium phosphate data and the tetramethylammonium phosphate data.

Table I contains the first-order specific rate constants, for the over-all disappearance of a phosphate species, k_t ; the first-order rate

constant for the disappearance of a species by the clipping of an orthophosphate from the end of a chain, k_e ; and the first-order rate constant for the disappearance of a species by the splitting out of a trimetaphosphate from the linear polyphosphates, k_m . Both k_t and k_m were obtained from the analytical data. The end-group clipping rate constants were calculated from

$$k_t = k_e + k_m \quad (1)$$

$$-\frac{dC}{dt} = k_t C = (k_e + k_m)C \quad (2)$$

where C is the concentration of the species in question. In the calculations used in this work, C was expressed as the percentage of the phosphorus in the phosphate under consideration with respect to the total phosphorus in the sample solution.

Discussion of Results

To compare the various phosphates the authors plotted the data on two types of graphs. The first plot was $\log k$ vs. pH for each phosphate species at each temperature. The second plot was $\log k$ vs. the number of phosphorus atoms contained in the phosphate at a fixed temperature and pH. The conclusions drawn from these data are based upon these graphs, but unfortunately they are too numerous to reproduce. It is recommended that the reader seriously interested in the results plot the data himself.

The rates of degradation of sodium hexa-, hepta-, and octaphosphates by all routes simultaneously are greater at pH 7 than at pH 4 or 11. It was not unexpected that the over-all degradation at pH 11 was less than it was at pH 7, but it was unexpected that the rate at pH 7 was greater than it was at pH 4 as seen in Figure 1.

In every case tested the degradation of the phosphates followed the first-order rate law with respect to the reacting phosphate. No extensive effort was made to prove that the first-order law was observed, but the

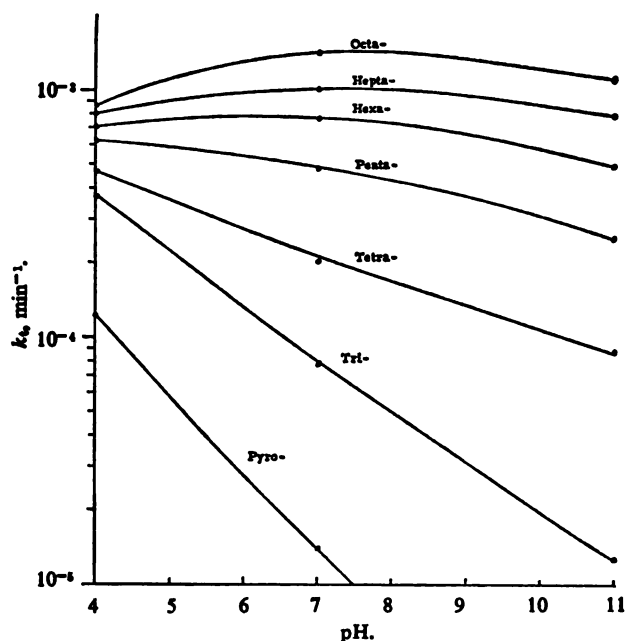


Figure 1. Specific rate constants for sodium polyphosphates as a function of pH at 60°: pyro- and tri- values from ref 59.

data contained no results which caused doubt that the first-order law was obeyed with the longer chain phosphates as it is with the shorter chain phosphates. The rate constants of Table I were derived from straight lines obtained when $\log C$ was graphed as a function of time. For test cases the straight-line relationship was maintained for three or more half-life periods. All of the rate constants, except the very small constants, are derived from data gathered during at least two half-life periods.

The stabilities of the polyphosphates decrease as the chain lengths increase, but the rate constants seem to be approaching some limiting value as chain length increases. The differences between the rate constants for tri- and tetraphosphates are much larger than the differences between hepta- and octaphosphates under the same experimental conditions as shown in Figure 2.

It is known that a chain phosphate may degrade by any one of at least three routes.⁹⁵ One mode of degradation results from the clipping of the end group of the chain to form orthophosphate and a phosphate chain one phosphorus atom shorter. A second mode is the degradation by the breaking of the chain somewhere in the middle of the chain to yield two chains. A third method of degradation results from the splitting out of a trimetaphosphate ring to leave a chain phosphate three phosphorus atoms shorter. Although the first and third methods of degradation were clearly evident, there were no clear indications when the total families were considered that the chain cleaved in the middle.

Rate constants were developed for the loss of the polyphosphates by splitting out trimetaphosphate. As shown in the midcolumns of Table I, the rates of loss of a phosphate by this route can be as great or greater than the loss by the hydrolysis of the ends of the chains.

The shortest chain phosphate which can degrade to trimetaphosphate is tetraphosphate. Only trimeta- and orthophosphate would remain. In the work with

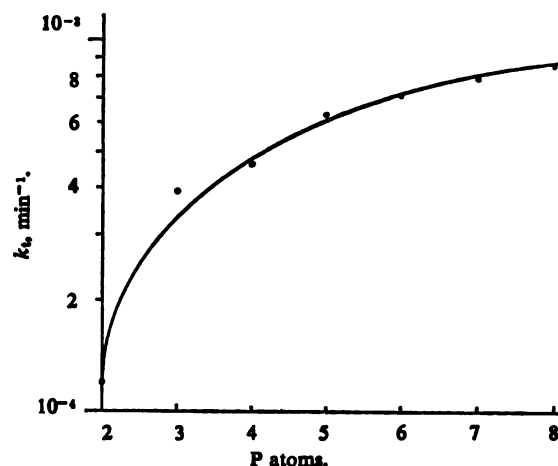
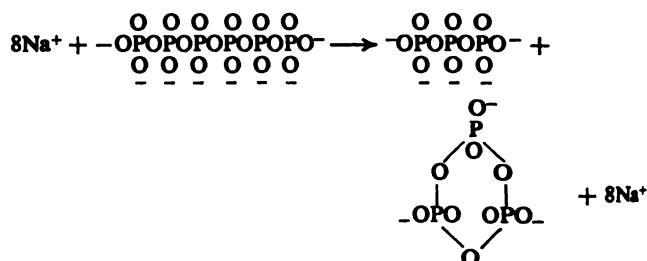


Figure 2. Specific rate constants for the total reaction of sodium polyphosphates as a function of molecular size at pH 4.0 and 60°: pyro- and tri- values from ref 59.

tetraphosphate, there was a small but detectable buildup of trimetaphosphate in the solutions. The concentrations of the trimetaphosphate was too small to yield reliable rate data. When the chain length of the phosphate was five phosphorus atoms or more, the buildup of trimetaphosphate was easily measured and rate constants were developed.

In the past there has been considerable speculation as to the mechanism of the "hydrolysis" of a chain phosphate to trimetaphosphate. It is the contention of the authors that this degradation is not hydrolysis at all but a reorganization of the phosphate as occurs in anhydrous systems when phosphates are heated. It can be seen that water need not be considered as a reactant. For example, the degradation of sodium hexaphosphate to trimetaphosphate and triphosphate may be represented as



and water is neither a reactant nor a product. In fact, a 1:1 mixture of trimetaphosphate and triphosphate is exactly the mixture one would expect from phase-diagram considerations¹²⁴ if an anhydrous sodium phosphate with a hexaphosphate composition were heated to speed the approach to equilibrium conditions.

The relationships among the rate constants for the tetramethylammonium phosphates were of a different form when compared to the corresponding sodium systems when a graph of $\log k_t$ vs. pH was constructed. This led to the conclusion that perhaps trimetaphosphate was not being formed in the tetramethylammonium systems as it was in the sodium systems. Heptaphosphate was converted to the tetramethylammonium salt and degraded at pH 11 and 60°. Small quantities of trimetaphosphate buildup could be

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ed during the study, but the concentration of triphosphate was never large enough to obtain a tentative analysis of this species. It is doubtful tetramethylammonium trimetaphosphate would even if anhydrous tetramethylammonium heptahate were heated to temperatures just high enough se it to reorganize. It can only be concluded that dium ions in the sodium polyphosphate system buted to the formation of the trimetaphosphate rms as a degradation product of the reaction.

activation energies for the degradation of a polyhate to trimetaphosphate are independent of the length of the phosphates from which the triphosphate forms. Conversely, the activation enare very dependent upon the pH of the solution. ctivation energies increase as the pH of the soluincreases (see Table I).

e the rate constant k_t (for the total reaction by all) has been obtained and the rate constant for lit-out of trimetaphosphate, k_m , is known, the onstant for end-group clipping, k_e , can be calcu-

The rate constant for end-group clipping, k_e , difference between the rate constant for all ns, k_t , and the rate constant k_m .

rate data for the end-group clipping at pH values id 7 are in accordance with similar data developed or works with pyro-, tri-, and tetraphosphates.^{6,59}

4 there are small differences between the values rate constants for the total reactions and the onstants for end-group clippings since the phosdegrades mostly by end-group clipping. Sigtly different data were obtained for the end-clipping at pH 11. At pH 11 the rates of degon by end-group clipping are independent of the length above five phosphorus atoms. The values for hexa-, hepta-, and octaphosphate are all the at pH 11 and 60°. The same is true for penta-, hepta-, and probably octaphosphate at pH 11 °.

activation energies for end-group clipping de-with increasing pH for each phosphate. This or was noted for sodium triphosphate⁵⁹ in a pre-report. The activation energies for sodium trihate at pH values of 4, 7, and 10 are 27.6, 28.0, .8 kcal, respectively.

data for the tetramethylammonium phosphate s are not sufficiently complete to draw many ant conclusions. The activation energies for al reaction of pentaphosphate are similar in value sodium system at pH 4 and 7, but the large in- in activation energy at pH 11 was not found in ramethylammonium system. This is attributed : observation that trimetaphosphate split-out ot occur to any appreciable extent in the tetrammonium system. In the sodium system pH increased, the temperature sensitivity of the aphosphate split-out became greater while the ature influence of the end-group clipping del sharply.

nerous studies have shown pyrophosphate is more in aqueous solutions than triphosphate. It has een demonstrated that triphosphate is more than tetraphosphate. The hydrolyses of shorter phosphates are catalyzed by hydrogen ions but hydroxyl ions, but the hydrolysis of the lower

membered ring phosphates, trimeta- and tetrametaphosphate, is catalyzed by both hydrogen and hydroxyl ions. No satisfactory explanations of these facts are known. This has probably resulted from the fact that the longer chain phosphates have been so difficult to prepare that no one has had the opportunity to compare the phosphates as a family at a variety of pH and temperature values.

The electron density about a POP linkage in a phosphate is very dependent upon the degree of polymerization of the phosphate in which it occurs. Kinetically, the most stable chain phosphate in aqueous solutions is pyrophosphate. The POP linkage in pyrophosphate is also the most electron-rich phosphate linkage possible. If one neglects the inner shells and considers the octet about the oxygens only, there are 56 electrons associated with the linkage. On the other hand, the most unstable of all phosphates in aqueous solution is phosphorus pentoxide, P_4O_{10} . This molecule has the minimum number of electrons per POP linkage it is possible for a phosphate to contain, namely 13.3 per POP linkage, neglecting the inner shells. These facts would surely lead one to believe there is a relationship between the electron density of a POP linkage and its stability in aqueous solutions. Table II shows the average number of electrons per POP linkage for the phosphate family.

Table II. The Electron Density of POP Linkages in Condensed Phosphates

Compound	Electrons in valence shells per POP linkage
Pyrophosphate	56
Triphosphate	40
Tetraphosphate	34.7
Pentaphosphate	32
Hexaphosphate	30.4
Heptaphosphate	29.3
Octaphosphate	28.6
Trimeta-, tetrameta-, penta-, metaphosphate, etc., or long-chain phosphate	24.0
Phosphorus pentoxide	13.3

Data are available for the first time to test the concepts presented above; it is desirable to ask under what conditions the concept should be tested. Reflecting upon the behavior of the longer chain phosphates makes it obvious that only the pH 4 data are of use, because the longer chain phosphates degrade by two routes at pH values of 7 and 11. At pH 4 the predominant reaction is end-group clipping. Figure 3 is a graph of the $\log k_e$ at pH 4 and 60° vs. the average number of electrons per POP linkage. The values for pyro- and triphosphates were taken from the work of Van Wazer, Griffith, and McCullough.⁵⁹ The 30° data treated in the same manner also yield a straight line but of greater slope.

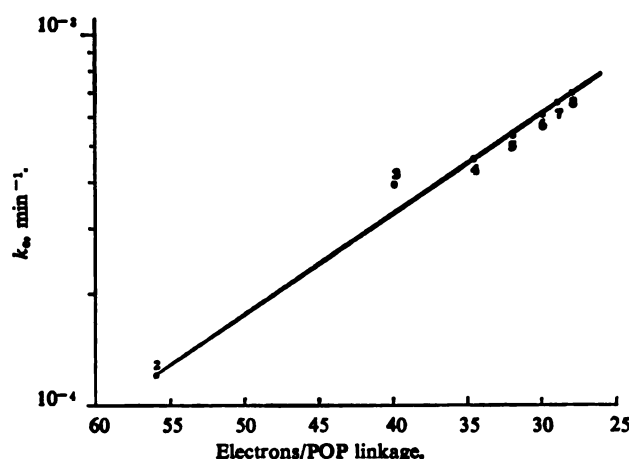


Figure 3. Specific rate constants for end-group clipping of sodium polyphosphates as a function of the average number of electrons per POP linkage: pyro- and tri- values from ref 59.

The number of electrons per POP linkage in a polyphosphate approaches the number of electrons per POP linkage in a ring metaphosphate as a limit, *i.e.*, 24.0 as the chain length of the polyphosphate approaches infinity. It is therefore possible to place an upper limit on the rate of hydrolysis of a long-chain phosphate as the phosphate degrades by end-group clipping in acidic media.

It is not surprising that pyrophosphate is the most stable of all phosphates in basic media. Moreover, since the ring metaphosphates have an intermediate number of electrons per POP linkage, these substances suffer both nucleophilic and electrophilic attacks.

The electron density per POP linkage is not the complete story on phosphate hydrolysis, however. The ring

metaphosphate's POP linkages are all isoelectronic, no matter how large or small the ring may happen to be. As previously shown by the authors,³⁴ the rate of degradation of a ring phosphate decreases as the size of the ring increases. The true ring hexametaphosphate is the most stable phosphate ever studied near neutral pH values. Unmistakably there are entropy considerations as well as electron-density considerations. The larger rings are resistant to hydrolysis because they are more flexible than the smaller rings and can distribute and dissipate the energy of collision as is evident from the very low activation energies for the hydrolysis of the large-ring phosphates.

Throughout the discussion of this work attention has been focused upon the rate of disappearance of a single species of phosphate without regard to the over-all degradation products. In a following article the phosphates will be treated as a family. Not only will the single species be considered, but also the relative concentration of the various degradation products which occur. Also a method was developed which allows one to predict the concentration of various species as a function of time based upon the simultaneous consideration of the rate constants presented in this work.

The data of this work were not treated as individual protonated species as has been done on several occasions with pyrophosphates.^{56,62,125} The treatment of protonated species is more mathematical than experimental and can easily be derived from these rate data and published *pK* values of the condensed phosphates¹²⁶ by modern computer techniques.

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Organic and Biological Chemistry

Machine Computation of Equilibrium Constants and Plotting of Spectra of Individual Ionic Species in the Pyridoxal-Alanine System¹

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Contribution from the Department of Biochemistry and Biophysics, Iowa State University, Ames, Iowa 50010. Received February 1, 1967

Abstract: A method is described by which a digital computer with an automatic plotter can draw a smooth curve to fit experimental spectral data points at 5-m μ intervals with supplemental points, where needed, at 2.5-m μ intervals. Programs have been written that compute, from spectral data at up to 75 wavelengths, as many as three successive dissociation constants for a light-absorbing compound. A least-squares method involving successive approximations is used to obtain the best fit of all pK values to 0.01 unit. The spectra of the individual ionic forms (up to four) are drawn, and the extinction coefficients are also punched out on cards. New data for pyridoxal at 50° are reported. Equilibria involving a second nonlight-absorbing component and reversible formation of a compound or complex are also considered. Methods are provided for finding the formation constant, the successive acid dissociation constants, and the absorption spectra of individual ionic forms for the compound or complex. The graphs of the log of the apparent formation constant vs. pH and the pH profiles of the concentrations (or percentages) of individual ionic forms are drawn automatically. An additional program provides for the plotting of experimental spectral data, together with calculated spectra, and the plotting of experimental data and calculated curves of absorbance vs. pH at any desired wavelength. Two systems involving formation of Schiff's bases are analyzed in detail.

Measurements of absorption spectra are used frequently to evaluate equilibrium and rate constants in complex chemical and biological systems. The availability of precise recording spectrophotometers makes it feasible to collect data over a broad range of wavelengths, but often, to simplify calculations, data at only one or a few selected wavelengths are employed in the computations.

The use of digital computers for the analysis of chemical equilibria has been developed by de Maine and Swright,³ Sillén and Ingri,⁴ Conrow, *et al.*,⁵ Sullivan, *et al.*,⁶ and Wiberg.⁷ With a modern high-speed computer, it is possible to treat very complex systems in which numerous equilibria of dissociation of protons and formation of complexes are taken into account. It is feasible to use spectral data at many wavelengths in such computations, and to obtain a graphical display of the results with an automatic curve plotter.

This report describes a method by which a digital computer with an automatic plotter fits a smooth curve to experimental points to closely reproduce the complete electronic spectral absorption curve of a substance. This method when used in conjunction with an appropriate computational program permits the evaluation of acid dissociation constants and formation constants for complexes and compounds and the automatic plotting of the spectra of individual ionic species. It also provides a direct comparison between experimentally observed spectra and those predicted from the equilibrium constants and the spectra of the individual ionic species. Dissociation constants and spectra of individual ionic forms have been evaluated for vitamin B₆ aldehyde (pyridoxal) at 50° and for 5-deoxypyridoxal at 25°. The system pyridoxal-alanine at 50° has been studied in detail and formation constants and acid dissociation constants for Schiff bases are presented for this system and for the system 5-deoxypyridoxal-leucine at 25°.

The approach described should be of use in studying many different problems of chemical equilibria. Programs will be made available to persons desiring them.

Recording and Plotting of Spectral Data

Data are transcribed from the tracings obtained with a standard recording spectrophotometer. If spectra change with time as a result of slow chemical reactions (e.g., between pyridoxal and alanine) it is necessary to extrapolate the spectra to zero time to analyze the initial equilibria. This is accomplished by measuring the spectra repeatedly at intervals of 10, 30, 60, 90, 120, and 180 min after mixing. The computer makes a linear extrapolation, taking into account the time of

1) Supported by a grant from the National Institutes of Health (AM-49). A preliminary report appeared in *Federation Proc.*, 25, 278 (1966). Part of this work was presented at the Second International Symposium on Chemical and Biological Aspects of Pyridoxal Catalysis, Moscow, USSR, Sept 1966. Journal Paper No. J-5499 of the Iowa Agricultural and Home Economics Experiment Station, Ames, Iowa, Project No. 1259.

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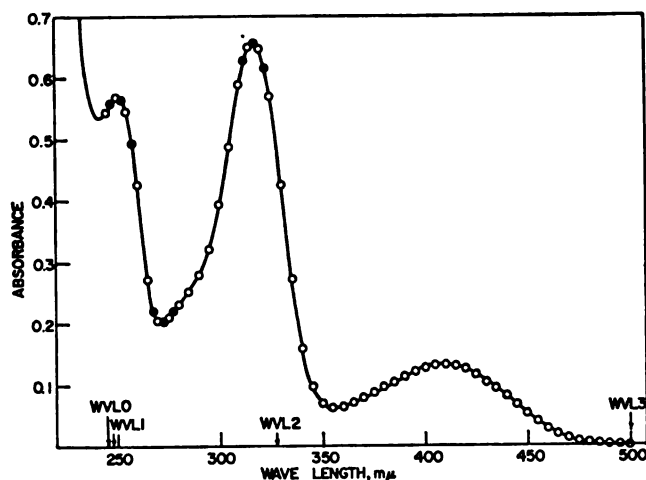


Figure 1. Method of transcription of data from experimentally obtained absorption spectra. The solid line is the absorption spectrum of a solution $1 \times 10^{-4} M$ in pyridoxal and $0.1 M$ in DL-alanine at pH 7.0 and 50° . This spectrum was selected as typical of those considered in this paper: O, points at $5\text{-m}\mu$ intervals between wavelength limits WVLO and WVL3 whose absorbance values, after any correction for solvent blanks, are transcribed to punched cards; ●, supplemental points added in the wavelength range WVL1–WVL2.

measurement of every point in the spectrum. According to the spectrum, suitable wavelength limits WVLO, WVLI, WVL2, and WVL3 are chosen (Figure 1). WVLO and WVL3 are lower and upper limits between which absorbance data are collected at $5.0\text{-m}\mu$ intervals. The spectral peaks of pyridoxal and its derivatives are sharper in the lower wavelength region than at longer wavelengths. To accurately portray the spectra in this lower region, supplemental data near the absorption peaks must be provided. These supplemental data are recorded in the region from WVL1 to WVL2, again at $5.0\text{-m}\mu$ intervals. Since we define $WVLI = WVLO + 2.5$, the supplemental data fall at wavelengths halfway between those of the principal set of data (Figure 1). In this work WVLO is either 230 or $245\text{ m}\mu$, WVL2 is $327.5\text{ m}\mu$, and WVL3 is $500\text{ m}\mu$. A total of 69 or 75 points is used.

It is aesthetically desirable to draw a smooth curve between experimental points when plotting a spectral curve. This is done by a two-step interpolation. In the first step, points are computed midway between each pair of experimental points by fitting segments of third-order equations to pass through four consecutive points. At the ends of the spectra, segments of second-order equations are fitted to three points. From this first step of the procedure, points at $2.5\text{-m}\mu$ intervals are available, half experimental and half interpolated. However, if a supplemental datum was recorded at a particular wavelength, the interpolated value is discarded in favor of the supplemental experimental one. The result of this operation is shown in Figure 2. The open circles on the two curves represent experimental data at $5.0\text{-m}\mu$ intervals and the closed squares the interpolated points. It is seen that for curve A, having a moderately sharp curvature, the calculated points fall very close to the true absorption curve, represented by the solid line. In curve B, which contains two very narrow peaks, the calculated points do not lie on the true curve. In this case, supplemental data (open triangles) must be included.

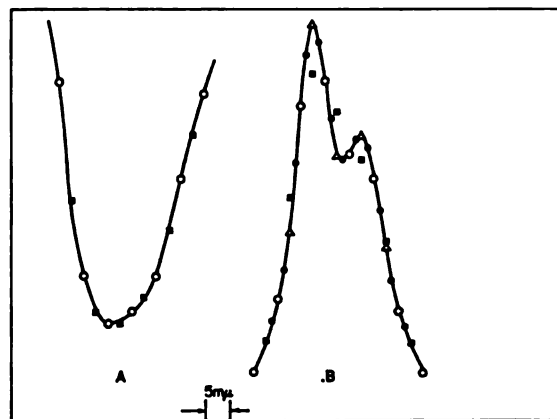
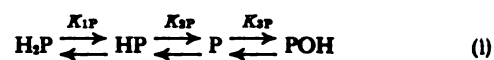


Figure 2. Comparison of interpolation procedure for curves with broad and narrow valleys and peaks. Curves A and B represent assumed experimental curves, —, with the selected data points at $5\text{-m}\mu$ intervals, O; Δ, supplemental data points, and ■, interpolated points from the first step (see text); ●, interpolated points from the second step.

In the second step, an entirely similar procedure using third-order equations is followed to obtain interpolated values between each pair of points at $2.5\text{-m}\mu$ intervals. These interpolated points obtained in the second step are indicated by small closed circles in Figure 2B. We now have points at $1.25\text{-m}\mu$ intervals. The automatic plotter locates these points and draws straight line segments between them to give the final curve.

Methods of Calculation

A. Successive Dissociation of Three Protons. In a compound like pyridoxal hydrochloride there are two readily dissociable protons, and the three ionic forms may be represented as H_2P , HP , and P . In strongly alkaline solution, a third dissociation occurs. We have designated the resulting form as POH , but no chemical significance is to be attributed to this symbol. The four ionic forms and three K_a values may be represented schematically as in eq 1.



The total concentration of all forms of pyridoxal, C_{tP} (equal to the sum of concentrations of the four individual forms), can be expressed as the product of the concentration of any one of the individual ionic forms and some function of the three K_a values and the pH (e.g., eq 2 and 3). The symbol a_H represents the ap-

$$C_{tP} = \alpha C_P \quad (2)$$

$$\alpha = 1 + a_H/K_{1P} + (a_H)^2/(K_{1P}K_{2P}) + K_{3P}/a_H \quad (3)$$

parent hydrogen ion "activity" as represented by the pH meter reading

$$a_H = 10^{-pH} \quad (4)$$

It is assumed that, for dilute solutions, concentrations of all other species may be used in the calculations. Equations 5–7 give the relationships of the concentrations of H_2P , HP , and POH to that of form P .

$$C_{H_2P} = (a_H)^2 C_P / (K_{1P}K_{2P}) \quad (5)$$

$$C_{HP} = a_H C_P / K_{1P} \quad (6)$$

$$C_{\text{POH}} = K_{\text{aP}} C_{\text{P}} / a_{\text{H}} \quad (7)$$

Least-Squares Calculation of Molar Extinction Coefficients of Individual Ionic Species. If it is assumed the Beer-Lambert law holds for all species, each molar absorptance, A , may be represented by

$$A = \sum_{j=1}^4 C_j \epsilon_j l \quad (8)$$

$j = 1, 2, 3$, and 4 refer to the four ionic species, P , HP , and H_2P , respectively, and l is the path length. In the remaining treatment, l is assumed to be 1 cm. At any one wavelength, the ϵ 's are constant but the concentrations, C_j , vary with pH. To obtain the values of ϵ at a certain wavelength, we must measure the absorbancies of at least four solutions of different pH and solve a set of simultaneous linear equations.

In general, we obtain data for more than four solutions, and use a least-squares method to obtain the values of the ϵ 's. Since we wish to obtain these values at each of the 69 to 75 selected wavelengths, the least-squares procedure is applied consecutively to the data at each wavelength.

The sum of the squares of the deviation, U , for all solutions at all values of pH and at all wavelengths is given by

$$U = \sum_{ik} \omega_k (A_{ik} - \sum_{j=1}^4 C_{jk} \epsilon_{jk})^2 \quad (9)$$

where the index i refers to the pH and k to the wavelength. A weighting factor, ω_k , is also introduced. It has been taken as 1.0 at higher wavelengths and as 2.0 at wavelengths between WVL0 and WVL2. In the latter region twice as many points (many interposed wavelength interval were used in the comparisons, and we wanted to weight the different specifications equally. Other weighting factors can be used if desired.

The values of the ϵ 's corresponding to the minimum of U are computed by standard methods. The value of U is an index of the goodness of fit and plays an important role in the subsequent automatic adjustment of $\text{p}K_{\text{a}}$ values. However, it is not a completely adequate index, because there is a possibility during the adjustment of $\text{p}K_{\text{a}}$ values, some extinction coefficients for some species will be negative. This became evident in early attempts to fit the data for pyridoxal when the computer moved the values of $\text{p}K_{\text{a}}$ to an incorrectly high value and fitted the data by giving that the spectrum of POH contained regions of negative absorption.

To diminish the possibility of arriving at a false minimum with negative extinction coefficients, a new measure of error, U_{a} , was defined

$$U_{\text{a}} = U + \sum_{j,k} (C_{jk} \epsilon_{\text{neg}})^2 \quad (10)$$

$\sum_{j,k} (C_{jk} \epsilon_{\text{neg}})^2$ represents the sum of squares of the solutions for all negative values of ϵ . These latter are weighted heavily in the summation by multiplication by the square of the total pyridoxal concentration, C_{TP} . This procedure is rather arbitrary, but to be effective.

Automatic Adjustment of $\text{p}K_{\text{a}}$ Values. Two methods have been employed for the adjustment of the values.

a. Program SWING. If the successive $\text{p}K_{\text{a}}$ values differ sufficiently, e.g., by about 3 units, each $\text{p}K_{\text{a}}$ can be adjusted independently. The procedure is to first inspect the original spectral data and to estimate within a few tenths of a $\text{p}K$ unit the successive $\text{p}K_{\text{a}}$ values. Of course, the dissociations must lead to a distinctly perceptible change in the spectrum. These trial values of the $\text{p}K_{\text{a}}$'s are supplied to the computer along with the experimental data. The least-squares calculation of molar extinction coefficients is performed and the sum of squares of deviations, U_{a} , is evaluated. Then the first $\text{p}K_{\text{a}}$ is altered by an increment of value, Δ (here $\Delta = 0.4$). All computations are repeated and a new value of U_{a} is determined and compared with the first one. Depending upon whether the difference between the two values of U_{a} is positive, negative, or zero, the $\text{p}K_{\text{a}}$ is varied again, either in the same direction or by 0.5Δ in the opposite direction. After about 12 cycles of adjustment and recalculation, the value of Δ falls to below 0.004 and the second $\text{p}K_{\text{a}}$ is adjusted next. If any two $\text{p}K_{\text{a}}$ values are close enough together to "overlap," it is necessary to repeat the entire calculation a second or third time to ensure a correct answer.

b. Program PITMAP. A second method for dealing with "overlapping" dissociation constants is based on the theory developed by Sillén and Ingri.⁴ When some of the adjustable constants have a correlation with others, the shape of the pit made by U_{a} in the multidimensional space of $\text{p}K_{\text{a}}$ values becomes so skewed that the direction of the change in constants should be transformed to those of the main axes of the ellipsoid made by the contour lines on the pit surface. Near the minimum point, the shape of the surface is assumed that of a paraboloid in multidimensional space, the equation of which can be established from the values of U_{a} for $0.5(N+1)(N+2)$ systematically chosen points (here, N represents the number of the constants being searched for). The $\text{p}K_{\text{a}}$ values corresponding to the minimum point on this surface may be computed directly from the equation so obtained. In a future report, the results of application of this method to data for pyridoxamine and other substances with overlapping $\text{p}K_{\text{a}}$'s will be described. The method was used in the present work only for evaluation of equilibrium constants in the systems containing Schiff's bases.

3. Standard Deviation. The standard deviation, σ , of each $\text{p}K_{\text{a}}$ value is given by eq 11 where $U_{\text{a}0}$ is the

$$\sigma = \left(\frac{2U_{\text{a}0}}{N_{\text{df}} \delta^2 U_{\text{a}} / \delta \text{p}K^2} \right)^{1/2} \quad (11)$$

value of U_{a} corresponding to the best value of $\text{p}K_{\text{a}}$ which has been found; N_{df} , the number of degrees of freedom, = (no. of solutions - no. of $\text{p}K_{\text{a}}$ values) \times (no. of wavelengths used). The standard deviation of the absorbance values is given by eq 12. The value of

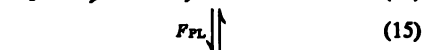
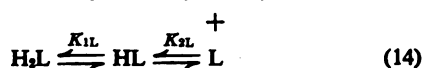
$$s = (U_{\text{a}0} / N_{\text{df}})^{1/2} \quad (12)$$

σ is computed by assuming a parabolic form for the variation of U_{a} with $\text{p}K_{\text{a}}$ in the range ± 0.01 of the best value of $\text{p}K_{\text{a}}$ which is found.

4. Comparison Plots of Calculated and Observed Spectra. **Program PLOT.** The absorbance of a solution can be expressed as the sum of the contributions of each molecular species present (eq 8). Since the concentrations of individual ionic forms and their extinction

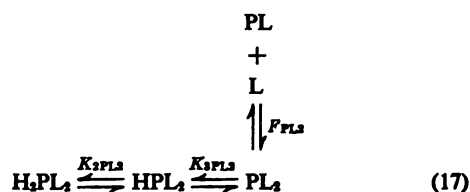
coefficients at all wavelengths have been computed, it is a simple matter, using eq 8, to calculate the expected absorbance at all wavelengths for a solution of any pH. If a pH is selected for which the spectrum has been measured experimentally, the experimental data may be plotted along with the calculated curve. A program has been written that does this. If no experimental data are available at exactly the pH selected, a linear interpolation is made between the data for two nearby pH values. In a similar way, the calculated absorbance at any wavelength may be plotted against pH, together with experimental points. If the selected wavelength is not one represented in the input data, an interpolation with a third-order equation is employed.

B. Reversible Formation of Schiff's Bases. The various equilibria of acid dissociation and formation of Schiff's bases in the system pyridoxal-alanine may be represented by the following scheme, which will also be applicable in many other cases.



P represents pyridoxal, L the amino acid, and PL the Schiff's base. The formation constant, F_{PL} , relates the concentrations of the anions of P and of L to the dianion of PL.⁸

For the system 5-deoxypyridoxal-L-leucine we have proposed additional equilibria leading to formation of a complex of unknown structure between the Schiff's base and the amino acids (eq 17).⁹ Four functions,



α , β , γ , and η , of the pH and of the acid dissociation constants are introduced.

$$\alpha = 1 + a_{\text{H}}/K_{2P} + (a_{\text{H}})^2/(K_{1P}K_{2P}) + K_{3P}/a_{\text{H}} \quad (18)$$

$$\beta = 1 + a_{\text{H}}/K_{2L} + (a_{\text{H}})^2/(K_{1L}K_{2L}) \quad (19)$$

$$\gamma = 1 + a_{\text{H}}/K_{3\text{PL}} + (a_{\text{H}})^2/(K_{2\text{PL}}K_{3\text{PL}}) + (a_{\text{H}})^3/(K_{1\text{PL}}K_{2\text{PL}}K_{3\text{PL}}) \quad (20)$$

$$\eta = 1 + a_{\text{H}}/K_{3\text{PL}_2} + (a_{\text{H}})^2/(K_{2\text{PL}_2}K_{3\text{PL}_2}) \quad (21)$$

If values for all the constants were known, it would be possible to compute the concentrations of the various species as follows. The total concentrations of pyridoxal (C_{P}) and amino acid (C_{L}) for any solution can be expressed by eq 22 and 23. The concentrations of

$$C_{\text{LP}} = \alpha C_{\text{P}} + \gamma C_{\text{PL}} + \eta C_{\text{PL}_2} \quad (22)$$

$$C_{\text{L}} = \beta C_{\text{L}} + \gamma C_{\text{PL}} + 2\eta C_{\text{PL}_2} \quad (23)$$

Schiff's base (C_{PL}) and of a complex of the latter with

(8) D. E. Metzler, *J. Am. Chem. Soc.*, **79**, 485 (1957).

(9) D. E. Metzler and K. Nagano, Proceedings of Second IUB Symposium on Chemical and Biological Aspects of Pyridoxal Catalysis, Moscow, Sept 1966, in press.

amino acid (if present) (C_{PL_2}) are given by eq 24 and 25 which define the formation constants, F_{PL} and F_{PL_2} .

$$C_{\text{PL}} = F_{\text{PL}} C_{\text{P}} C_{\text{L}} \quad (24)$$

$$C_{\text{PL}_2} = F_{\text{PL}_2} C_{\text{PL}} C_{\text{L}} \quad (25)$$

The value of C_{P} is obtained through successive approximations. If an excess of amino acid is present, the first estimate of C_{L} is given by eq 26 and successive estimates of C_{P} and C_{L} by eq 27 and 28. Concentrations

$$C_{\text{L}} = C_{\text{L}}/\beta \quad (26)$$

$$C_{\text{P}} = C_{\text{LP}}/[\alpha + (\gamma + \eta F_{\text{PL}_2} C_{\text{L}}) F_{\text{PL}} C_{\text{L}}] \quad (27)$$

$$C_{\text{L}} = C_{\text{L}}/[\beta + (\gamma + 2\eta F_{\text{PL}_2} C_{\text{L}}) F_{\text{PL}} C_{\text{P}}] \quad (28)$$

of the other three ionic forms of pyridoxal are given by eq 5-7. The concentrations of the various forms of the Schiff's base are given by eq 29-33.

$$C_{\text{H}_2\text{PL}} = (a_{\text{H}})^2 C_{\text{PL}}/(K_{1\text{PL}}K_{2\text{PL}}K_{3\text{PL}}) \quad (29)$$

$$C_{\text{H}_2\text{PL}} = (a_{\text{H}})^2 C_{\text{PL}}/(K_{2\text{PL}}K_{3\text{PL}}) \quad (30)$$

$$C_{\text{HPL}} = a_{\text{H}} C_{\text{PL}}/K_{3\text{PL}} \quad (31)$$

$$C_{\text{H}_2\text{PL}_2} = (a_{\text{H}})^2 C_{\text{PL}_2}/(K_{2\text{PL}_2}K_{3\text{PL}_2}) \quad (32)$$

$$C_{\text{HPL}_2} = a_{\text{H}} C_{\text{PL}_2}/K_{3\text{PL}_2} \quad (33)$$

1. Molar Extinction Coefficients of Individual Ionic Species. We assume as before that the Beer-Lambert law holds and that the experimental absorbance for a particular solution and a particular wavelength is given by eq 8 where $j = 1-11$ designate the eleven ionic species, POH, P, HP, H_2P , PL, HPL, H_2PL , H_2PL_2 , H_2PL_2 , H_2PL_2 , and H_2PL_2 , respectively.

Although 11 light-absorbing ionic species are included, these ordinarily will not all be present in significant amounts. In the system pyridoxal-alanine, there is no evidence for the complex HPL_2 , and even in the system 5-deoxypyridoxal-leucine, where HPL_2 is present, the ionic forms H_2PL_2 and PL_2 exist in such small quantities that they have a very small effect on the over-all spectrum. Their spectra were assumed, for the purposes of computation, to be identical with those of H_2PL and PL, respectively. Thus, we had to consider only seven of the possible 12 species in either system; for pyridoxal + alanine, POH, P, HP, H_2P , PL, HPL, and H_2PL ; and for 5-deoxypyridoxal + leucine, P, HP, H_2P , PL, HPL, H_2PL , and HPL_2 . Since the ϵ 's for POH, P, HP, and H_2P were already known, extinction coefficients remained unknown for only four species. These were obtained by a least-squares method as described previously. It is usually feasible to evaluate a maximum of four unknown sets of extinction coefficients at once, and depending upon the details of the system under investigation, it may be a different set of four for one system than for another. A program has been written which permits one to state conveniently the appropriate simplifications and to specify which sets of ϵ 's (up to four) are to be evaluated.

The error function is defined as in eq 9 except that the second set of terms is multiplied by 100 to discourage strongly the obtaining of false solutions with negative extinction coefficients in some regions.

2. Adjustment of Values of pK_a and Log F . 1. Program GRID. In seeking the best values for the pK_a 's and formation constants we may regard the error func-

, U_a , as a variable which is dependent upon the trial parameters" (values of the pK_a 's and $\log F$'s). The minimum value of U_a may be visualized as lying in a multidimensional "pit" in the hypersurface defined by U_a as a function of the trial parameters. We seek to find the values of the trial parameters at the bottom of the pit. In the systems under consideration there is a strong correlation among the trial values of F_{PL} and the two pK_a 's, pK_{2PL} and pK_{3PL} . Likewise the values of F_{PL} and pK_{3PL} are strongly correlated. Hence the direct method of varying each parameter independently (program SWING) cannot be applied. The simplest approach is to vary each parameter by a small amount, Δ , both in the positive and negative directions and to evaluate U_a for each of the three resultant trial values. If this is done for all the parameters and for all possible combinations of the altered values, an n -dimensional grid of 3^N values of U_a is obtained, where N is the number of constants being studied. If $N = 4$ and we use data for all wavelengths in 30 test solutions, the computation takes almost 10 min and is excessively expensive. It is more practical to vary only three constants at once, the computation amounting to about 4 min.

The results of the computation are inspected to determine which values of the trial parameters gave a minimum U_a , and three difference values of each parameter are chosen, usually more closely spaced than for the first "grid." The procedure can be repeated as often as the new set of trial parameters gives a smaller value of U_a than the minimum value obtained previously. For the first grids we have used values of $\Delta = 0.4$ and for later ones $\Delta = 0.1$. Final refinement of the parameters is done with program PITMAP (1b).

Sequence of Computations. A workable procedure for the solution of problems of the type considered here is as follows. (1) Initially make spectral measurements on several solutions containing a high concentration of the second component, L, and from an examination of the spectra choose initial trial values for pK_a 's of PL. Also measure spectra at a constant pH in a region where formation of PL is extensive for several lower concentrations of component L. This will permit the choice of an initial trial value of F_{PL} . Collect for the initial computations the minimum necessary number of experimental spectra. This number always be at least as great as the number of unknowns (pK_a 's, $\log F$'s, and spectra of individual ionic forms). (3) Start the computation with the data for several concentrations of amino acid and adjust pK_{2PL} , pK_{3PL} , and F_{PL} using program GRID and $\Delta = 0.4$. (4) Repeat using a grid of $\Delta = 0.1$. (5) Use program PITMAP with $\Delta = 0.01$ which will not only refine the trial parameters but will punch out on cards the spectra of the individual ionic forms of PL which are needed for step 6. (6) Using program PLOT, compare calculated and experimental plots of absorbance against pH and wavelength. If a good fit is obtained, the problem is solved. (7) If systematic errors are indicated for different concentrations of amino acid, consider what additional equilibria must be added. An exact procedure can be given for finding the values of the additional equilibrium constants which may be required. The grid method with refinement with program PITMAP in several steps was used in this work.

One must always ask whether the spectra obtained are reasonable from a chemical viewpoint.

Results

5-Deoxypyridoxal. The simplest case studied is that of 5-deoxypyridoxal which exists in three ionic forms. From spectra at 24 values of pH from 1.4 to 12.9, the pK_a values of 4.16 and 8.02 were evaluated in 118 sec of computation (Table I). The plots comparing computed and observed absorbances show a nearly perfect fit, the standard deviation of the absorbances, s , amounting to only 0.001 absorbance unit. A few extinction coefficients are given in Table II.

Table I. Calculated Values of pK_a with Standard Deviations

	This research $pK_a \pm \text{std dev}$	Lit. ^a	Lit. ^b
5-Deoxypyridoxal	4.16 ± 0.003 (25°) 8.02 ± 0.004	4.17 (25°) 8.14	
Pyridoxal	4.13 ± 0.008 (50°) 8.37 ± 0.008 13.04 ± 0.023	4.20 (25°) 8.66 13	4.23 8.70

^a D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc.*, **77**, 2431 (1955). ^b V. R. Williams and J. B. Nielsens, *Arch. Biochem. Biophys.*, **53**, 56 (1954).

Table II. Absorption Maxima and Molar Extinction Coefficients of Various Ionic Forms of the Compounds Studied

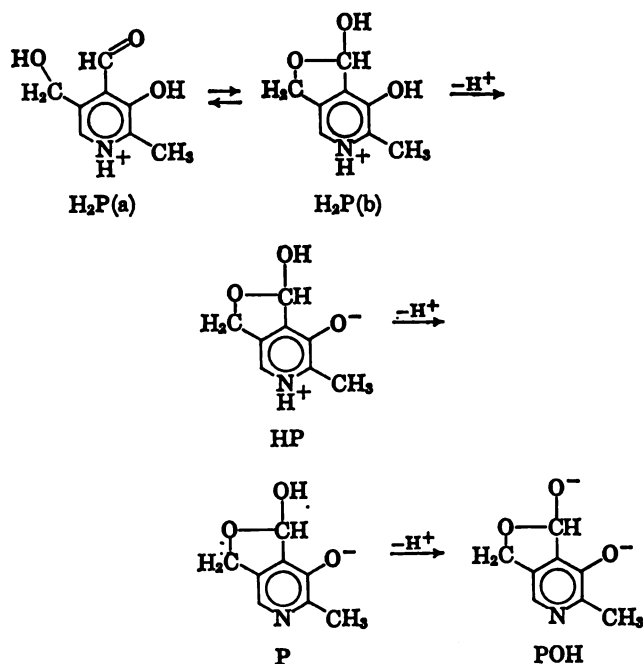
Ionic form	5-Deoxypyridoxal, 25°		Pyridoxal, 50°	
	λ_{max} , mμ	$\epsilon \times 10^{-3}$	λ_{max} , mμ	$\epsilon \times 10^{-3}$
H ₂ P	294 342	6.28 1.88	288	8.61
HP	324 381	2.97 4.22	254 318	5.51 8.13
P	263 (shoulder) 391	3.48 6.33	236 302 394	9.37 4.61 2.97
POH			245 299	8.18 7.55

Pyridoxal. Pyridoxal exists in solution largely as the internal hemiacetal, four ionic forms of which are shown in Scheme I. Each of these is considered to be in equilibrium with a smaller amount of free aldehyde, the structure of which, H₂P(a), is drawn only for form H₂P. The structure assigned to POH is, however, not completely certain.

The first two pK_a values have been determined previously at 25°. In this study the spectra and pK_a values have all been measured at 50° because related kinetic studies are being conducted at this temperature.

Spectra were measured for 19 solutions at pH values of 1.03, 3.14, 3.58, 3.91, 4.36, 4.66, 5.60, 6.55, 6.87, 7.52, 7.92, 8.35, 8.65, 9.25, 9.75, 10.16, 12.15, 12.82, and 13.16. No buffers were used, but the pH was adjusted with HCl or KOH. An ionic strength of 1.0 was maintained by addition of KCl. Figure 3 shows the spectra of the four ionic forms. That of form POH is presented for the first time. Figures 4 and 5 show plots of calculated and observed spectra at two selected pH values and spectrophotometric titration curves at three selected wavelengths as drawn by the automatic plotter. The agreement is good, even at the highest

Scheme I



pH. The pK_a 's are given in Table I and extinction coefficients at the maxima in Table II.

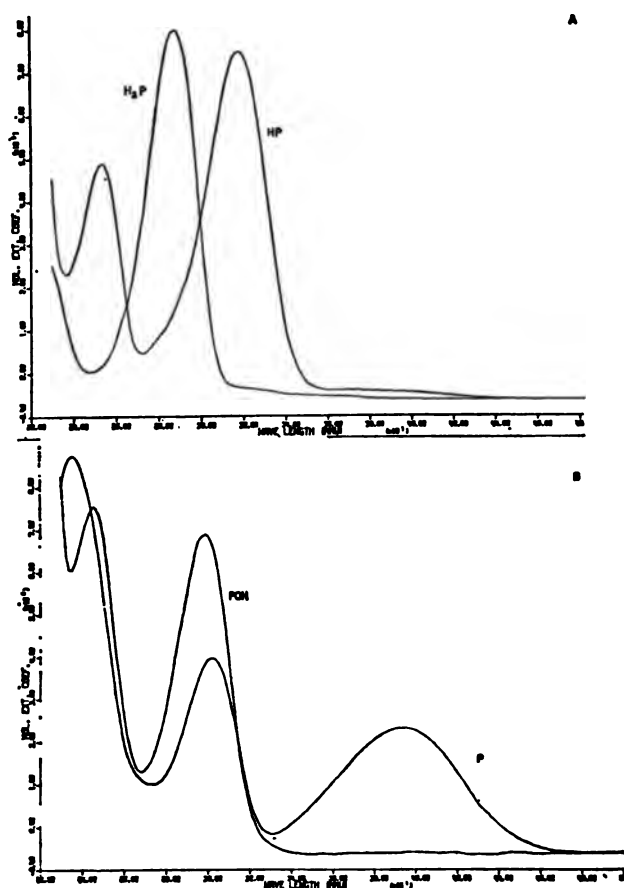


Figure 3. Absorption spectra of the four ionic forms of pyridoxal at 50°C: graph A, H_2P and HP ; graph B, P and POH .

Pyridoxylidene-DL-alanine. This Schiff's base, formed from the rapid, reversible reaction of alanine with pyridoxal, exists in the three ionic forms H_2PL , HPL , and PL whose probable structures are shown below.

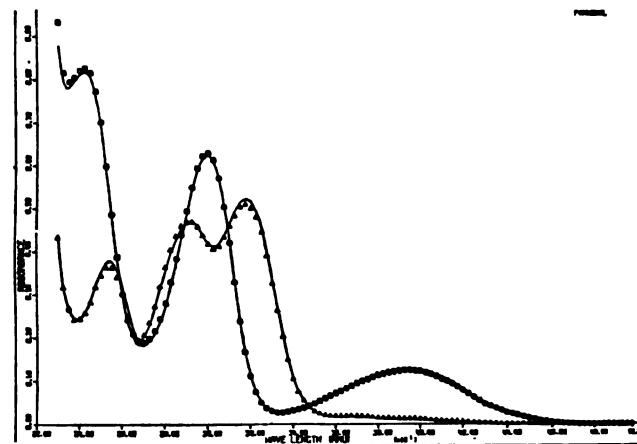


Figure 4. Calculated absorption spectra of solutions of $10^{-4} M$ pyridoxal at two pH values plotted together with experimental points, temperature 50°C: Δ , pH 4.36; \circ , pH 13.16.

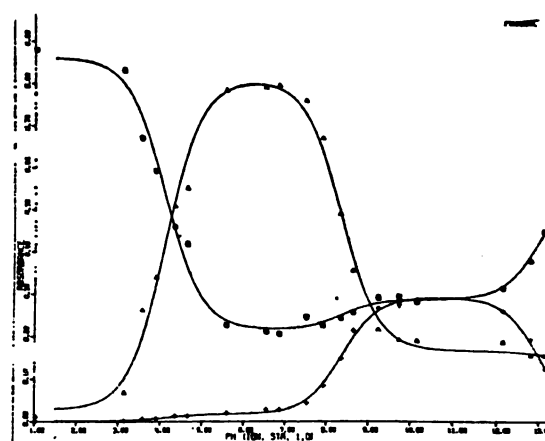
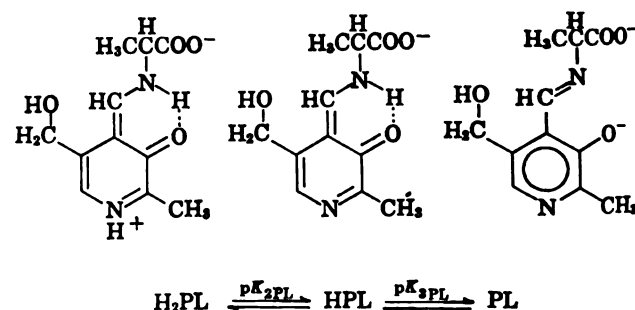


Figure 5. Plots of absorbance vs. pH at selected wavelengths for a $10^{-4} M$ solution of pyridoxal at 50°C: +, 394 $m\mu$; Δ , 318 $m\mu$; \circ , 288 $m\mu$.

The formation and acid dissociation constants are given in Table III, and the spectra of the three ionic species are shown in Figure 6 and in Table IV. These were evaluated from data for a total of 45 experimental solu-



tions of pyridoxal concentration $10^{-4} M$ and alanine concentrations from 0.05 to 0.45 M (see Experimental Section). The comparison plots of observed vs. computed spectra, of which those in Figures 7-9 are typical, were all reasonably satisfactory. Figure 7 shows spectra at three values of pH for solutions 0.1 M in alanine and $10^{-4} M$ in pyridoxal, while the pH profiles in Figures 8 and 9 are for solutions 0.05 and 0.45 M in alanine, respectively, and $10^{-4} M$ in pyridoxal. The existence of forms containing more than one molecule of pyridoxal,

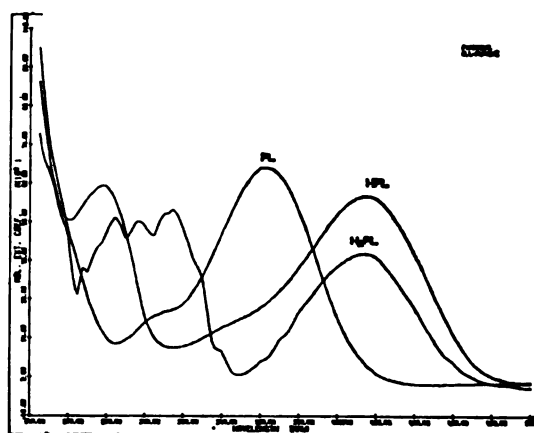


Figure 6. Absorption spectra of the three ionic forms of pyridoxylidene-DL-alanine at 50°. The unevenness of the spectrum of H_2PL results from the fact that this form exists in very small amounts so that experimental errors lead to uncertainty in the spectrum, especially at the lower wavelengths.

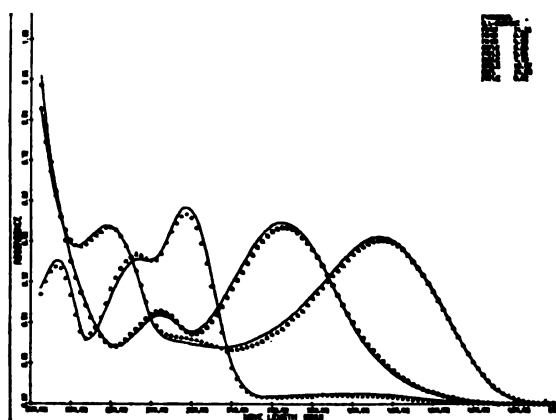


Figure 7. Calculated absorption spectra for solutions of 10^{-4} M pyridoxal containing 0.2 M alanine at three values of pH plotted together with experimental points, temperature 50°: +, pH 4.53; Δ, pH 8.40; O, pH 11.11.

e.g., P_2L_2 , was ruled out by measurement of 18 solutions containing 100 times higher concentrations of pyridoxal and 0.45 M alanine using spacers in the spectrophotometer cells to cut the path length. Calculated and observed spectra agreed equally satisfactorily for these solutions. The standard deviation, s , was 0.013 absorbance unit.

Table III. Calculated Values of pK_a and F with Standard Deviations

	5-Deoxy- pyridoxal + L-leucine, 25°*	Pyridoxal + DL-alanine, 50°
pK_{2PL}	6.51 ± 0.009	6.26 ± 0.018
pK_{1PL}	11.73 ± 0.023	9.91 ± 0.007
pK_{2PL_2}	7.17 ± 0.13	
pK_{1PL_2}	13.19 ± 0.006	
F_{PL}	9.93 ± 0.49	14.50 ± 0.20
F_{PL_2}	0.49 ± 0.01	
pK_a Values of Amino Acid Used for Calculation		
pK_{1L}	2.33^b	2.54 ± 0.008
pK_{2L}	9.74^b	9.40 ± 0.014

* See ref 9. ^b "The Merck Index of Chemicals and Drugs," 7th ed, Merck and Co., Inc., 1960, p 607.

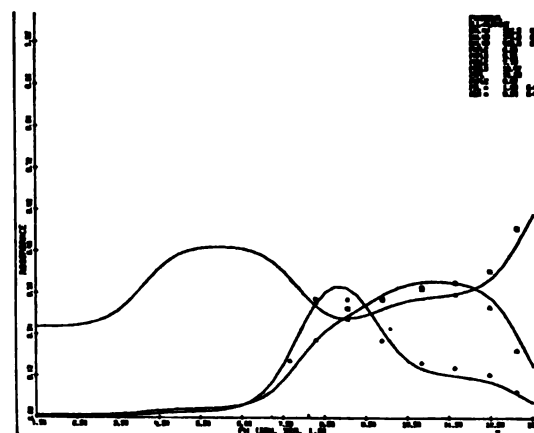


Figure 8. Plots of absorbance vs. pH at selected wavelengths for a 10^{-4} M solution of pyridoxal containing 0.05 M DL-alanine at 50°: +, 420 mμ; Δ, 3.75 mμ; O, 302.5 mμ.

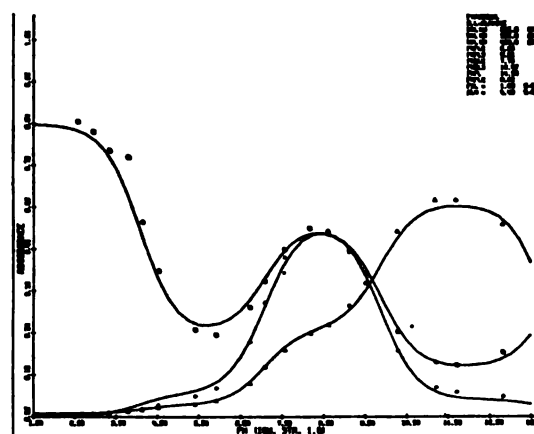


Figure 9. Plots of absorbance vs. pH at selected wavelengths for a 10^{-4} M solution of pyridoxal containing 0.449 M alanine at 50°: +, 420 mμ; Δ, 365 mμ; O, 285 mμ.

No buffers were added, and for some solutions the measurement of pH was not completely precise. A few points, e.g., in Figure 9, deviate from the computed curve. During early attempts to analyze the data, other possible species, e.g., PL_2 and HPL_2 , were included in the chemical model. The amounts of such species, if they exist, were found to be immeasurably small.

Table IV. Absorption Maxima and Molar Extinction Coefficients of Various Ionic Forms of the Schiff's Bases Studied

Ionic form	5-Deoxypyridoxylidene-L-leucine, 25°*		Pyridoxylidene-DL-alanine, 50°	
	λ_{max} , mμ	$\epsilon \times 10^{-3}$	λ_{max} , mμ	$\epsilon \times 10^{-3}$
H_2PL	289	5.85	~300	5.3
	414	7.61	414	4.0
HPL	284	8.48	278	6.13
	420	5.66	416	5.81
PL	343	4.92	~305	2.1 (shoulder)
			363	6.71
HPL_2	286	7.92		
	422	5.59		

* See ref 9.

5-Deoxypyridoxylidene-L-leucine. Results for the system 5-deoxypyridoxal-L-leucine, at 25°, have been reported briefly elsewhere⁹ and will be summarized

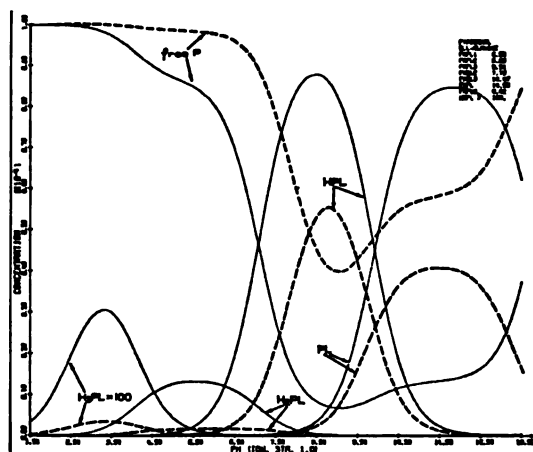


Figure 10. Plot of the computed pH profile of concentrations of free pyridoxal (all forms), H_2PL (multiplied by 100), H_3PL , HPL , and PL for solutions of $10^{-4} M$ pyridoxal containing $0.449 M$ DL-alanine, —, and $0.05 M$ DL-alanine, ----, at 50° . The concentration of H_2PL was computed on the assumption that $pK_{PL_1} = 2.5$, the same as that of alanine. Of course the true value of this pK might be quite different and the fit would still be good.

here. This system is a favorable one for study because of the high degree of formation of the Schiff's base over a broad range of pH. Initially it was assumed that the three forms of the Schiff's base, H_2PL , HPL , and PL , were the only forms present and the equilibrium constants were obtained from the data for solutions containing 0.05 and $0.1 M$ leucine. However, the spectra of solutions containing $0.01 M$ L-leucine could not be predicted accurately using these constants. Introduction of a complex, HPL_2 , resolved the difficulty. This was found to have a spectrum nearly identical with that of HPL and apparently is a complex of the latter species with the anion of L-leucine. The spectra are shown elsewhere⁹ and only the constants are given in Table III. The spectrum of HPL is very similar to that reported previously for pyridoxylidene-DL-valine⁹ while that of PL is surprisingly different, possessing an absorption maximum at $343 m\mu$. The precise spectrum of H_2PL was obtained. It absorbs maximally at $414 m\mu$ and possesses a higher molar extinction coefficient than does HPL .

In considering various problems of equilibria and kinetics, it is useful to know the concentration of each ionic form present at a particular pH. These pH profiles may be computed readily using the auxiliary program designated PROFILE. Figure 10 shows the results of such a program for the pyridoxal-DL-alanine system and alanine concentrations of both 0.449 and $0.1 M$. This program also computes another useful function, the pH-dependent apparent formation constant which has been designated previously as K_{pH} ⁸ (eq 34). The

$$K_{pH} = \gamma C_{PL} / \alpha C_P \beta C_L \quad (34)$$

term αC_P represents the total of all free forms of pyridoxal, etc. In Figure 11 a plot of $\log K_{pH}$ vs. pH is shown for both the pyridoxal-alanine and deoxypyridoxal-leucine systems.

Discussion

The methods described here permit the automatic evaluation of from one to three successive acid dissociation constants for compounds for which each ionic

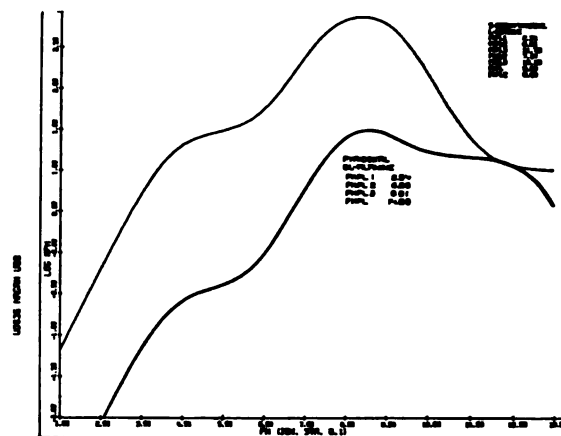


Figure 11. Plots of the logarithm of the apparent formation constant (K_{pH}) vs. pH for 5-deoxypyridoxylidene-L-leucine at 25° and for pyridoxylidene-DL-alanine at 50° .

form possesses a substantially different spectrum, the rapid evaluation of formation constants and acid dissociation constants of complexes or compounds formed reversibly in the presence of a second nonlight-absorbing component, and plotting of complete absorption spectra of all ionic species which contribute significantly to the absorption of light. They should have widespread use. The advantages of this method for obtaining dissociation constants are: (1) a least-squares method assures the best values for dissociation constants and extinction coefficients of individual ionic forms at all wavelengths. (2) The method is rapid. (3) Precise spectra of intermediate ionic forms are provided, whereas previously tedious calculation was often required. (4) A large number of plots of the type displayed in Figures 4, 5, 7, 8, and 9 may be obtained readily and inexpensively. These permit a visual judgement of goodness of fit and show at a glance at what wavelengths and under what conditions of pH, concentration, etc., discrepancies exist. (5) Data for pK_a 's and extinction coefficients of individual ionic forms are stored on punched cards or by other means in digital form. The data are thus immediately available for use in calculations of chemical equilibria and kinetics in more complex systems.

The method of evaluation of formation constants is superior to the widely used procedure of Ketelaar, *et al.*,¹⁰ because (1) it uses data at many different wavelengths, (2) it yields pK_a values for the compound or complex when its absorption spectrum is altered by association or dissociation of protons, (3) complete absorption spectra of the various forms of the compound or complex are computed, (4) a series of comparison graphs showing experimental data plotted with the computed curves provide a means of judging directly the goodness of fit, and (5) the chemical model can be varied easily, *e.g.*, by introducing additional equilibria, and can readily be tested to determine whether a better fit is obtained. The method can be applied directly to many chemical and biochemical problems including study of enzyme-substrate complexes and can be used to advantage in handling various kinetic problems as will be discussed in a future paper. The

(10) J. A. A. Ketelaar, C. Van de Stolpe, and H. R. Gersmann, *Rec. Trav. Chim.*, 71, 499 (1951); J. A. A. Ketelaar, C. Van de Stolpe, A. Goudsmit, and W. Dzacubas, *ibid.*, 71, 1104 (1952).

ach should be of value in various problems of complex formation.¹¹

transcription of data points by hand from experimental graphs used in this study is tedious and often to introduction of errors, the most serious of must be traced and removed before acceptable are obtained. However, with the computer ams available, the many users of recording spectrometers may immediately employ these meth- A more desirable system will be to collect data ly in digital form, and equipment for doing this is ly available commercially. Doubtless, within a ears older methods of handling spectrophoto- data will be completely obsolete. An important tage of the newer methods will be that complete al data can be sent between laboratories over one wires. Thus a much more efficient sharing ormation will be available.

ring the course of this study many questions have for which full answers are not yet available. For ple, "How great must be the differences between ectra of two successive ionic forms in order to the evaluation of the pK_a 's?" It is clear that each iable group must affect the spectrum. Thus, if a ound possesses two groups of identical micro- dissociation constants, but the dissociation of roup has no effect on the spectrum, the two step-dissociation constants of the compound cannot terminated from spectral data alone. In such cases spectra and titration data are required.

s necessary in our method to provide to the com- an initial estimate for each pK_a . If all of the pK s are well separated it is easy to do this by inspec- of the data. Even if the initial guess is poor, both ams SWING and PITMAP lead to a rapid selection of orrect value. However, if the pK_a values are ; difficulties may be anticipated, especially if ' initial guesses are made. We are investigating of this type.

important question is "What is the minimum er of experimental spectra which must be meas- in order to obtain precise answers?" It appears io more than the minimum which are theoretically red (for the determination of pK_a 's, three for the pK_a and two for each successive pK_a) are needed, at a few more are to be recommended. In gen- he usual "common sense" judgement of the chem- regarding the number and distribution of pH values : samples should be followed.

other question concerns the treatment of experi- al errors. Errors in the spectra may vary with the length, being higher where the slope of the spectral is steep. Accordingly, it would be desirable to the weighting factors, ω_k , with the wavelength for solution. However, this has not been done in study. The standard deviations in the pK_a 's ery low (Table I) and are considerably less than we would judge to be the experimental error in the measurements. However, the standard error is ctly evaluated and represents a useful index of the ducibility of the computations. The standard of the absorbances, s (eq 12), represents an aver- alue for all wavelengths and all solutions and does

not indicate whether systematic errors exist in certain regions of wavelength or pH. That such systematic errors do exist for some solutions is obvious from inspection of comparison plots of the type of Figures 4 and 7. If the experimental pH is near a pK value, a small error in pH will lead to large systematic deviations, even though the value of s may be acceptably small. The careful examination of a series of plots of the type of Figures 4, 5, 7, 8, and 9 is extremely valuable in deciding whether observed systematic deviations are within acceptable limits as set, for example, by the precision of pH measurement or whether the assumed chemical model is inadequate.

A particular problem in the evaluation of pK_a 's arises when incomplete data are available for a dissociation step. Pyridoxal is an excellent example. No data were obtained above pH 13.16, but pK_{1P} is 13.0. As was mentioned earlier, before steps were taken to discourage the assignment of negative extinction coefficients, the computer preferred to assign a higher value of pK_{1P} and negative extinction coefficients to POH in the region around 390 $m\mu$. But what is the possibility that the true solution is for a pK_{1P} value lower than 13.0 and higher extinction coefficients for POH around 390 $m\mu$? An acceptable but less perfect fit to the data could be obtained by letting pK_{1P} be as low as 12.74. However, the computed spectrum of POH in this case possessed another absorption band at 390 $m\mu$ with $\epsilon 0.8 \times 10^3$ (27% of that of P), a result which seems very unlikely on chemical grounds.

Information on spectra and pK values is now available for a small number of different Schiff's bases.^{8,12} For all of these the spectrum of form HPL is similar, but striking differences are observed in the spectrum of form PL and in the pK for dissociation of HPL to PL. The basic causes of these differences are not understood, but we believe that the study of other analogs of pyridoxal and of other amino acids will give information which will permit us to understand these variations and to interpret them in the light of possible significance to the events which take place on a surface of enzymes which employ pyridoxal phosphate as a coenzyme.

Experimental Section

Chemicals. Pyridoxal·HCl (Sigma Chemical Co.), DL-alanine (Nutritional Biochemicals Corp.), and L-leucine (methionine-free, Mann Research Laboratories, Inc.) were used without further purification. 5-Deoxypyridoxal was synthesized by Dr. C. Iwata in this laboratory.

Measurements of pH. A Beckman Model G pH meter was used. Commercially available standard buffer solutions (Beckman Instruments, Mallinckrodt Chemical Works, or Matheson Coleman and Bell) were used, but later the high pH buffers were replaced by the National Bureau of Standards 0.01 *M* borax buffer of pH 9.18 at 25° and 9.01 at 50°. All pH values below 12 were determined at 50° by setting the temperature compensator at 25° and standardizing with the dial set at a reading of $^{250}/_{125}$ times the pH of the standard buffer at 50°. The meter reading for the unknown sample was then multiplied by $^{250}/_{125}$. When the pH exceeded 12, the temperature compensator had to be set at 40° (its upper limit) in order to keep the high pH readings on the scale. The meter was adjusted so that the test solutions could be read on the scale. Two pH standards (phosphate at pH 6.83 and borax at pH 9.01) were read at the same temperature and the pH of the test sample was established by a linear extrapolation.

K. Nagano, H. Kinoshita, and Z. Tamura, *Chem. Pharm. Bull.*, **11**, 999 (1963).

(12) T. C. French, D. S. Auld, and T. C. Bruice, *Biochemistry*, **4**, 77 (1955).

Test Solutions. Pyridoxal was studied in unbuffered solutions of ionic strength 1.0. The pH and ionic strength were maintained by addition of suitable amounts of KCl, HCl, and KOH. Deoxypyridoxal was studied in buffered solutions of ionic strength 0.1.

Stock solutions of 2×10^{-4} M pyridoxal-HCl and 5-deoxypyridoxal were prepared. They could be stored for a month in a refrigerator without any noticeable change in spectrum. Sample solutions were prepared before measurement by mixing 10 ml of the stock solution of the vitamin B₆ derivative with a 10-ml aliquot of a suitable buffer solution or with the appropriate amount of HCl, or KOH and KCl.

Mixtures of pyridoxal and DL-alanine were studied in unbuffered solutions of ionic strength 1.0 in order to avoid the effects of buffers on the reaction rates which are also under investigation. The pH and ionic strength were maintained by addition of suitable amounts of KCl, HCl, and KOH. Stock solutions of various concentrations of DL-alanine (0.1, 0.2, 0.4, and 0.898 M of ionic strength 2.0) were prepared. Sample solutions were prepared before measurement by mixing 10 ml of the stock solution of pyridoxal maintained at 50° with a 10-ml aliquot of a suitable alanine solution maintained at 50°.

Spectra were obtained for 45 different solutions (eight for 0.05 M alanine, five for 0.1 M alanine, 17 for 0.2 M alanine, and 15 for 0.449 M alanine) in the absence of any special buffers at an ionic strength of 1.0. The measured pH values were: 4.13, 4.52, 5.41, 5.92, 6.73, 7.09, 7.57, 8.18, 8.62, 9.13, 9.53, 10.29, 11.21, 11.71, and 12.83 for 0.449 M alanine; 4.53, 5.00, 5.35, 5.57, 6.55, 7.05, 7.47, 7.95, 8.40, 8.69, 9.21, 9.23, 9.48, 10.24, 11.11, 12.08, and 13.07 for 0.2 M alanine; 7.00, 7.95, 8.61, 12.30, and 13.16 for 0.1 M alanine; and 7.66, 8.28, 9.04, 9.87, 10.82, 11.62, 12.45 and 13.10 for 0.05 M alanine solutions. The sum of squares of the deviations, U_a , for 45 solutions was 0.50.

The interaction of 5-deoxypyridoxal with L-leucine was studied in buffered solutions of ionic strength 0.1 except at very high pH where the ionic strength exceeded 0.1. Stock solutions of 3×10^{-4} M 5-deoxypyridoxal and of various concentrations of L-leucine (0.015, 0.075, and 0.15 M of ionic strength 0.15) were prepared. Sample solutions were prepared by mixing 10 ml of the stock solution of 5-deoxypyridoxal with a 20-ml aliquot of a suitable buffered leucine solution. Spectra were determined for 39 different solutions (13 for 0.01 M L-leucine, ten for 0.05 M L-leucine, and 16 for 0.1 M L-leucine) in the presence of the indicated buffers at an ionic strength of 0.1. The measured pH values were: 3.28, 4.12, 4.40, 4.62, 5.91 (acetate buffers), 7.33, 7.62, 8.83, 9.59,

10.59, 11.00, 11.27 (potassium carbonate buffers), 11.70, 12.62, 12.99 (KOH) for 0.1 M L-leucine; 3.34, 4.85, 6.17 (acetate buffers), 7.91, 9.81, 10.79, 11.00 (potassium carbonate buffers), 11.71, 12.23, 12.71 (KOH) for 0.05 M L-leucine; 5.98, 6.41, 7.09, 7.70, 8.18 (potassium phosphate buffers), 8.69, 9.13, 10.01, 10.30, 10.80, 11.08 (potassium carbonate buffers) for 0.1 M L-leucine solutions. The sum of squares of deviations for 39 solutions was 0.28, which means that the fitness of the calculated spectra to the observed is excellent.

Titration of DL-Alanine. Titration of DL-alanine was at 50° using a Radiometer Model TTT1 automatic pH titrator. 50 ml of 0.02 M DL-alanine solution containing 0.02 N HCl and 0.98 M KCl was prepared. The solution (10 ml) was titrated with 1.0 N NaOH solution which was prepared from 50% aqueous solution of analytical grade NaOH and kept in a polyethylene bottle. The data were treated by our own computer program to obtain the following pK_a values: $pK_{a1} = 2.54 \pm 0.008$ and $pK_{a2} = 9.014 \pm 0.014$.

Spectra. All measurements were made with a Cary Model 14 recording spectrophotometer with a thermostated cell holder. The scanning rate was 71 mμ/min. The temperature of the solution in the cuvette was measured by use of VECO Model 41A7 thermometer (Victory Engineering Corp.) and associated galvanometric apparatus. Absorbances were read from the charts to the third decimal place and were entered on 80-column FORTRAN coding form for transfer to punched cards at the computation center.

Computational Programs. Programs are written in the language FORTRAN IV for use with the IBM 360-50 computer. The autographing was done by use of the IBM 1627 (Cal-Comp) incremental plotter. Complete programs are available upon request.

Acknowledgments. The authors are indebted to Mrs. M. Nagano for making most of the experimental measurements, to Dr. C. Iwata for the preparation of the 5-deoxypyridoxal, to Drs. H. Jespersen, G. Scraen, N. Hutton, and other members of the staff of the State University Computation Center, to Drs. Kudo, John Foss, and Jon Applequist, and Mr. R. Johnson for advice in the writing of the manuscript.

(13) K. Nagano, H. Tsukahara, H. Kinoshita, and Z. Tamura, *Pharm. Bull. (Tokyo)*, 11, 797 (1963).

The Crystal and Molecular Structure of 7 α -(1-(*R*)-Hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrothebaine Hydrobromide (19-Propylthevinol Hydrobromide)

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Abstract: The crystal structure of the hydrobromide salt of a Diels–Alder adduct derivative of thebaine (19-propylthevinol) has been determined *via* the phase-determining heavy-atom method. The crystals, which are orthorhombic with the space group $P2_12_12_1$, have the unit cell dimensions $a = 10.60$, $b = 22.34$, and $c = 10.14$ Å. Calculation of a three-dimensional Patterson function, followed by several cycles of electron density and finally least-squares refinement, yielded the complete structure. Both the relative configuration at C_{13} and the absolute configuration of the molecule as a whole were established, the latter *via* anomalous scattering techniques, and the assignments made previously by Kalvoda, *et al.*, for the morphine series were confirmed. The molecular shape, which is partly defined by a complex cage structure, is severely distorted when compared with an idealized Dreiding model. An observed intramolecular hydrogen bond suggests a favored sp^3 rather than sp^2 hybridization for an ether oxygen atom. Accurate bond lengths and valency angles have been obtained and all the protons associated with the rigid molecular framework have been located, including the quaternizing proton, which is in close proximity to a bromide anion.

has been reported by Bentley and Hardy¹ that the preparation of compounds more rigid and complex than morphine could lead to physiologically active substances at least as effective as analgesics as morphine, not exhibiting its unwanted side effects. A series of such compounds, ready access to which was provided by the Diels–Alder addition of dienophiles to thebaine, has been studied in these laboratories and their interesting chemistry reported.²

In view of the fact that prior knowledge of the detailed molecular structure of the morphine alkaloids obtained *via* X-ray crystallographic analysis had been limited, it was considered to be imperative to initiate a comprehensive study of at least one of these compounds. Thus, certain aspects of the molecular geometry would be established and a relationship might be gained between the more subtle structure details and observed physical characteristics.

Experimental Section

The preparation of the compound which was chosen for this work has been reported by Bentley, *et al.*³ 19-Propylthevinol (I) is the 1-(*R*)-hydroxy-1-methylbutyl-*t*-carbinol obtained from 7 α -yl-6,7,8,14-tetrahydro-6,14-*endo*-ethenotetrahydrothebaine by treatment with propylmagnesium iodide.

Single crystals⁴ of 19-propylthevinol·HBr were obtained in various sizes by slow crystallization from an aqueous ethanolic solution to which an equivalent of HBr was added. Oscillation, Weissenberg, and precession photographic work established the crystals as orthorhombic, with the unit cell lattice constants $a = 10.60$ Å, $b = 22.34$ Å, and $c = 10.14$ Å. The space group is $P2_12_12_1$, which assignment was made due to the absence of all reflections of the $h00$, $0k0$, and $00l$ for which h , k , or l are odd. The cell constants as obtained with film techniques were confirmed using a XRD-6 diffractometer equipped with a Eulerian cradle. The measured density, 1.383 g/cc, is in good agreement with the calculated value of 1.397 g/cc for a cell content of four molecules of $C_{24}H_{32}NO_4 \cdot HBr$.

(1) K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1963).

(2) K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, *in press*.

(3) We wish to thank Dr. C. F. Howell of Lederle Laboratories for kindly supplying the samples.

A specimen of approximate dimensions of $200 \times 100 \times 60$ μ was chosen for the intensity data collection after inspection under polarized light and additional photographic fingerprinting had shown it to be a single crystal. Its mosaic spread was found to vary from 0.4 to 0.6° and three-dimensional intensity data were taken for those reflections present in the octant with the least variation. Cu $K\alpha$ radiation was used, with a divergent incident beam, with the stationary counter–stationary crystal technique. Balanced Co and Ni filters were used throughout, and the take-off angle of the X-ray tube was 2.2° . A preliminary investigation had shown the peak widths to vary only slightly, from 0.5° at low scattering angles to about 1.0° at 2θ values of 100° . The photographic work had shown that all diffraction was limited to the reflections accessible within a sphere determined by this range. During the course of the data gathering several reflections were monitored as a means for observation of possible decay and/or misalignment of the crystal. No decomposition could be detected.

In all, 1772 independent reflections were monitored, of which 516 were deemed to be too weak to be measurable with sufficient accuracy, since they exhibited a count rate smaller than twice that of the background.

Even though the linear absorption coefficient ($\mu_r = 28.0$) indicated that absorption corrections were unnecessary, a systematic variation of the count rate of the polar reflections ($00l$) upon rotation of φ was observed and was attributed to the noncylindrical shape of the crystal and the corresponding difference in the X-ray path lengths. A φ -dependent correction was therefore applied in the subsequent data reduction, which also included the conventional Lorentz and polarization corrections.

The crystal structure was elucidated by the phase-determining heavy-atom method.⁴

A three-dimensional Patterson function $P(u, v, w)$ was computed with the input data, $|F|^2$, sharpened with a coefficient $(Z^2_{Br}/f^2_{Br} \exp[2B(\sin \theta/\lambda)^2])$, where Z_{Br} is the atomic number of bromine, f_{Br} the scattering amplitude of a bromide ion at rest at a Bragg angle θ , and B is an over-all temperature factor, which was taken to be 2.5 Å². Perusal of the Harker sections at u , v , and $w = 1/2$ led at once to the deduction of coordinates for the bromide ions. Assignment of phases based on the calculated contributions of these ions and a subsequent Fourier synthesis ($\rho(1)$) led to the location of 11 additional atomic sites, six of which seemed to form a ring system. Refinement of the phases by the inclusion of the additional atoms followed by a second density map calculation ($\rho(2)$) yielded 11 more atoms, of which one was latter found to be incorrectly placed. A third cycle of Fourier refinement revealed

(4) J. M. Robertson and I. Woodward, *J. Chem. Soc.*, 219 (1937); 36 (1940).

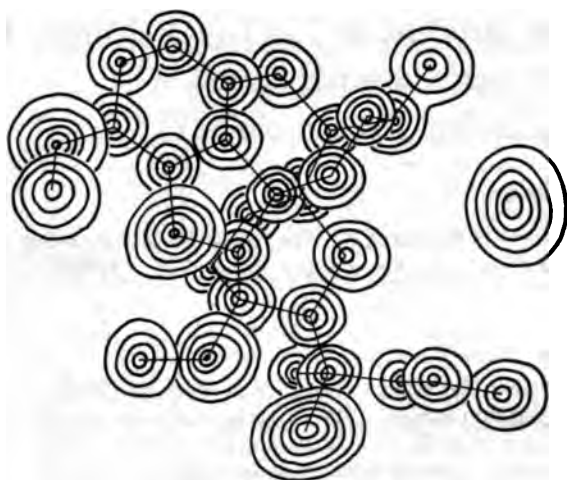


Figure 1. Final three-dimensional electron-density distribution shown by means of superimposed contour sections drawn parallel to (001) through the calculated atomic centers. Contour intervals 1.5 eÅ^{-3} , except around the bromide ion, where it is 7 eÅ^{-3} .

the complete structure. The average difference between the observed and calculated form factors at this stage was 28%. Two cycles of isotropic block-diagonal least-squares refinement afforded a drop in R to 0.18 but it was observed that several of the atoms showed large temperature factors, thus placing doubt as to their actual location. A fourth density map ($\rho(4)$) was calculated, omitting these atoms from the phase calculations. This led to the repositioning of two of the atoms (the methyl group on C_{18} , and C_1 of the phenyl ring), but the three other peaks returned in the previously assigned positions. Refinement of the light atoms, which were given individual isotropic temperature factors, while the bromide ions were allowed to vibrate in an anisotropic fashion, led in three more cycles of block-diagonal refinement to an R value of 0.086. Two cycles of anisotropic refinement of the lighter atoms then yielded an R of 0.078.⁴ At this stage it was found that the parameter shifts were insignificant compared to the calculated standard deviations, and therefore the refinement was terminated.⁵ The value of R including all unobserved reflections as $0.5F_{\text{min}}$ was 0.12.⁷

A composite final electron density map was evaluated and an area covering one molecule is shown in Figure 1 which contains superimposed sections taken through the centers of the atoms, and is drawn in a direction parallel to (001). The corresponding atomic arrangement is explained in Figure 2. The coordinates and thermal parameters obtained are given in Tables I and II and their standard deviations in Table III. The latter were determined from the least-squares residuals by application of the equation⁸

$$\sigma^2(x_i) = \sum_j w_j (\Delta F_j)^2 / [(n - s) \sum_j w_j (\delta F_j / \delta x_i)^2]$$

(5) The theoretical atomic scattering factors for carbon, nitrogen, oxygen, and bromine used in all the structure factor calculations were taken from the "International Tables for X-Ray Crystallography," Vol. III, The Kynoch Press, Birmingham, 1962, where bromine was corrected for anomalous dispersion. All calculations were carried out on an IBM 7094 digital computer at the ITT Data Processing Center, Paramus, N. J. The Fourier program used was that of Sly-Shoemaker-van den Hende; the least-squares, distance, and other peripheral calculations were carried out using our own programs.

(6) The weighting of the contributions of the individual reflections to the residuals was based on the following scheme: for reflections with $|F| > 10F_{\text{min}}$ the weight w was given by $w = 10F_{\text{min}}/|F|$, for $4F_{\text{min}} < |F| < 10F_{\text{min}}$, $w = 10$, and for $|F| < 4F_{\text{min}}$, $w = |F|/4F_{\text{min}}$.

(7) A table with the final values of F_o and F_c and the phase angles α has been deposited as Document No. 9371 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington, D. C. 20540. A copy may be secured by citing the document number and by remitting \$2.50 for photoprints, or \$1.75 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

(8) D. W. J. Cruickshank, *Acta Cryst.*, **2**, 65 (1949); **3**, 72 (1950).

Table I. Atomic Coordinates and Isotropic Temperature Factors

Atom	x/A	y/B	z/C	B
C ₁	0.4277	0.2578	0.2288	6.88
C ₂	0.4700	0.2080	0.2980	6.94
C ₃	0.5901	0.2006	0.3523	6.39
O ₃	0.6268	0.1449	0.3996	8.35
Me ₃	0.7170	0.1439	0.4930	9.44
C ₄	0.6707	0.2490	0.3489	5.54
O ₄	0.7970	0.2526	0.3814	5.25
C ₅	0.8410	0.3129	0.3445	4.29
C ₆	0.9337	0.3121	0.2271	4.95
O ₅	1.0473	0.2820	0.2481	5.39
Me ₄	1.0467	0.2188	0.2818	7.06
C ₇	0.9674	0.3809	0.2111	3.55
C ₈	0.8533	0.4144	0.1528	3.59
C ₉	0.6084	0.4032	0.1304	4.36
C ₁₀	0.4921	0.3598	0.1347	4.61
C ₁₁	0.5100	0.3073	0.2316	5.11
C ₁₂	0.6222	0.3027	0.2997	5.43
C ₁₃	0.7269	0.3500	0.3042	4.29
C ₁₄	0.7331	0.3729	0.1616	3.01
C ₁₅	0.6964	0.4001	0.4039	4.82
C ₁₆	0.5755	0.4342	0.3659	4.12
N	0.5890	0.4544	0.2269	4.30
NMe	0.4770	0.4941	0.1834	7.30
C ₁₇	0.7651	0.3211	0.0701	3.88
C ₁₈	0.8680	0.2903	0.1043	4.27
C ₁₉	1.0880	0.3949	0.1346	4.12
O ₁₉	1.1965	0.3741	0.2050	5.45
Me ₁₀	1.0867	0.3702	-0.0084	7.63
Pr ₁	1.1044	0.4678	0.1387	5.95
Pr ₂	1.1043	0.4932	0.2717	6.65
Pr ₃	1.1291	0.5622	0.2700	7.47
Br	0.7626	0.5681	0.2214	5.03

Table II. Anisotropic Temperature Factors as Obtained for the Different Atoms of the Form^a

$$T = e^{-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)}$$

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C ₁	1135	317	1936	91	-196	-52
C ₂	452	265	1139	444	352	321
C ₃	2600	85	1535	172	-1043	626
O ₃	1927	260	2036	-93	-95	417
Me ₃	3335	283	2371	116	-665	83
C ₄	593	434	642	-186	748	46
O ₄	1460	250	1498	-185	292	-37
C ₅	996	260	1061	-67	-213	112
C ₆	1165	123	1221	180	-892	488
O ₅	975	255	1315	-97	117	95
Me ₄	1207	260	1275	-26	776	135
C ₇	261	140	1430	226	327	-432
C ₈	628	207	636	-104	266	102
C ₉	474	147	856	112	227	222
C ₁₀	850	356	1673	-156	756	-368
C ₁₁	552	121	1080	185	276	96
C ₁₂	1223	373	1172	-301	-6	8
C ₁₃	860	207	1364	27	282	-124
C ₁₄	1163	271	892	-369	176	-94
C ₁₅	1631	293	279	-372	279	303
C ₁₆	1363	265	1549	371	-117	-117
N	497	166	1042	143	404	-67
NMe	832	225	1994	-94	-42	728
C ₁₇	802	155	754	52	142	16
C ₁₈	1089	247	642	24	26	76
C ₁₉	827	183	1156	97	-383	-11
O ₁₉	632	345	1701	-67	155	-48
Me ₁₀	948	608	1567	45	338	-396
Pr ₁	1792	332	1530	-58	-196	-29
Pr ₂	1878	204	1404	66	-431	235
Pr ₃	1237	264	1140	84	544	398
Br ⁻	1208	178	1532	77	-6	-34

^a Values given are multiplied by 10^4 .

Table III. Standard Deviations of the Final Atomic Coordinates (Å)

Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$	Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
C ₁	0.010	0.012	0.012	C ₁₂	0.009	0.011	0.009
C ₂	0.012	0.016	0.013	C ₁₃	0.009	0.009	0.009
C ₃	0.014	0.013	0.013	C ₁₄	0.007	0.008	0.008
C ₄	0.010	0.011	0.011	C ₁₅	0.009	0.011	0.009
Me ₃	0.019	0.017	0.016	C ₁₆	0.011	0.014	0.012
C ₅	0.009	0.012	0.010	N	0.007	0.008	0.008
O ₄	0.007	0.007	0.007	NMe	0.009	0.013	0.015
C ₆	0.007	0.009	0.008	C ₁₇	0.008	0.009	0.008
C ₇	0.009	0.011	0.010	C ₁₈	0.009	0.010	0.009
O ₆	0.006	0.007	0.007	C ₁₉	0.008	0.010	0.008
Me ₆	0.014	0.011	0.013	O ₁₉	0.006	0.007	0.007
C ₇	0.006	0.007	0.007	Me ₁₉	0.012	0.015	0.012
C ₈	0.007	0.009	0.008	Pr ₁	0.012	0.012	0.012
C ₉	0.008	0.010	0.009	Pr ₂	0.013	0.013	0.013
C ₁₀	0.008	0.010	0.010	Pr ₃	0.012	0.014	0.015
C ₁₁	0.009	0.011	0.011	Br	0.001	0.001	0.001

Discussion of the Structure

The spatial configuration of the molecule of 19-propylthevinol, as shown in projection in Figure 2, in many ways resembles that of codeine and morphine, as described by Lindsey and Barnes⁹ and by Mackay and Hodgkin.¹⁰

Since both of these previous analyses were performed with two-dimensional intensity data, we feel compelled to describe the molecular geometry of I with some detail.

Moreover, the absolute configuration of the morphinoids had not been confirmed previously by X-ray analysis even though the elegant chemical work of Kalvoda, *et al.*,¹¹ leaves little doubt as to its being well established.

The average sp²-carbon-sp²-carbon single bond length, of 1.543 Å (Table IV), and the average bond length in the aromatic A ring, 1.392 Å, as well as the sp²-carbon-sp²-carbon length of 1.335 Å, do not differ significantly from expected values.¹²

Table IV. Table of Interatomic Distances

Atoms	Distance, Å	Atoms	Distance, Å
C ₁ -C ₂	1.389	C ₉ -C ₁₄	1.518
C ₁ -C ₁₁	1.409	C ₉ -C ₁₀	1.570
C ₂ -C ₃	1.397	C ₉ -N	1.519
C ₂ -C ₄	1.378	C ₁₀ -C ₁₁	1.541
C ₂ -O ₃	1.391	C ₁₁ -C ₁₂	1.379
O ₃ -Me ₃	1.346	C ₁₂ -C ₁₃	1.534
C ₃ -O ₄	1.380	C ₁₂ -C ₁₄	1.535
C ₃ -C ₁₂	1.398	C ₁₂ -C ₁₅	1.541
O ₄ -C ₅	1.473	C ₁₂ -C ₁₇	1.521
C ₅ -C ₆	1.543	C ₁₂ -C ₁₈	1.540
C ₅ -C ₁₃	1.523	C ₁₂ -N	1.486
C ₅ -C ₇	1.586	N-NMe	1.545
C ₅ -O ₆	1.396	C ₁₇ -C ₁₈	1.335
O ₆ -Me ₆	1.451	C ₁₇ -Me ₁₉	1.551
O ₆ -C ₁₈	1.507	C ₁₇ -O ₁₉	1.431
C ₇ -C ₈	1.541	C ₁₈ -Pr ₁	1.638
C ₇ -C ₁₀	1.529	Pr ₁ -Pr ₂	1.463
C ₇ -C ₁₄	1.578	Pr ₂ -Pr ₃	1.565

(9) J. M. Lindsey and W. H. Barnes, *Acta Cryst.*, **8**, 227 (1955).
 (10) M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, 3261 (1955).
 (11) J. Kalvoda, P. Buchschacher, and O. Jeger, *Helv. Chim. Acta*, **38**, 1847 (1955).
 (12) L. E. Sutton, Ed., "Tables of Interatomic Distances and Configuration in Molecules and Ions," Special Publication No. 11, The Chemical Society, London, 1958, p S12.

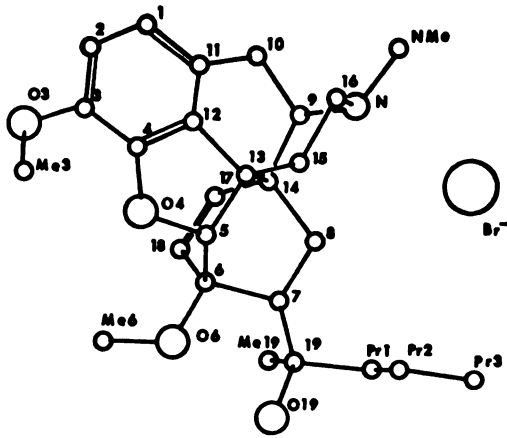


Figure 2. The atomic arrangement corresponding to Figure 1.

The carbon-nitrogen single bonds, which average 1.516 Å, are longer than expected, however, while the carbon-oxygen bond lengths are in the normal range.

The lengths of the bonds around the atom labeled Pr₁ are quite anomalous, and there is no satisfactory chemical explanation for this effect. We therefore consider it possible that the Pr₁ carbon atom has been misplaced by about 0.1 Å by the least-squares refinement procedure.

A comparison of the results with an idealized Dreiding model shows that the molecule is subject to considerable distortion. The phenyl ring itself is flat, but it can readily be understood that the spacial requirements of the complex cage structure connected to it explain why the connecting bonds (C₄-O₄, C₁₂-C₁₃, and C₁₁-C₁₀) are not coplanar with the six phenyl carbons.

As is usually observed in methyl phenyl ethers, the 3-methoxyl carbon atom does not lie in the phenyl carbon plane. The five-membered oxygen-containing ring is planar and the piperidyl system is in the chair conformation with the N-methyl equatorial.

In the bicyclo[2.2.2]octene cage, the carbon atoms 17 and 18 are the ones originally present and labeled as C₈ and C₇ in the morphinoids. The ring C₈-C₁₈-C₁₇-C₁₄-C₁₃ has, because of the added C₇-C₈ bridge, a different conformation than in morphine, where it is found as a pseudo chair.

As a result of this analysis the conformation at C₁₉ has been established. The hydroxyl oxygen, O₁₉, is coplanar with O₆, C₆, and C₁₉, and the methyl group, Me₁₉, is oriented toward the morphine ethenyl bridge. This result is in agreement with stereochemical considerations of the Grignard coupling which was carried out at C₁₉ in the preparation of I, since it is reasonable to assume that the MgI ion would preferably interact with both the C₁₉ and C₆ oxygen atoms in the Grignard complex.

The 19-hydroxyl group forms an intramolecular hydrogen bond with the ether oxygen O₆. The 6-methyl group is located in such a manner as to facilitate this bonding with the free pairs of O electrons. The O-O distance is 2.63 Å, and the position of the proton, which was located from a difference density map calculation (Figure 3), indicates a O-H...O hydrogen bond angle of 111.2°, with H-O₁₉ and H-O₆ distances of 1.05 Å and 1.79 Å, respectively. The location of the hydroxyl proton, which is virtually coplanar with the C₆-O₆-Me atoms, seems to indicate that the ether

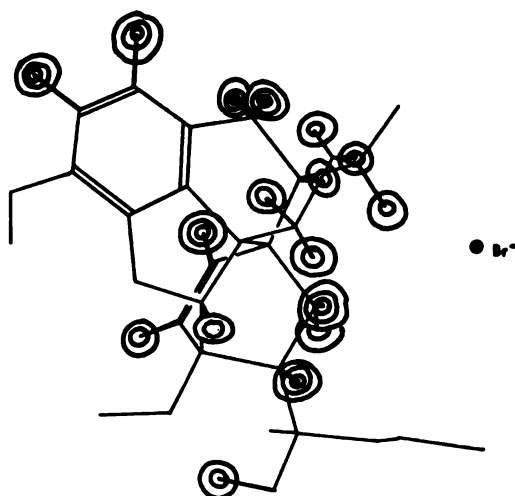


Figure 3. Hydrogen atom positions as obtained from $F_o - F_c$ synthesis. Contours drawn represent 0.1 electron/Å³.

oxygen has an unshared pair of electrons emanating from the atomic center in the same plane as the bonded electrons. This implies that the oxygen atom is not an sp^3 hybrid, but rather that it is sp^2 , trigonal. This is supported by the $C_6-O_5-Me_4$ valence angle of 120°. In view of this it should also be observed that the angle $C_7-O_5-Me_3$, 117°, is close to the ideal trigonal value of 120°.

The closest nonbonded intramolecular distances are given in Table V, and Table VI is a list of valency bond

Table V. Nonbonded Intramolecular Distances below 3.00 Å

Atoms	Distance, Å	Atoms	Distance, Å	Atoms	Distance, Å
C ₁ -C ₂	2.48	C ₁ -C ₁₈	2.50	C ₁₅ -C ₁₈	2.54
C ₁ -C ₄	2.86	C ₂ -C ₃	2.55	C ₁₅ -C ₁₇	2.81
C ₁ -C ₁₀	2.56	C ₂ -C ₁₈	2.48	C ₁₈ -N	2.86
C ₁ -C ₁₃	2.40	C ₂ -C ₁₄	2.61	C ₁₈ -C ₁₆	2.55
C ₂ -O ₅	2.41	C ₂ -C ₁₇	2.40	C ₁₈ -C ₁₇	2.49
C ₂ -C ₄	2.37	O ₅ -C ₁₉	2.81	C ₁₈ -C ₁₈	2.85
C ₂ -C ₁₁	2.36	O ₅ -O ₁₉	2.63	C ₁₈ -C ₁₈	2.56
C ₂ -C ₁₃	2.66	C ₇ -C ₁₈	2.80	C ₁₈ -N	2.47
C ₂ -Me ₃	2.33	C ₇ -C ₁₄	2.54	C ₁₈ -C ₁₄	2.99
C ₂ -O ₄	2.50	C ₇ -C ₁₇	2.90	C ₁₈ -C ₁₈	2.41
C ₂ -C ₁₁	2.81	C ₇ -C ₁₈	2.52	C ₁₈ -N	2.45
C ₂ -C ₁₃	2.37	C ₇ -C ₉	2.62	NMe-C ₁₈	2.51
O ₅ -C ₄	2.43	C ₈ -C ₁₈	2.49	C ₁₈ -Pr ₁	2.60
Me ₃ -C ₄	2.81	C ₈ -C ₁₇	2.43	O ₁₉ -Pr ₁	2.41
Me ₃ -O ₄	2.81	C ₈ -C ₁₈	2.82	O ₁₉ -Pr ₂	2.91
C ₄ -C ₅	2.30	C ₈ -C ₁₂	2.83	Pr ₁ -Pr ₂	2.51
C ₄ -C ₁₁	2.45	C ₈ -C ₁₈	2.47	Me ₁₉ -Pr ₁	2.65
C ₄ -C ₁₃	2.38	C ₈ -C ₁₈	2.93	C ₇ -Me ₁₉	2.57
O ₄ -C ₅	2.51	C ₉ -NMe	2.52	O ₄ -Me ₄	2.93
O ₄ -C ₁₂	2.32	C ₉ -C ₁₆	2.51	C ₉ -O ₅	2.49
O ₄ -C ₁₃	2.43	C ₉ -C ₁₇	2.55	C ₉ -Me ₄	2.47
C ₅ -C ₇	2.43	C ₁₆ -C ₁₈	2.51	C ₉ -C ₁₉	2.64
C ₅ -C ₈	2.99	C ₁₀ -C ₁₄	2.58	C ₇ -O ₁₉	2.43
C ₅ -C ₁₂	2.37	C ₁₀ -N	2.53	C ₇ -Pr ₁	2.53
C ₅ -C ₁₄	2.56	C ₁₁ -C ₁₈	2.60	C ₇ -Pr ₂	2.96
C ₅ -C ₁₆	2.55	C ₁₁ -C ₁₄	2.87	C ₈ -C ₁₉	2.53
C ₅ -C ₁₇	2.90	C ₁₂ -C ₁₄	2.41	C ₈ -Pr ₁	2.92

angles. A survey of these angles reveals that most ring bond angles are slightly larger than the expected sp^3 valence angles, which must be caused by the constraints placed upon them by the fusion of such a large number of rings into a single molecular skeleton in order to

Table VI. Valency Angles for 19-Propylthiovinol

Atoms	Angle, deg	Atoms	Angle, deg
C ₁₁ -C ₁ -C ₂	115	C ₁₁ -C ₁₈ -C ₁₈	126
C ₁ -C ₂ -C ₃	126	C ₁ -C ₁₈ -C ₁₈	108
C ₂ -C ₃ -C ₄	118	C ₁₈ -C ₁₈ -C ₁₈	102
C ₂ -C ₃ -O ₅	120	C ₁₈ -C ₁₈ -C ₁₄	103
C ₂ -C ₃ -O ₅	122	C ₁₈ -C ₁₈ -C ₁₈	112
Me ₃ -O ₅ -C ₂	117	C ₁ -C ₁₈ -C ₁₄	114
C ₂ -C ₃ -C ₁₃	117	C ₁ -C ₁₈ -C ₁₈	113
C ₂ -C ₃ -O ₄	130	C ₁₈ -C ₁₈ -C ₁₈	113
C ₁₃ -C ₂ -O ₄	113	C ₁₈ -C ₁₈ -C ₈	107
O ₅ -C ₂ -C ₄	113	C ₁₈ -C ₁₈ -C ₉	108
O ₅ -C ₂ -C ₁₃	108	C ₁₈ -C ₁₈ -C ₁₇	109
C ₂ -C ₃ -C ₁₃	108	C ₁ -C ₁₈ -C ₉	115
C ₂ -C ₃ -C ₇	102	C ₁ -C ₁₈ -C ₁₇	103
C ₂ -C ₃ -C ₁₈	110	C ₁ -C ₁₈ -C ₁₇	114
C ₂ -C ₃ -O ₄	116	C ₁₈ -C ₁₈ -C ₁₈	112
C ₂ -C ₃ -O ₅	107	C ₁₈ -C ₁₈ -N	108
C ₂ -C ₃ -C ₁₈	109	C ₁ -N-C ₁₈	113
O ₅ -C ₂ -C ₁₈	112	C ₁ -N-NMe	111
C ₂ -C ₃ -C ₄	109	C ₁₈ -N-NMe	112
C ₂ -C ₃ -C ₁₉	116	C ₁₈ -C ₁₇ -C ₁₈	115
C ₂ -O ₅ -Me ₄	120	C ₁₈ -C ₁₈ -C ₁₇	115
C ₂ -C ₃ -C ₄	111	C ₁ -C ₁₈ -O ₁₉	111
C ₂ -C ₃ -C ₁₄	109	C ₁ -C ₁₈ -M ₁₉	113
C ₂ -C ₃ -C ₁₉	114	C ₁ -C ₁₈ -Pr ₁	106
C ₁ -C ₂ -N	109	O ₁₉ -C ₁₈ -M ₁₉	111
C ₁ -C ₂ -N	110	O ₁₉ -C ₁₈ -Pr ₁	103
C ₂ -C ₁ -C ₁₁	113	M ₁₉ -C ₁₈ -Pr ₁	112
C ₁ -C ₁ -C ₁	121	C ₁₈ -Pr ₁ -Pr ₂	114
C ₁ -C ₁ -C ₁₃	119	Pr ₁ -Pr ₂ -Pr ₃	112
C ₁ -C ₁ -C ₁₈	119		
C ₁₁ -C ₁ -C ₄	124		

Table VII. Short Intermolecular Nonbonded Approaches

Br-Pr ₁	3.99 ^a
Br-Pr ₂	3.89 ^a
Br-C ₈	4.01 ^b
Br-C ₉	3.87 ^b
Br-C ₁₇	3.86 ^b
Br-C ₂	4.06 ^c
Br-Me ₄	3.98 ^c
Br-C ₅	3.79 ^a
Br-C ₁₈	4.02 ^a
Br-N	3.18 ^a
Br-NMe	3.58 ^a
Br-C ₁₈	3.70 ^a
Br-C ₁₈	3.89 ^b
C ₁ -C ₁₇	3.91 ^d
C ₁ -C ₁₈	3.60 ^d
C ₁ -O ₁₉	3.58 ^a
C ₁ -Me ₁₉	4.00 ^e
C ₂ -O ₄	3.83 ^a
C ₂ -O ₅	3.90 ^a
C ₂ -Me ₁₉	3.64 ^a
C ₂ -Me ₁₉	3.83 ^a
O ₄ -NMe	3.64 ^a
O ₄ -Pr ₁	3.62 ⁱ
Me ₃ -Pr ₁	3.62 ⁱ
Me ₃ -O ₄	3.89 ^a
Me ₃ -O ₁₉	3.10 ^a
Me ₃ -Pr ₁	4.00 ⁱ
C ₁₈ -O ₁₉	3.23 ^a

The superscripts refer to the following positions of the atom mentioned last: ^a x, y, z ; ^b $1.5 - x, 1 - y, 0.5 + z$; ^c $1 - x, -0.5 + y, 0.5 - z$; ^d $0.5 + x, 0.5 - y, 1 - z$; ^e $-1 + x, y, z$; ^f $0.5 + x, 0.5 - y, -z$; ^g $-0.5 + x, 0.5 - y, 1 - z$; ^h $-0.5 + x, 0.5 - y, -z$; ⁱ $2 - x, -0.5 + y, 0.5 - z$.

allow it some "breathing space." The results are consistent with the nmr and infrared spectral data.¹⁸

The bromide ions are located in such a manner that a very strong interaction exists with the basic nitrogen of the piperidyl ring. The quaternizing N-proton is located from the nitrogen in the general direction of a single bromide anion, with the short N...Br approach distance of 3.17¹⁰ Å. The N-H...Br ionic bond angle is 107° with N-H and H...Br distances of 1.08 and 3 Å, respectively. The errors in the bond distances are estimated at ±0.02 Å, and those in the valency angles as ±3°.

All other short intermolecular distances seem to give only the expected van der Waals contacts (see Table VII). Apart from the above described van der Waals bonding and the ionic N-H...Br interactions no other intermolecular forces seem to hold the lattice together. This may explain the relatively high thermal stability which is ascribed to the terminal atoms of the functional groups.

Absolute Configuration Determination

The absolute configuration was established using the anomalous dispersion of the bromide ions, which causes reflections (h, k, l) and ($\bar{h}, \bar{k}, \bar{l}$) to be different in both phase and scattering amplitude, in violation of Friedel's law. Two methods were used: first, the more obvious one in which the structure was refined first with observed crystal planes assigned as (hkl) and then as ($h, -k, -l$). Even though no dramatic difference in overall R was observed (0.078 and 0.084, respectively) a complete review of the data showed that for most of the reflections no large changes were calculated, but that

3) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Reil, C. T. Nora, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, in press.

Table VIII. Anomalous Scattering Data for 19-Propylthiovinol

h	k	l	$F_o(+++)/F_o(---)$	$F_o(+++)/F_o(---)$
8	1	1	1.061	1.112
8	2	4	1.053	1.101
7	2	1	1.115	1.110
2	1	3	1.100	1.101
7	5	5	0.948	0.877
9	7	2	1.055	1.103
1	2	2	1.080	1.102
1	2	5	1.096	1.108
5	12	2	1.027	1.110
5	12	3	0.887	0.880
6	15	1	0.903	0.896
4	10	4	0.909	0.885
4	10	5	0.858	0.853
4	15	2	0.889	0.859
2	11	3	1.121	1.108
2	12	5	1.084	1.105
1	12	4	1.047	1.115

some showed dramatic differences between $F_o(hkl)$ and $F_o(-h, -k, -l)$. For all reflections where this difference was more than 10% in $|F_o|$ it was obvious that the hand originally chosen was the correct one; for these planes $R(+++)$ and $R(---)$ were 0.107 and 0.152, respectively. In order to confirm this result the intensities of the ($-h, -k, -l$) reflections were measured.¹⁴ The data are shown in Table VIII, and they confirm the other work.

In all figures the absolute configuration has been depicted.

(14) J. M. Bijvoet, *Proc. Koninkl. Ned. Akad. Wetenschap.*, B52, 313 (1949); A. F. Peerdeman, A. J. van Bommel, and J. M. Bijvoet, *ibid.*, 54, 3 (1951).

The Crystal and Molecular Structure of N-Brosylmitomycin A

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Abstract: The structure of N-brosylmitomycin A, a crystalline derivative of an anticancer antibiotic extracted from soil isolates of *Streptomyces verticillatus* strains, has been determined using X-ray crystallographic techniques. The crystals are monoclinic with $a = 19.70$, $b = 8.24$, $c = 16.05$ Å, $\beta = 95.80^\circ$, space group C2, and there are four molecules per unit cell. The structure was solved using the heavy atom method and refined using Fourier and least-squares techniques. The mitomycin molecule contains four fused ring systems, one of which is an aziridine. Evidence was found indicating an interaction between the lone electron pairs of the two ring nitrogen atoms. The molecules are held in the crystal by continuous chains of N-H...O hydrogen bonds and a strong affinity between bromine atoms and the components of quinoid rings of adjacent molecules. The crystals are solvated with 0.5 mole of benzene/mole of antibiotic located in voids of the structure. The absolute configuration of the molecule has been determined from the comparison of observed and calculated structure factors utilizing the anomalous scattering contribution of bromine and sulfur for Cu K α radiation with respect to alternative atomic positions.

Three soil isolates of *Streptomyces verticillatus*, Lederle strains AA-849, AB-286, and AB-929, were found to produce mixtures of ethyl acetate extractable

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antibiotics which were active in bacterial mouse protection tests.² When purified preparations made

(2) D. V. Lefemine, M. Dann, F. Barbatschi, W. K. Hausmann, V. Zbinovsky, P. Monnikendam, J. Adam, and N. Bohonos, *J. Am. Chem. Soc.*, 84, 3184 (1962).

from these cultures were compared by paper chromatography they appeared to contain the same groups of antibiotics, five of which were isolated in crystalline form. The characterization of several of these compounds showed that they were identical with mitomycin A, B, and C and porfiromycin, and were of a new and unusual structural type, representing the first naturally occurring examples of an aziridine elaborated by a microorganism.^{3a} A considerable amount of chemical degradation and related studies had correctly identified all atoms and their interconnections, but several details which were of interest, such as the relative stereochemistry of the asymmetric carbons, could not be established *via* classical means.

The present paper deals with the structure elucidation using single-crystal, X-ray diffraction methods of the N-brosyl derivative of one of the components of the antibiotic mixture, mitomycin A, of which a preliminary report has appeared elsewhere.⁴

Experimental Section

Crystals of N-brosylmitomycin A suitable for X-ray examination were obtained by the slow evaporation of a solution of methylene chloride and benzene (1:4).⁴ The crystals were deeply colored red laths and occasionally they displayed end-face development. The crystal chosen for X-ray examination also proved to be of sufficient quality for intensity data collection and its dimensions were approximately $0.8 \times 0.3 \times 0.05$ mm.

The X-ray work was carried out with Cu K α radiation and a General Electric XRD-5 equipped with a single-crystal orienter and a scintillation counter assembly. A preliminary survey of the diffraction pattern indicated that the crystal system was monoclinic with $a = 19.70$, $b = 8.24$, $c = 16.05$ Å, $\beta = 95.80^\circ$. The only reflections that were systematically absent were of the type $h + k = (2n + 1)$. Therefore, the space group was either C2, Cm, or C2/m. The latter was eliminated because it is centrosymmetrical and Cm was rejected because it contains a mirror plane (mitomycin A is an optically pure isomer). The space group C2 was verified upon examining the Patterson function of the crystal. The bromine-bromine and the sulfur-sulfur vectors and their cross vectors could be interpreted only in terms of the equivalent positions of space group C2.

A chemical analysis of the crystals (dried at 78° under vacuum) indicated an empirical formula corresponding to $C_{24}H_{28}N_4O_5SBr$. This carbon content is high by three with respect to the formula of the antibiotic derivative and suggested 0.5 mole of benzene solvate/mole of N-brosylmitomycin A.⁴ The solvation was corroborated by flotation density measurements in aqueous potassium iodide solution ($d_{\text{obsd}} = 1.55$ g cm $^{-3}$; $d_{\text{calcd}} = 1.554$ g cm $^{-3}$, based on four N-brosylmitomycin A and two benzene molecules per unit cell).

Before initiating three-dimensional, intensity-data collection, the quality of the crystal was assessed by measuring the mosaic spreads of several reflections at different ϕ and χ values. The spreads were found to be single peaked and symmetrical, and varied from 0.4 to 0.7° in width as a function of ω (background to background). The quadrant of reciprocal space that included the narrowest and most symmetrical spreads was selected for intensity measurements. The intensities were obtained using the stationary crystal-stationary counter technique with balanced Ni-Co filters. Of the 1481 reflections accessible to $d_{\text{min}} = 1.0$ Å ($2\theta_{\text{max}} = 100^\circ$), 1352 (91.3%) were taken to be observable.

Throughout the data collection, the intensities of three convenient reflections were monitored as a function of X-ray exposure to the crystal. During the first 6 hr of exposure, the monitored reflections

remained essentially constant but during the last 6 hr of data collection, they showed a continuous and slow decrease in intensity (maximum decrease of 6% after 12 hr of exposure). Consequently, the latter half of the intensity data was corrected for this fall off. The intensities were also corrected approximately for absorption (as a function of azimuthal angle ϕ).⁷ The absorption correction was found to be 2θ dependent, and it was approximated with a weighted mean correction that was more appropriate for the higher order reflections. The maximum:minimum ratio of the correction was 2.4. Finally, Lorentz and polarization factors were applied to the modified intensities converting them into relative structure amplitudes.

The Structure Determination

The structure was solved using the phase-determining, heavy-atom method.⁸ A three-dimensional Patterson function was computed sharpened with $(z_{\text{Br}}/f_{\text{Br}})^3$, where z_{Br} and f_{Br} are, respectively, the atomic number of bromine and the scattering form factor of bromine at rest. The effect of such a sharpening procedure is to enhance the bromine-bromine vectors to point bromine atom interactions with thermal motion. The sulfur atom interactions are also enhanced by this procedure, but not as much, while the light atom interactions are sharpened least of all. The bromine-bromine and sulfur-sulfur interactions were readily recognized in the Harker section at $v = 0$. From the (x, z) coordinates thus obtained, the bromine-sulfur interactions in general positions were identified. The latter also gave the relative y coordinates of bromine and sulfur.

Before proceeding with a structure factor computation, the positions of the two carbon atoms of the brosyl group that are bonded to the bromine and the sulfur atoms were inferred. The procedure was relatively straightforward and involved only the assumptions: (1) that all four atoms lie on a straight line and (2) the bond distances of C-Br and C-S. The crucial point of the procedure proved to be the correct identification of the Br-S vector belonging to a single molecule. There were two vectors of approximately the correct length; however, one could be eliminated because of its close proximity to a twofold rotation axis, thus giving rise to packing problems.

Structure factors were now computed based on the positions of the bromine, the sulfur, and the two inferred phenyl carbon atoms and an isotropic thermal parameter of $B = 3.0$ Å 2 . The calculated phases were then assigned to the observed structure amplitudes and a three-dimensional electron density (ρ_1) was computed. This electron density contained 45 peaks greater than 1.7 eÅ $^{-3}$ (carbons included in the structure-factor computation are also included in this count). Of these peaks, 30 were shown to belong to the molecule, seven were eliminated because of close approaches to the brosyl system or the bromine atom, and two others were disregarded because they were situated too close to a twofold rotation axis.⁹ The remaining six peaks were all positionally isolated from the main body of peaks and eventually were shown to be spurious. At this

(3) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84**, 3185 (1962); (b) *ibid.*, **84**, 3186 (1962).

(4) A. Tulinsky, *ibid.*, **84**, 3188 (1962).

(5) We thank Dr. J. H. Mowat of Lederle Laboratories for preparing the N-brosyl derivative and for growing the crystals.

(6) This observation was also supported with gas chromatographic measurements. We should like to thank Mr. A. Mistretta of Lederle Laboratories for carrying out these measurements.

(7) S. Silvers and A. Tulinsky, *Acta Cryst.*, **16**, 579 (1963).

(8) J. M. Robertson and I. Woodward, *J. Chem. Soc.*, 219 (1937); 36 (1940).

(9) Symmetry-related peaks in the present instance belong to independent molecules unless the molecule itself has twofold rotation symmetry and additionally utilizes the crystallographic twofold rotor. Since the latter was not applicable to the antibiotic, the two peaks near the twofold rotation axis would give rise to unacceptably short van der Waals contacts. At a later stage of the work, these peaks were, in fact, shown to belong to the structure, and the way in which they are will be indicated below.

the brosyl system was easily identified and it was to a three-membered ring (known to be aziridine) in turn was fused to two fused five-membered (see Figure 1). From ring B, the density was that ambiguous; either ring B was fused to a membered ring bearing short side chains (shown by broken lines in Figure 1) or a long side chain emanated from B. Also, there was a two-atom chain at bridgehead position between rings A and B (X) seemingly longer chain at Y.

At this point, consultation with the Lederle group and in the chemical structure determination of the bicyclics revealed a general agreement between their chemical structure and the one described above. Using additional chemical information and the location of smaller peaks ($1.3\text{--}1.6\text{ eA}^{-3}$, marked by asterisks in Figure 1) the remainder of the structure shown in Figure 1 (as broken lines) was recognized. Two of the smaller peaks proved to be part of a quinone system bearing methyl and methoxyl groups. The other peak formed part of a carbamoyloxymethyl chain ($\text{CH}_2\text{OCONH}_2$) (side chain Y, partially shown). Finally, the fused five-membered rings were finally known to be a pyrrolizine system (contained bridgehead nitrogen).

Structure factor and electron-density computations were now carried out: (1) the first (ρ_1) based on complete structure including atoms of correct chemical identity, and (2) the second (ρ_2) included bromine, and 25 carbon atoms (the crystallographically ambiguous structure; solid line structure of Figure 1). Both computations included an over-all isotropic temperature factor of $B = 3.0\text{ \AA}^2$. The latter computation was performed as a precautionary measure and also to compare the results of including the complete structure. Temperature factors for these structure factor computations were 0.22 and 0.28, respectively.

Comparison of the two resulting electron densities of 132 of the atoms included in the computation of ρ_2 included atoms (except two in ρ_1) in both densities increased 2.5 times or more. The two atoms which were stationary in ρ_1 (the methyl of the bridgehead ethyl and the carbamate nitrogen) had other real peaks ($\sim 1.6\text{ eA}^{-3}$) within bonding distance of groups. In the end, it was shown that an initial choice was originally made in both instances.

Atoms not included in structure factor computations remained essentially unchanged or increased in height in ρ_1 . Nitrogen and oxygen atoms, in contrast to carbon, appeared $1\text{--}3\text{ eA}^{-3}$ greater than the carbon atoms in this density and confirmed the chemical identities employed to obtain ρ_2 . Finally, all unused peaks of ρ_1 decreased or became vanishingly small in both ρ_2 and ρ_3 .

Two peaks ignored in ρ_1 because they were too close to a twofold rotation axis ($\approx 1.2\text{ \AA}$) persisted and increased in height in both ρ_2 and ρ_3 . Furthermore, two new peaks developed significantly in this region (0.0 eA^{-3}) and they were located on the twofold axis. It became apparent that these peaks represented the molecules which were utilizing twofold rotation symmetry to accommodate along the crystallographic c axis. Thus, the 0.5 mole of benzene of solvation was satisfactorily accounted for since the multi-

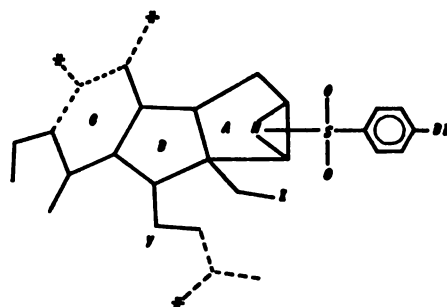


Figure 1. Atomic arrangement identifiable from ρ_1 and inferred from chemical considerations.

licity of the twofold position in space group $C2$ is two.¹⁰

Refinement of the structure, including a half-benzene molecule, was now commenced through electron- and difference-density computations. After one cycle, individual isotropic thermal parameters were obtained from the difference density and these were included into structure factor computations. In all, six cycles of refinement were carried out in this manner and R decreased to 0.146. At this stage, refinement by the method of least squares was initiated.

The Least-Squares Refinement

The structure was first refined by conventional diagonal least-squares techniques. The weighting scheme adopted assigned unit weights ($w = 1.0$) to all reflections with $4|F_{\min}| < |F| < 10|F_{\min}|$; $w = |F|/4|F_{\min}|$ when $|F| \leq 4|F_{\min}|$; and $w = 10|F_{\min}|/|F|$ for reflections with $|F| \geq 10|F_{\min}|$. This scheme resembles the Hughes weighting and simultaneously takes into account variations in the measured intensity data due to the counting statistics. Isotropic refinement converged after three cycles in which only the non-zero structure amplitudes were included and an R of 0.109 was obtained. A three-dimensional electron density map was calculated at this stage and it clearly indicated a large amount of anisotropy for both the bromine and sulfur atoms. This was allowed for in some additional refinement by introducing both heavy atoms as slightly separated, but thermally coupled half-atoms. A considerable improvement in bond distances and valency angles resulted but R was not affected much.

Inclusion of all atoms with anisotropic correction factors and subjecting the data to additional refinement yielded a large change in R , which became stationary at 0.087, and caused significant changes in some of the bond distances. A difference density map was computed, but in general the regions in which the hydrogen atoms were expected to be located were poorly defined. Therefore, the refinement process was terminated. The final positional and anisotropic thermal parameters are given in Table I, and the standard errors of the positional parameters are given in Table II. (The observed and calculated structure factors are available from the authors.)

(10) It should be remarked here that from the onset of the work, the one half mole of benzene of solvation was puzzling, especially in view of the fact that the crystal proved to be an excellent X-ray scatterer (91.3% of the data was observable to 1- \AA resolution). Such behavior was not consistent with disordered benzene of solvation as the one half mole would suggest.

Table I. Final Positional and Anisotropic Thermal Parameters^a

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>B</i> ₁₁	<i>B</i> ₂₂	<i>B</i> ₃₃	<i>B</i> ₁₂	<i>B</i> ₁₃	<i>B</i> ₂₃
Br	0.51422	0.50000	0.13205	281	1613	455	66	137	-120
S	0.22439	0.16162	0.15784	227	1028	221	34	36	-9
Ph1	0.30650	0.25157	0.14812	188	269	171	310	-134	51
Ph2	0.34954	0.27258	0.22431	211	1388	321	85	166	-7
Ph3	0.32259	0.31170	0.07327	258	981	151	386	42	70
Ph4	0.41411	0.34954	0.21744	147	1718	328	185	-12	317
Ph5	0.38493	0.38562	0.06751	379	1024	276	135	21	38
Ph6	0.42783	0.40172	0.13849	245	3325	97	-511	66	170
C1	0.17730	0.47555	0.14156	331	1173	245	-251	176	-297
C2	0.18842	0.43940	0.23212	251	1593	240	-363	73	260
C3	0.10817	0.55605	0.11861	147	1082	231	680	91	287
C4	0.12667	0.51127	0.27368	214	217	339	21	-14	-48
C5	0.08848	0.40434	0.33459	189	1405	169	-115	-17	90
C6	0.02029	0.37873	0.28454	165	252	282	134	-38	39
C7	0.01826	0.44726	0.20879	171	39	151	345	-52	369
C8	-0.03995	0.28770	0.30701	178	1345	307	284	23	-307
C9	-0.09885	0.28665	0.24291	115	1815	395	239	29	58
C10	-0.10110	0.34542	0.16691	104	265	252	606	-72	18
C11	-0.04241	0.43837	0.14456	222	1503	87	-61	-107	31
C12	-0.16063	0.32536	0.09958	275	2282	474	-286	-62	56
C13	-0.18431	0.24511	0.34415	283	2948	512	-118	164	-113
C14	0.10441	0.77575	0.32587	213	1152	318	153	69	57
C15	0.11997	0.24511	0.36145	113	86	335	169	-42	232
C16	0.21795	0.16369	0.45709	44	261	413	447	67	323
O1	0.20237	0.09838	0.07938	239	1294	433	144	35	-234
O2	0.23069	0.06661	0.23145	225	2128	474	284	72	87
O3	0.15177	0.65270	0.30881	134	798	383	91	98	-120
O4	0.18707	0.28912	0.40933	135	656	320	115	10	11
O5	0.19117	0.03085	0.45591	296	153	618	279	-51	-168
O6	-0.03849	0.21898	0.37502	179	2241	542	7	-25	106
O7	-0.04248	0.50850	0.07902	259	2299	196	129	-49	139
O8	-0.15546	0.20054	0.26759	209	1716	542	-34	-10	-9
N1	0.16834	0.30736	0.17228	167	299	268	326	110	-108
N2	0.07523	0.53547	0.20003	148	235	88	546	82	-6
N3	0.27685	0.21003	0.49369	167	1368	490	14	63	-180
B1	0.50000	0.06325	0.50000	436	1396	286	-196	288	-122
B2	0.50000	0.40322	0.50000	399	2792	276	-389	273	-284
B3	0.44802	0.14945	0.45348	439	2993	575	-327	372	-198
B4	0.44798	0.31978	0.45204	332	3502	223	-118	115	306

^a The anisotropic temperature factors which were used in the calculations were of the form $T = e^{-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)}$. All *B* values are multiplied by a factor of 10⁴.

Structure of the Molecule

An inspection of the interatomic distances (Figure 2) shows that there are few anomalies present in the structure of N-brosylmitomycin A. Major interest

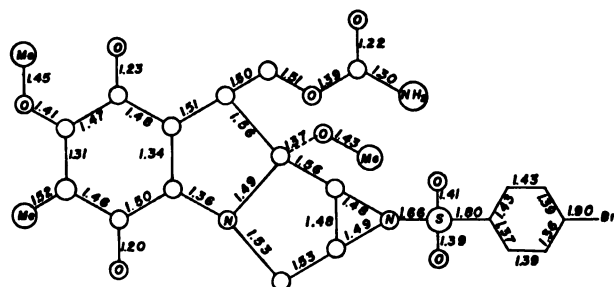


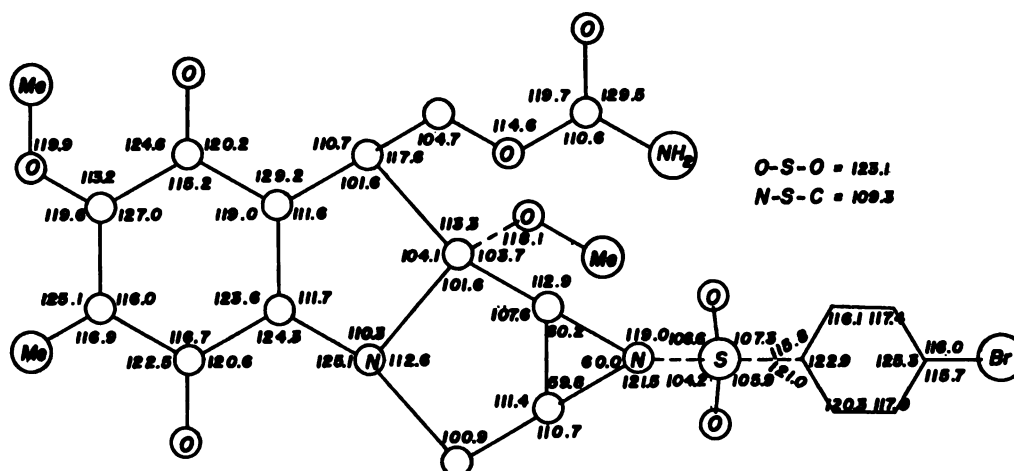
Figure 2. Final bond distances.

lies with the aziridine ring system, which consists of three bonds of equal length. The C-N distances of 1.48 and 1.49 Å are normal for single carbon-to-nitrogen bonds. The exocyclic bond angles N(1)-C(1)-C(3) of 110.7° and N(1)-C(2)-C(4) of 112.8° (Figure 3;

see Figure 4 for labeling) indicate that the carbon atoms tend to retain their tetrahedral configuration despite the considerable shortening of the C-C bond to 1.48 Å. The atoms C(4), C(2), C(1), and C(3) of ring A are coplanar. The angle between the plane defined thusly and the aziridine ring is 104°, and the distance between the indole nitrogen N(2) and N(1) is 2.69 Å.

As one would expect, N(2) behaves much like an amide nitrogen owing to its ability to participate in the conjugation of the quinoid system. However, it is observed in ultraviolet absorption spectra that mitomycin A is bathochromic with respect to model compounds^{2b} and that its extinction coefficient is considerably smaller, which is indicative of a lower energy system.

This may be accounted for by the fact that N(2) is observed to be nonplanar and thus is impaired in its ability to take part in the conjugation. N(2) is 0.3 Å out of the plane defined by C(3), C(4), and C(7), and on the opposite side of that plane as the aziridine nitrogen, N(1). Furthermore, an inspection of the bond angles shows that it is more tetrahedral than trigonal. Even though one could ascribe this to the fact that



e 3. Final bond angles.

is part of two five-membered rings and therefore subject to distortion of its valency angles, a more plausible reason becomes obvious upon inspecting the orientation and position of the orbitals occupied by the free lone pairs of electrons of N(1) and N(2). If N(2) were planar, these would be subject to overlap, and the ob-

II. Standard Deviations of the Positional Parameters, as Obtained from Least-Squares Residuals

Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
Br	0.001	0.001	0.001
S	0.003	0.003	0.003
Ph1	0.010	0.010	0.010
Ph2	0.011	0.012	0.012
Ph3	0.012	0.012	0.011
Ph4	0.011	0.014	0.012
Ph5	0.014	0.013	0.013
Ph6	0.009	0.013	0.010
C1	0.011	0.010	0.011
C2	0.009	0.010	0.010
C3	0.012	0.014	0.012
C4	0.010	0.009	0.011
C5	0.010	0.011	0.010
C6	0.010	0.010	0.011
C7	0.010	0.009	0.009
C8	0.012	0.013	0.012
C9	0.011	0.015	0.013
C10	0.011	0.011	0.011
C11	0.010	0.011	0.009
C12	0.011	0.014	0.014
C13	0.012	0.016	0.015
C14	0.011	0.013	0.012
C15	0.009	0.008	0.010
C16	0.010	0.010	0.011
O1	0.008	0.009	0.009
O2	0.009	0.012	0.010
O3	0.007	0.007	0.008
O4	0.007	0.007	0.008
O5	0.009	0.007	0.010
O6	0.008	0.011	0.010
O7	0.008	0.010	0.008
O8	0.008	0.009	0.010
N1	0.008	0.008	0.009
N2	0.008	0.008	0.007
N3	0.009	0.011	0.012
B1	0.02	0.02	0.02
B2	0.02	0.03	0.02
B3	0.01	0.02	0.01
B4	0.01	0.02	0.01

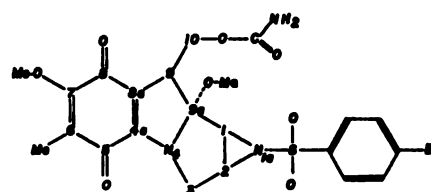
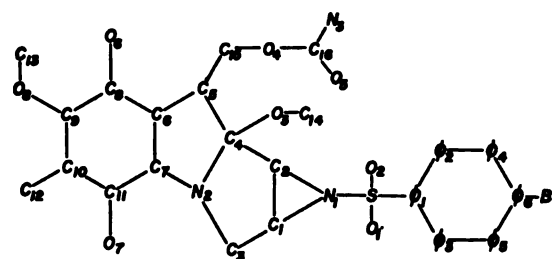


Figure 4. Key to X-ray (top) and chemical labelings (bottom).

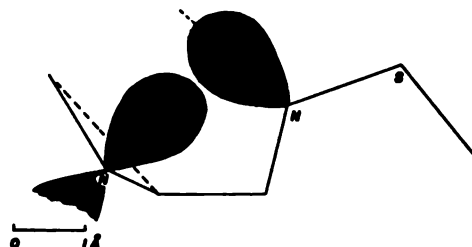


Figure 5. Schematic view of interaction of unshared electrons.

served deformation of N(2) is sufficient to avoid this to a great extent, as is indicated in Figure 5.

The nonplanarity of N(2) also affects other parts of the molecule. The substitution of an amide-type nitrogen at C(7) and an O-Me group at C(9) would, in the case of a normal planar molecule, be expected to result in: (a) a shortening of the C-N single bond owing to its participation in the conjugated system, (b) a simultaneous lengthening of the double bond C(7)-C(6), and, possibly, (c) a shortening of the C-O-Me bond due to the influence of the *p*-mide group.

It is observed that the C-N bond is indeed shortened. However, no shortening of the C-O bond is observed,

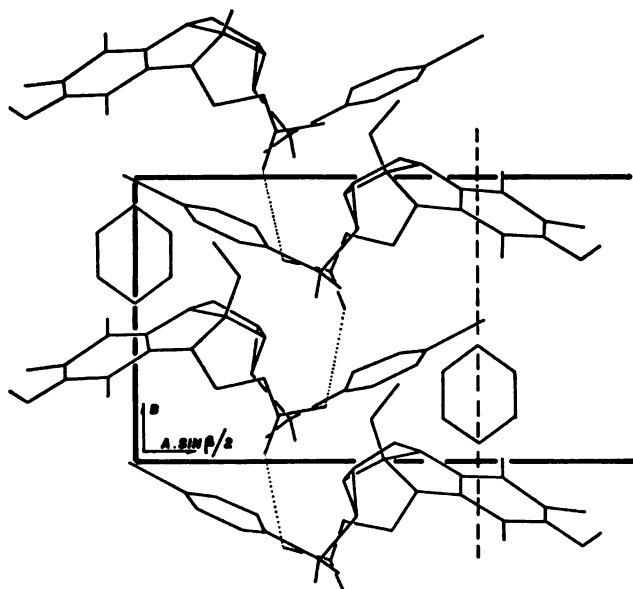


Figure 6. Projection of crystal structure as viewed along the *c* axis (one-half unit cell shown).

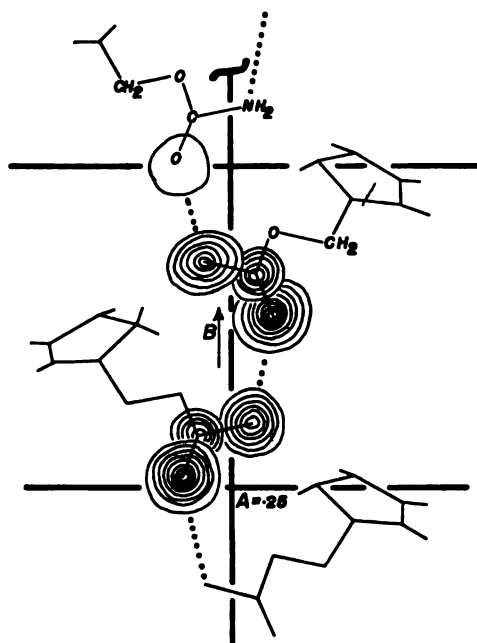


Figure 7. Hydrogen-bonding scheme.

which may be attributed to the fact that N(2) is not coplanar with the quinoid system, so that hyperconjugation with O(7) is not expected to occur.

From the above it may also be concluded that the nonbasic behavior of N(1) which is atypical for an aziridine nitrogen atom, even when part of a [3.1.0] bicyclic system, is due to the steric interference of its fourth valence pair with the free *p* orbital of N(2). In the free base this should also inhibit its ability to invert, as is indicated in nuclear quadrupole measurements. N(1) may therefore actually be considered as an optically active site produced by steric interference.

Some interesting observations may also be made about the brosyl group. First, the sulfonyl group is nearly tetrahedral with the exception of the angle between the O-S-O bond, which is 123°. Second, the bromine atom is nearly equidistant to the carbon atoms

Table III. Short Intermolecular Approaches*

A1-A2		Type	<i>d</i> , Å	A1-A2		Type	<i>d</i> , Å
A1	A2			A1	A2		
O6	B4	a3	3.53	Br	C8	f3	3.91
O8	C2	a3	3.75	Br	C9	f3	3.81
O7	C3	b2	3.33	Br	C10	f3	3.72
C13	C16	c2	3.39	Br	C11	f3	3.79
C13	N3	c2	3.34	Br	C14	f3	3.89
O6	B3	c3	3.78	Br	N1	f3	3.96
C6	B3	c3	3.89	Ph1	O7	f3	3.84
C8	B3	c3	3.82	Ph2	O7	f3	3.96
C14	B4	c3	3.87	Ph2	O8	f3	3.60
O2	O3	d1	4.00	Ph3	O7	f3	3.60
O2	C14	d1	3.87	Ph4	O8	f3	3.33
O5	C14	d1	3.31	Ph4	C8	f3	3.96
S	C12	d3	3.76	Ph4	C9	f3	3.64
Ph1	C10	d3	3.81	Ph5	O7	f3	3.42
Ph1	C11	d3	3.94	Ph5	C12	f3	3.78
Ph1	C12	d3	3.67	Ph6	O7	f3	3.44
Ph2	C10	d3	3.79	Ph6	O8	f3	3.71
Ph2	C11	d3	3.78	Ph6	C9	f3	3.65
Ph4	C7	d3	3.91	Ph6	C10	f3	3.74
Ph4	C11	d3	3.71	Ph6	C12	f3	3.92
Ph6	C11	d3	3.86	O3	O8	f3	3.94
O1	C12	d3	3.50	O3	C13	f3	3.31
O2	O8	d3	3.77	O6	B1	f3	3.51
O2	C12	d3	3.73	C2	C13	f3	3.87
O2	C13	d3	3.53	C5	B1	f3	3.57
O5	C13	d3	3.03	C6	B1	f3	3.84
O6	B2	d3	3.33	C8	B1	f3	3.86
O5	N3	d4	2.817	C14	B2	f3	3.78
O5	B4	d4	3.68	O3	N3	f4	3.37
O6	B2	d4	3.33	O4	O5	f4	3.65
C16	N3	d4	3.82	O4	N3	f4	3.84
O1	C12	e2	3.46	O6	B1	f4	3.51
O7	O7	e2	3.18	C5	B1	f4	3.57
Ph3	O1	e4	3.40	C6	B1	f4	3.84
Ph5	O1	e4	3.28	C8	B1	f4	3.86
Ph2	B4	f1	3.98	C14	N3	f4	3.58
N3	B3	f1	3.53	C14	B2	f4	3.78
N3	B4	f1	3.62	C14	B3	f4	3.93
O4	C13	f2	3.98	C14	B4	f4	3.83
O5	C13	f2	3.68	O3	O5	g1	3.94
Br	O1	f3	3.97	C14	C15	g1	3.92
Br	C6	f3	3.96				
Br	C7	f3	3.88				

* Type refers to the following positions: 1 = *x*, *y*, *z*; 2 = $-x$, $-y$, $-z$; 3 = $x + 0.5$, $y + 0.5$, z ; 4 = $-x + 0.5$, $y + 0.5$, $-z$, located in the cell whose origin is displaced from the reference unit cell by: a = $-a$, $-b$, 0; b = $-a$, 0, $-c$; c = $-a$, 0, 0; d = 0, $-b$, 0; e = 0, 0, $-c$; f = 0, 0, 0; g = 0, *b*, 0.

forming the quinoid ring of another molecule (see Table III). From the foregoing, it is reasonable to conclude that there is a negative charge present on the oxygen atoms of the sulfonyl group causing the increased O-S-O angle (SO₂ is a more electron-withdrawing group than bromine). The bromine atom in turn compensates for this by interacting with the quinoid system.

The observed N-S distance of 1.663 Å shows that this bond contains some double bond character. No comparison is possible with similar systems since the literature contains only one reference to a N-S bond, that in SO₂(N(CH₃)₂)₂, where it is found to be 1.623 Å.¹¹ A single bond would probably have a length of about 1.73 Å [derived from atomic radii of S (1.04 Å), N (0.74 Å), and an electronegativity correction for N-S of -0.05 Å].

(11) T. Jordan, W. Smith, and W. N. Lipscomb, *Tetrahedron Letters*, 37 (1962).

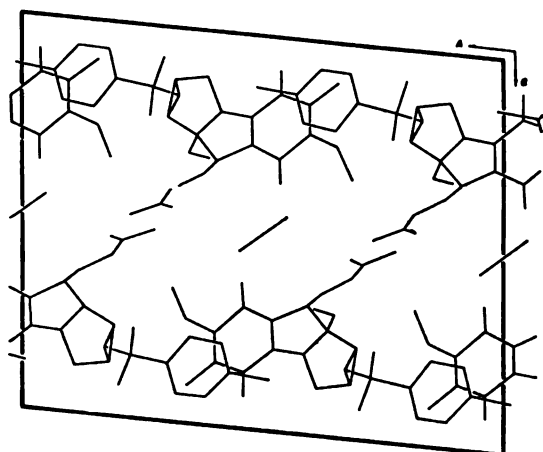


Figure 8. Arrangement of the molecules as viewed along the *b* axis.

Molecular Packing in the Crystal Lattice

The structure is held together *via* infinite chains of hydrogen bonds in the direction of the *b* axis between the side functional groups of different molecules, as may be seen from Figures 6 and 7. The N-H...O distance of 2.817 Å indicates a fairly strong interaction. This hydrogen-bonding scheme provides within each unit cell parts of two sets of these chains which seem to be joined together by the donor-acceptor relationship of the bromine and quinoid groups already discussed. It is within this framework that the benzene molecules of solvation are located in such a way as to provide the greatest number of possible van der Waals contacts. A complete listing of all intermolecular distances smaller than 4 Å is given in Table III. Figure 8 provides a schematic view of the molecular packing as viewed in the direction of the *b* axis and clearly delineates the solvate-containing channels.

Absolute Configuration Determination

At the time when the absolute configuration of the molecule became of interest, the crystal used for data

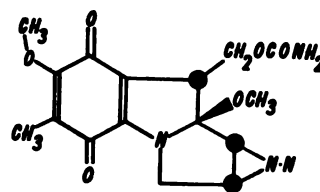


Figure 9. Absolute configuration.

collection was no longer available for intensity measurement of the reflections for which the largest deviations from Friedel's law could be expected. However, it is possible to determine the hand of the molecule without knowledge of these data by computing *R* values for selected sets of reflections with large differences between the calculated structure amplitudes for the two enantiomorphs.¹³

For the 67 reflections with differences of more than 10% $|F_c|$, and magnitudes larger than 15 (electron-scattering units), it was found that when the reflections were assigned as (*hkl*), *R* was calculated as 0.150; however, if they were considered to be of the type ($\bar{h}\bar{k}l$), *R* was 0.122. This procedure was repeated for all reflections with $|F_o|$ larger than 25, in which case the results were 0.153 and 0.109, respectively. This clearly suggests that the hand which was originally chosen was incorrect,¹³ and the absolute configuration of mitomycin A determined in this manner is depicted in Figure 9. In addition to the two *R* values for the large differences it was found that the over-all *R* values (0.094 and 0.087) were also consistent with the above.

Acknowledgment. A. T. is grateful to the National Institutes of Health, U. S. Public Health Service (USPHS 3698), and Lederle Laboratories, Division of the American Cyanamid Company, for supporting this research.

(12) J. H. van den Hende and N. R. Nelson, *J. Am. Chem. Soc.*, **89**, 2901 (1967).

(13) Originally, the reflections were assigned (*hkl*) in a right-handed coordinate system.

Reactions of Carbon Vapor. IV. Reactions of Metastable Carbon Atoms (1S) with Olefins^{1,2}

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Abstract: Carbon atoms have been produced in a low-intensity carbon arc under high vacuum, a method which yields a mixture of ground-state (3P) and metastable excited-state species (1D and 1S). Using a 16-v (ac) arc, the metastables are the most abundant. The chemistry of the 1S species in reactions with olefins is reported here; it reacts with one molecule of olefin by insertion into the double bond to form an allene.

We have previously reported the reactions of olefins with ground-state (3P) carbon atoms produced in a low intensity carbon arc under high vacuum.⁴⁻⁶ We now report on the reactions of these olefinic substrates with carbon atoms in the metastable excited 1S state.

The 1S state of atomic carbon is known to lie 2.7 eV above the ground state.⁷ Yilmaz has predicted the radiative half-life of 1S carbon atoms on purely theoretical bases⁸ to be 2 sec for the process $^1S_0 \rightarrow ^1D_2$.

Calculations using the Boltzmann equation

$$(n_{1S}/n_{3P}) \propto e^{-2.7\text{eV}/kT}$$

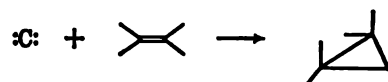
would indicate that at an arc temperature of 5000°K much less than 1% of the vaporized atomic carbon would be in the 1S state. However, Ornstein, *et al.*,⁹ and later Mason¹⁰ found that the distribution among excited states of species Ba⁹, Zn⁹, CN¹⁰ in a low-pressure arc is not described by the Boltzmann relation. Electronic excitations greatly in excess of that predicted from the Boltzmann equation were observed. The explanation given was that excitation was caused by electron bombardment in the absence of an equilibrating medium, *e.g.*, air. This mechanism of excitation has been demonstrated to apply in arc and hot-filament vaporizations of carbon species (unpublished results).

In our system where the pressure in the region of the arc is $\sim 10^{-4}$ torr (mean free path of ~ 50 cm), one might expect significant quantities of atomic carbon in the 1S state to be produced.

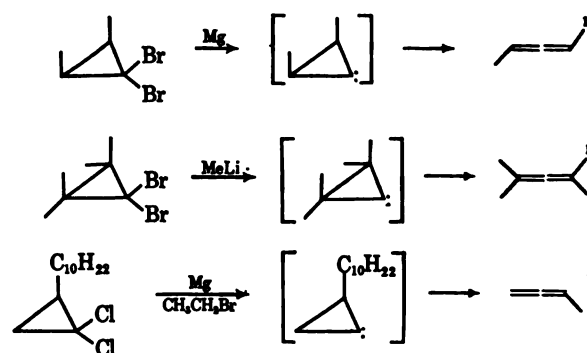
The reactions of ^{13}C , produced by nuclear transformation processes, with ethylene have been extensively studied.¹¹⁻¹⁴ In this system allene has been

found to be an important product (18%). However, owing to difficulties previously discussed,⁶ it is not possible to define which electronic state of carbon is producing the allene.

By analogy with other carbene reagents, a carbon atom would be expected to add to the double bond of an olefinic substrate producing a cyclopropylidene intermediate.



A major reaction pathway for cyclopropylidenes prepared in solution is rearrangement to allenic products.¹⁵⁻¹⁸



However, since these species were generated in the presence of strong Lewis bases in the reaction media, they were probably complexed by these bases and were not "free carbenes." In the system used for our work the species would be expected to be "free" as there is only hydrocarbon present.

This paper describes the reactions of 1S carbon atoms with olefins; the only products in significant amounts are the allenes resulting from insertion of the carbon atom into the double bond.

Method

The carbon arc and molecular flow system used in this study were as previously described.¹⁹ In all of these

(1) For paper III in this series, see: P. S. Skell and R. R. Engel, *J. Am. Chem. Soc.*, **88**, 4883 (1966).

(2) A preliminary communication has appeared: P. S. Skell and R. R. Engel, *ibid.*, **87**, 1135 (1965).

(3) National Science Foundation Cooperative Graduate Fellow, 1963-1966.

(4) P. S. Skell and R. R. Engel, *J. Am. Chem. Soc.*, **87**, 1135 (1965).

(5) P. S. Skell and R. R. Engel, *ibid.*, **87**, 2493 (1965).

(6) R. R. Engel and P. S. Skell, *ibid.*, **88**, 3749 (1966).

(7) G. Herzberg, "Atomic Spectra and Atomic Structure," Dover Publications, New York, N. Y., 1944, p 142.

(8) H. Yilmaz, *Phys. Rev.*, **100**, 1148 (1955).

(9) L. S. Ornstein, H. Brinkmann, and A. Beunes, *Z. Physik*, **77**, 72 (1932).

(10) R. C. Mason, *Physica*, **5**, 777 (1938).

(11) C. MacKay, P. Polack, H. E. Rosenberg, and R. Wolfgang, *J. Am. Chem. Soc.*, **84**, 308 (1962).

(12) J. Dubrin, C. MacKay, and R. Wolfgang, *ibid.*, **86**, 959 (1964).

(13) M. Marshall, C. MacKay, and R. Wolfgang, *ibid.*, **86**, 4741 (1964).

(14) J. Dubrin, C. MacKay, and R. Wolfgang, *ibid.*, **86**, 4747 (1964).

(15) W. von E. Doering and P. M. LaFlamme, *Tetrahedron*, **2**, 75 (1958).

(16) L. Skattebøl, *Tetrahedron Letters*, 167 (1961).

(17) T. L. Logan, *ibid.*, 173 (1961).

(18) L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963).

(19) P. S. Skell, L. D. Wescott, Jr., J. P. Golstein, and R. R. Engel, *J. Am. Chem. Soc.*, **87**, 2829 (1965).

ions a 16-v (ac) arc was employed which produced mixture of ground- and excited-state carbon atoms as well as triatomic carbon. The arc current shows fluctuations in intensity going as high as 100 amp averaging about 40 amp. Time-delay reactions were as previously described using a neopentane matrix.

The allenic products were separated from the excess rate by fractional distillation using a 36×0.5 in. air-jacketed column packed with glass helices, followed by vacuum distillation and gas phase chromatography. They were identified by their infrared mass spectra, measured on the materials collected from the gas chromatograph. A 22-ft column (0.25 in. diameter) of 30% hexamethylphosphorotriamide on Chromopack was used.

Results and Discussion

Electronic State of Carbon Atoms Leading to Time-Delay Studies. In carbon vapor reactions of olefins using continuous arcing with continuous deposition of substrate, the allene, resulting from reaction of the carbon atom into the double bond, was formed to the extent of ~45% of the carbon atom reaction product (*vide infra*), the remainder being distributed among a number of products.

By depositing a layer of neopentane (~2 g) on the liquid nitrogen cooled walls of the reaction flask and operating the carbon arc for a short period of time (~0.3 sec) ~0.3 mg of vaporized carbon can be deposited. This amount of carbon, diffusion into the matrix immediately occurs. If ~5 g of reactive olefin is added later, causing temporary liquefaction of the system, all products found in the "continuous" reaction are present, except for the allenic product which has essentially disappeared. The carbon atom precursors for these have decayed to a lower electronic state in this process.

By noting the amount of allene present after a time delay, ~2%, the half-life of this precursor has been estimated at ~2 sec.²

It is reasonable to assign to the allene-forming carbon atoms the designation of 1S on the following bases: the decay of this species of excited carbon increases the amounts of products resulting from both ground-state (3P) and another excited-state (1D) carbon species; this species brings higher energy to the transition (as is shown by the products, allenes *vs.* cyclopropane ring formation) than the 3P and 1D state species (*infra*).

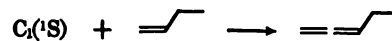
Reaction of 1S Carbon Atoms with Isobutylene. Reaction of $C_1(^1S)$ with isobutylene formed, as the product which can not be attributed to 3P and 3-methyl-1,2-butadiene which was identified by comparison of its infrared and mass spectra with those of the known material. The 3-methyl-1,2-butadiene comprised up to 40 mole % of the atomic carbon reaction products.



using a 16-v (ac) carbon arc.

Reaction of 1S Carbon Atoms with 1-Butene. Reactions with 1-butene yielded a single product, 2-pentadiene, which could be attributed to the $C_1(^1S)$.

It was identified by comparison of its infrared mass spectra with those of the known compound.

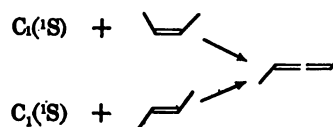


In the reaction using a 16-v (ac) carbon arc, the 1,2-pentadiene made up 45 mole % of the total carbon atom reaction product.

D. Reaction of 1S Carbon Atoms with Propylene. The sole product attributable to the reaction of 1S carbon atoms with propylene was the 1,2-butadiene which accounted for 45 mole % of the total product from carbon atom reactions using a 16-v (ac) arc. It was identified by comparison of its infrared and mass spectra with those of the known compound.



E. Reaction of 1S Carbon Atoms with *cis*- and *trans*-2-Butene. From the reaction of either *cis*- or *trans*-2-butene with 1S state carbon atoms, 2,3-pentadiene is the only product, from *cis*-2-butene 42 mole % and from

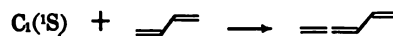


trans-2-butene 43 mole % of the total carbon atom products.

The 2,3-pentadiene was identified by comparison of its infrared and mass spectra with those of the known material.

The earlier report⁴ of this reaction indicated two products from 1S carbon atoms, 2,3-pentadiene and an unidentified substance. The latter, on separation from the other components of this distillation fraction, proved to be 2,3-pentadiene; it had been trapped with the higher boiling reaction products, and its identity was not recognized immediately because different gas chromatography columns were used for further analysis of the low- and high-boiling fractions.

F. Reaction of 1S Carbon Atoms with 1,3-Butadiene. The reaction of 1,3-butadiene with 1S carbon atoms yielded a product not found in 3P and 1D reactions, a single substance easily separated from the excess substrate and assigned the structure of 1,2,4-pentatriene on the basis of its infrared and mass spectra. Its infrared spectrum corresponded to that reported for 1,2,4-pentatriene²⁰ and its low-voltage mass spectrum showed



a parent peak at m/e 66 corresponding to C_5H_6 . Using a 16-v (ac) arc 1,2,4-pentatriene comprises 47 mole % of the total carbon atom reaction products.

G. Competition Reactions of Olefins for 1S Carbon Atoms. Competition reactions were run by equilibrating a known mixture of the olefins in the vacuum line and depositing this mixture on the cooled walls of the reaction flask while arcing. The reaction mixture was handled in the usual manner; product analysis was done by gas chromatography. The relative rates can then be calculated from the relative amounts of products. The results are shown in Table I. Although the differences are small, the order of reactivities

(20) L. Miginiac, *Compt. Rend.*, 247, 2156 (1958).

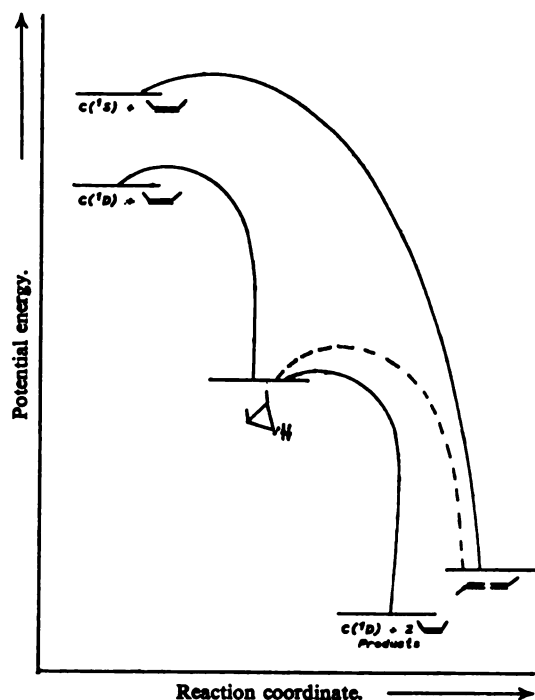


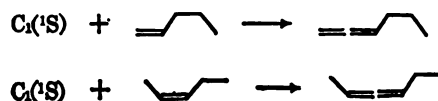
Figure 1. Energy profile for reaction of atomic carbon with olefins.

is in accord²¹ with the proposal of a singlet attacking species of low selectivity.^{22,23}

Table I

Olefin	Rel rate of reaction with $C_1(^1S)$	Product
	1.44	
	1.06	
	1.92	
	5.21	
	(1.00)	

H. Reaction of 1S Carbon Atoms with a Mixture of 1-Pentene and *cis*-2-Pentene. The reaction of 1S carbon atoms with a mixture of 1-pentene and *cis*-2-pentene (ratio of 1.35:1.0) yielded two products, 1,2-hexadiene and 2,3-hexadiene, in the ratio 3.1:1.0. They were identified by comparison of their infrared and mass spectra with those of the known compounds.



These two products accounted for 25% of the *total* carbon vaporized using a 16-v (ac) arc (38% of the atomic carbon).

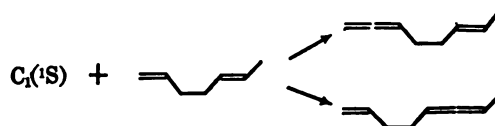
(21) The high relative reactivity of 1-butene is anomalous. Although in the other cases (sections H and I) the α -olefinic site is attacked more readily than the internal site, the differences are not as great as here. We have no explanation for this unusual reactivity.

(22) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956).

(23) W. von E. Doering and W. A. Henderson, Jr., *ibid.*, **80**, 5274 (1958).

This result indicates that the 1S carbon atom reacts 2.3 times as rapidly with the α -olefinic site as with the internal olefinic site.

I. Reaction of 1S Carbon Atoms with 1,5-Heptadiene. From the reaction of 1S atomic carbon with 1,5-heptadiene (one peak on gas chromatograph; presumably one isomer), two products were obtained, 1,2,6-octatriene and 1,5,6-octatriene, which were identified by their infrared and mass spectra.



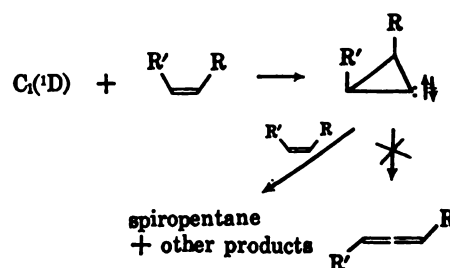
These two products were formed in the ratio 2.7:1.0, insertion into the α -olefinic site being favored over insertion at the internal olefinic site. This result compares favorably with that for a mixture of 1-pentene and *cis*-2-pentene (*vide supra*).

Using a 16-v (ac) arc, these two products accounted for 28% of the *total* carbon vaporized (42% of the atomic carbon).

J. Conclusions. In the time-delay experiments, carbon deposited on a neopentane matrix, using a delay of 15 sec, the only substances not present in the product mixtures being the allenes. After 15 sec most of the 1D atoms are still present; they do not react with olefins to form allenes. Moreover, the decay of the precursor of the allenes enhances the yields of all of the 1D products²⁴ by approximately the same factor, *i.e.*, their total yields are increased but they remain in about the same proportion, except for the spiropentanes (also derived from 1P).

Thus, the 1S carbon atoms are the only species leading to the formation of allenes. Also, it seems as if the allenes account for all or almost all of the 1S carbon produced. Small amounts of the 1D products may be formed from 1S carbon atoms but certainly not large quantities, unless they are coincidentally produced in the same proportions as from the 1D atoms. If such were the case, it would necessitate a common intermediate for the reactions of 1S and 1D carbon atoms which is not in accord with the evidence (*vide infra*).

It has been established that the reaction of 1D carbon atoms with olefinic substrate leads to the formation of a singlet cyclopropylidene intermediate.²⁵ This intermediate then reacts with a second molecule of olefin leading to products. *None* of this intermediate rearranges to allene under our reaction conditions: liquid nitrogen cooling and a high concentration of olefin.

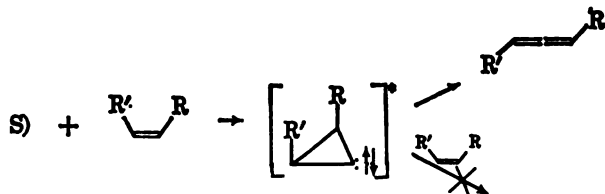


(24) Reports on the details of the reactions of the 1D state will be presented elsewhere.

(25) Reference 2 and unpublished results.

the energy of activation for rearrangement must be lower than the energy of activation for addition to the molecule of olefin (Figure 1). At room temperature in solution rearrangement of singlet cyclopropylenes to allenes takes place readily,¹⁵⁻¹⁸ in competition with olefin addition.

The ¹S atom addition to an olefin should have a resemblance to the ¹D addition, the major difference being the 33-kcal/mole extra energy brought to the transition state by the higher energy atom. If this hot singlet cyclopropylidene were an intermediate of life-time sufficient to permit trapping by olefins, the yields of allenes would vary with changing the substituents and R' since these substituents would be expected to



influence the rate of ring opening to the allene. This is the case, the yields of allenes being 40-47% with variation in substituents reported here. Thus it follows the hot singlet cyclopropylidene is not a trap-

pable intermediate. For ¹S + olefin the cyclopropylidene configuration may only represent a transition state.

Since the activation energy for ring opening of a normal singlet cyclopropylidene (from ¹D) is small, the species in the reactions of C₁(¹S) may bypass this configuration and go directly to the allene; the hot species may not be able to lose its surplus energy fast enough to lead to a thermally equilibrated cyclopropylidene intermediate.

The relative reactivities of olefins in competition for ¹S atoms is not highly informative since the spread of reactivities is small. Perhaps it is most significant that butadiene is less reactive than monoolefins, ruling out transition states with radical character.

An interesting and disturbing feature of these matrix systems must relate to their physical nature. The striking differences in reactivity of CH₃ groups for ¹S insertions in neopentane and isobutane was noted earlier in this study. Perhaps for related reasons the double bond of 1-butene is more reactive than those in propene, 1-pentene, and 1,5-heptadiene (terminal bond). No electronic rationalization of this effect is apparent.

Acknowledgment. We acknowledge the financial support of the Air Force Office of Scientific Research and the Army Research Office (Durham).

A Simple Theory for Predicting the Effects of Substituent Changes on Transition-State Geometry^{1,2}

Edward R. Thornton

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania. Received December 5, 1966

Abstract: A simple technique for analyzing the effects of substituent changes on transition-state geometry is outlined. The basic idea is to consider the effects of substituents as linear perturbations of the vibrational potentials for the normal coordinate motions both parallel to and perpendicular to the reaction coordinate motion. Effects parallel to the reaction coordinate then correspond closely to predictions based on "Hammond's postulate," while effects perpendicular to the reaction coordinate introduce a previously neglected effect which is expected to be smaller than the parallel effect in many, but not all, cases. Examples of application of the theory to S_N2, E2, S_N1, and other reaction mechanisms are presented. The theory is discussed in terms of the forces on nuclei predicted by the Hellmann-Feynman theorem. Using precise potential energy curves for diatomic molecules calculated by computer from spectroscopic data, it is concluded that the approximation that the perturbation is linear, if a relatively small substituent change is made, is probably a very good one. The result is: (1) any substituent change which makes an increase (decrease) in the normal coordinate *X* of a molecule or transition state more difficult will lead to a perturbed equilibrium geometry in which *X* is decreased (increased) if the force constant for *X* motion is positive, but in which *X* is increased (decreased) if the force constant for *X* motion is negative; (2) the effect of a substituent change on a normal coordinate motion can be predicted from the effect of the substituent on the reacting bond(s) nearest to the substituent and involved in that motion; (3) when two reacting bonds are equidistant from the substituent, the effect of the substituent should be nearly equal on both if both are of the same strength in the unperturbed transition state, but should be greater on the stronger than on the weaker (and greater on a σ than on a π bond); (4) an electron-supplying (withdrawing) substituent should make a bond more difficult to extend (compress) if attached to the basic, *i.e.*, more electronegative atom, end of the bond, but more difficult to compress (extend) if attached to the acidic, *i.e.*, less electronegative atom, end of the bond; (5) the substituent effect on geometry is the sum of individual effects on each normal coordinate.

Since substituent effects upon a stable molecule's structure, energy, and other properties are reasonably well understood in a qualitative way, it is fascinating to try to apply this qualitative understanding to

) Supported in part by the Atomic Energy Commission (Contract

predict the effects of the substituents on the structure, energy, and other properties of transition states, or

No. AT(30-1)-3041) and by the National Science Foundation (Grants No. GP-2937 and GP-6047).

(2) Cf. (a) L. J. Steff and E. R. Thornton, to be published; (b) G. J. Frisone and E. R. Thornton, to be published.

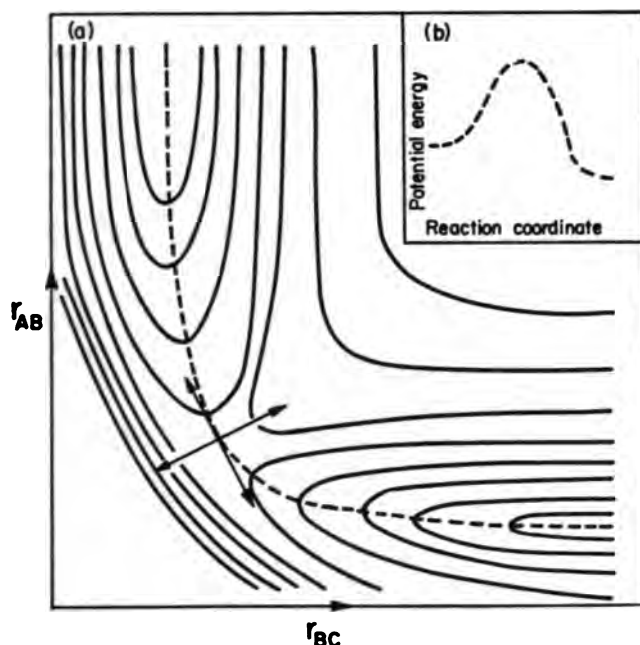


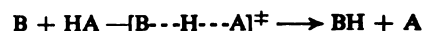
Figure 1. (a) Contour surface for the reaction $A + BC \rightarrow AB + C$. Contours of constant (electronic) potential energy for nuclear displacement plotted as a function of the bond distances r_{AB} and r_{BC} . The reaction coordinate is the dashed line. Parallel and perpendicular motions are shown as double-headed arrows. The reaction is assumed to proceed without any bending of the ABC angle from 180° , so that the potential energy depends only on r_{AB} and r_{BC} . (b) Plot of potential energy vs. distance along the reaction coordinate.

activated complexes, for various reactions. The relative success of transition-state theory³ in describing and making predictions about rates and mechanisms of thermal reactions, together with the considerable (though approximate) theoretical justification of the method, make it reasonable to discuss reaction mechanisms in terms of a transition state of definite geometry corresponding to the point of highest electronic energy⁴ along the most favorable path by which reacting molecules may be converted into products. Other, necessarily higher energy, reaction paths exist which do not pass through the transition-state geometry.

The motion corresponding to the reaction coordinate which has negative restoring force at the transition

state is shown as a dashed line in Figure 1 for the simple case of a linear approach of A to BC, A displacing C.

Since a transition state is defined as being at a potential energy extremum (saddle point) and, therefore, its internal nuclear motions consist of vibrations analogous to the normal vibrations of stable molecules in the sense that, at the geometry of the extremum, no forces act on the nuclei, it is not unreasonable to suppose that structural predictions based on principles established for stable molecules would carry over in considerable detail to transition states. The "Hammond postulate"⁵ and various extensions⁶ have been used to make predictions about transition-state geometry from reactant, intermediate, and/or product geometries and enthalpies of reaction. A noteworthy, early example of the application of principles similar to those of the Hammond postulate is the explanation of the Brønsted catalysis law⁷ in terms of the crossing of potential energy curves for the bonds being made and broken in a proton-transfer reaction, e.g.



Although these generalizations seem fundamentally reliable, certain experimental results seem to conflict⁸ with predictions, and a "rule" has been suggested⁹ which seemed to correlate all known data. In analyzing the results of our^{2a} and other studies of E2 (elimination, bimolecular) reactions, certain ambiguities and inconsistencies were discovered. A major ambiguity is that the statement of this rule⁹ in terms of "reacting bonds" and "reacting orbitals" implicitly assumed that there was only one reacting bond in a single reacting orbital, whereas E2 transition states clearly involve more than one. It might be possible to modify the rule to eliminate the ambiguity. However, the present author believes there are inconsistencies in the (admittedly *a posteriori*) theoretical model, the major one being the assumption that because supplying electrons to, say, the X group of a X-Y bond is expected to make that bond longer at the transition state (of a reaction in which that bond is being made or broken), the increased X-Y bond length implies a decreased electron supply at Y. It now seems almost certain that supply of electrons to X would, while increasing the X-Y bond length, nevertheless *increase* the electron supply at Y;⁹ the predictions of the rule would then be reversed in certain cases.

Although approximate models tend to justify it, an assumption equivalent to the idea that "if a bond is

(3) Cf. S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941; H. Eyring, D. Henderson, B. J. Stover, and E. M. Eyring, "Statistical Mechanics and Dynamics," John Wiley and Sons, Inc., New York, N. Y., 1964; H. Eyring and E. M. Eyring, "Modern Chemical Kinetics," Reinhold Publishing Corp., New York, N. Y., 1963; K. J. Laidler and J. C. Polanyi, *Progr. Reaction Kinetics*, 3, 1 (1965); J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963; M. M. Kreevoy in "Investigation of Rates and Mechanisms of Reactions," Part II, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter XXIII; also several other chapters in Parts I and II; "The Transition State," Special Publication No. 16, The Chemical Society, London, 1962; D. Rapp, "On Experimental Tests of the Validity of the Transition State Theory of Chemical Reaction Rates," Report 6-90-62-126, Lockheed Missile and Space Company, Sunnyvale, Calif., 1962; H. S. Johnston, *Advan. Chem., Phys.*, 3, 131 (1960); "Gas Phase Reaction Rate Theory," The Ronald Press Co., New York, N. Y., 1966; V. N. Kondrat'ev, "Chemical Kinetics of Gas Reactions," Pergamon Press and Addison-Wesley Publishing Co., Inc., Reading, Mass., 1964; E. R. Thornton, "Solvolysis Mechanisms," The Ronald Press Co., New York, N. Y., 1964.

(4) The electronic energy as a function of nuclear geometry is, of course, in the (Born-Oppenheimer) approximation that electron motion is always very fast relative to nuclear motion, used as the potential energy for nuclear motions.

(5) G. S. Hammond, *J. Am. Chem. Soc.*, 77, 334 (1955): "If two states, as, for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structures." A less well-known, but earlier, statement of a similar principle is given by J. E. Leffler, *Science*, 117, 340 (1953).

(6) K. B. Wiberg, *Chem. Rev.*, 55, 733, 737 (1955); A. Streitwieser, Jr., *ibid.*, 56, 571 (1956).

(7) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter X; R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, Chapter VIII; J. Horvut and M. Polanyi, *Acta Physicochim. URSS*, 2, 505 (1935); R. P. Bell, *Proc. Roy. Soc. (London)*, A154, 414 (1936).

(8) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, 84, 817 (1962).

(9) This conclusion can be approximately justified by considering that the primary effect will be electron supply to X and therefore to Y. The primary effect will be partly offset by the secondary effect of increased X-Y bond length, but only partly offset because in the Born-Oppenheimer approximation electron motions determine the motions (and, therefore, the average positions) of the nuclei, not the other way around.

harder to break, it will become more broken at the transition state" is usually required for such predictions. This type of assumption is very hard to justify in its full form because of the property of a transition state: its energy is the *minimal energy maximum*, i.e., the maximum barrier required by the most favorable reaction path. Expressing the properties of functions that have simultaneous minima in one or more dimensions and maxima in another is difficult to do in any way which leads to generalizations.

The problems which arose in application of the above generalizations made it seem likely that a new approach was required. The basic innovation of the "rule" was consideration of transition-state structural effects directly, rather than by comparison with reactants, products, or intermediates, all of which differ in energy by relatively large amounts from the transition state.¹⁰ The prediction of the effect of substituents on transition-state structure, if possible, was clearly desirable. It then became obvious that previous generalizations had largely considered such effects in terms of geometric changes "along the reaction coordinate," i.e., changes in fraction of product-like character of the transition state, and had all but ignored effects upon all modes of *vibration* of the transition state, i.e., of the transition-state geometry perpendicular to the reaction coordinate. These "parallel" and "perpendicular" directions are shown as arrows in Figure 1, corresponding to the tangent to the reaction coordinate at the transition-state point and the perpendicular to the tangent. In the simple case illustrated in Figure 1, where there are only two geometric variables—two bond lengths—it can be seen that the parallel motion stretches one bond while compressing the other, while the perpendicular motion either stretches or compresses both bonds simultaneously.

A simple perturbation method has emerged which (at least in principle) takes account of both parallel and perpendicular shifts in transition-state geometry. It is outlined, illustrated, criticized, and approximately justified in the following sections.

Simple Perturbation Method. In analyzing the effect of a substituent on a transition state, we are interested in determining the effect on each bond in turn. This will be quite straightforward for a stable molecule in which one had adequate empirical and theoretical data to predict how a substituent (say, electron supply) should change the force constant or bond strength (of each type of bond). For a transition state there is the complication that motion of the nuclei along the reaction coordinate is not a truly vibrational motion (it has a negative restoring force), though motion corresponding to all the other normal vibrations of the transition state is truly vibrational (with positive restoring force). Substituent effects upon motions with both positive and negative restoring forces turn out to have quite different geometric effects; therefore, one must consider which nuclei actually move in the reaction coordinate motion.

The nuclei of the transition state may in principle

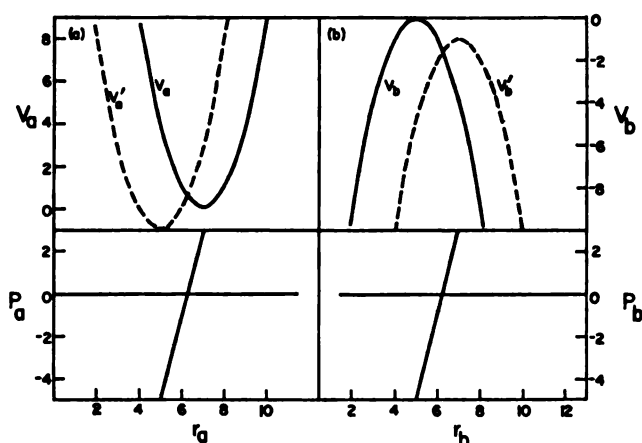


Figure 2. Plots of parabolic potentials, V , together with the perturbations, P , which, when added to V , give the new parabolic potentials, V' . Note that the slope of P_a is exactly equal to the slope of P_b . (a) Effect expected for perpendicular motion; (b) effect for parallel motion.

move during the reaction coordinate motion (though some may be prohibited from moving by symmetry), but the major displacements will undoubtedly be of those nuclei which participate in bonds that are being made or broken during the course of reaction. Such *reacting bonds*⁸ can be singled out for study. It can be assumed that groups attached through nonreacting bonds to the nuclei involved in the reacting bonds will approximately follow along with those nuclei as the reacting bonds undergo reaction-coordinate motion. Furthermore, if the reaction coordinate motion involves largely changes in length of reacting bonds (as would be the case in many reactions), bending motions may reasonably be left out of consideration. The case where only one reacting bond is present (relatively unusual) is simplest. In this case the only important motion corresponding to the reaction coordinate is the stretching (for a dissociation reaction) or compression (for an association reaction) of the reacting bond. A plot of energy vs. bond length will then look like the curve in Figure 1b, but the abscissa will not be the curved reaction coordinate shown for the displacement reaction of Figure 1a; the abscissa will simply be the length of the reacting bond.

The vibrational energy of a molecule is a nearly quadratic function of the displacement of the nuclei from their equilibrium positions. The effect of a substituent upon one of the bonds of a molecule is to make small changes in energy, equilibrium bond length, and force constant. Since such effects are relatively small, it can be expected that they will be approximately described by the addition of a linear function of distance to the reference, "unperturbed" curve.¹² The result for a model with a parabolic potential energy function and an exactly linear perturbation is shown in Figure 2a. The shift in the energy of the extremum is caused mainly by the vertical position of the linear perturbation, but the extremum also shifts to longer or

¹⁰ The danger of "crossover" effects (or even "double-cross" effects) in potential energy curves for differently substituted systems is considerable in some cases.¹¹

¹¹ J. D. Roberts, "Notes on Molecular Orbital Calculations," Benjamin, Inc., New York, N. Y., 1962, p 93; R. D. Brown, *Rev. (London)*, **6**, 72 (1952).

¹² This approach was originally suggested by a discussion of secondary isotope effects in terms of such perturbations, given by E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963). A similar technique has also been used for discussion of the changes in geometry and energy of ordinary molecules upon addition or removal of an electron to form ions and upon electronic excitation: J. P. Malrieu, *Theoret. Chim. Acta*, **4**, 434 (1966).

shorter bond length. The same perturbation in fact causes a greater shift of bond length the less the curvature of the unperturbed curve, as will be shown below. The effect of substituents on bond geometry can, therefore, be predicted (approximately, of course) as in Figure 2a by empirically or theoretically estimating the slope (sign and magnitude) of the perturbation. Although it is assumed that the perturbation is linear, the *direction* of the effect is dependent mainly on the slope (positive or negative) of the perturbation at the point of the unperturbed extremum.

In the case of Figure 2a, if we assume that the perturbation slope was caused by adding an electron-supplying substituent to the molecule, it can be interpreted as follows: the electron-supplying substituent makes bond extension more difficult and bond compression easier. Such an effect probably explains the effects of substituents on the O-H stretching vibrations of substituted phenols;¹³ electron-supplying substituents in the phenyl ring increase the vibration frequency.

In the case of a transition state, the potential energy as a function of distance along the reaction coordinate (Figure 1b) can be approximated as an inverted parabola in the region of the potential energy maximum, as shown in Figure 2b. There is no theoretical reason why the effects of substituents in perturbing the potential energy along the reaction coordinate should be different from substituent effects on true molecular vibrations. The same linear perturbation shown in Figure 2a produces the dashed curve of Figure 2b, and it can be assumed with considerable confidence that the resulting change in geometry would be observed for a substituent change which made motion (from left to right) along the reaction coordinate *more difficult*.

Empirical data, which will aid in making predictions about ionic reactions where charge accumulation or dispersal occurs, are available; prediction is more difficult for radical or molecular reactions. Hopefully, further data on stable molecules, such as effects of substituents on vibrational frequencies, will give predictions of the direction of the perturbation for most kinds of bonds.

The basic ideas described can readily be applied to reactions having more than one reacting bond. Several reacting bonds can be considered simultaneously by considering the normal vibrations of the transition state and estimating the effects of substituents on the normal vibrations,¹⁴ e.g., the parallel and perpendicular motions in Figure 1a. Each normal vibration can be considered to have a potential energy curve as a function of normal coordinate displacement similar to Figure 2a, except the reaction coordinate motion, which will be similar to Figure 2b.

In many cases only the reacting bonds closest to the substituent will be important in determining the perturbation, provided one can estimate their relative displacements in the normal coordinate motions. It is essential to consider at least two reacting bonds simultaneously if they are equidistant from the substituent,

(13) L. L. Ingraham, J. Corse, G. F. Bailey, and F. Stitt, *J. Am. Chem. Soc.*, **74**, 2297 (1952).

(14) This, of course, assumes that the forces are simply harmonic, i.e., linear in displacement, and so is an approximation. Also, it will be noted that this is a classical, not quantum mechanical, idea. However, the quantum mechanical solution of the problem of describing nuclear vibrations nevertheless utilizes normal coordinates.

e.g., if substitution were made at B in the reaction $A + BC \rightarrow AB + C$, where AB and BC were reacting bonds and are equidistant (both terminate at atom B) from the substituent.

The net effect of a substituent on transition-state geometry can be obtained by estimating the position of the perturbed extremum along each normal coordinate as in Figure 2 and then adding the effects for all normal coordinates to find the total. Again it should be noted that, to a very good approximation, only those normal coordinates involving reacting bonds and/or nuclei near the substituent will add appreciably to the total.¹⁵ The ideas just described are best explained by concrete examples, but before discussing examples, some of the qualitative ideas suggested should be examined in more detail.

The constructions in Figure 2 can be expressed algebraically. If the unperturbed extremum is placed at the origin, the assumption that the unperturbed curve is parabolic and that the perturbation is linear gives

$$V = \frac{1}{2}kX^2$$

$$P = mX + b \quad (1)$$

$$V' = \frac{1}{2}kX^2 + mX + b \quad (2)$$

where V is the unperturbed energy (solid line), k is the force constant (>0 for Figure 2a, <0 for Figure 2b), X is the deviation of the normal coordinate from its equilibrium value (the equilibrium geometry is usually defined as $X = 0$ for all normal coordinates of a molecule), P is the (linear) perturbation, m the slope and b the intercept of P , and V' is the perturbed energy (dashed line). By setting the derivative of V' with respect to X equal to zero, the extremum of the perturbed curve (which is also a parabola) can be seen to be¹² at

$$X_{ex} = -m/k \quad (3)$$

For example, positive m gives a shorter bond for positive k , a longer bond for negative k , as shown in Figure 2. The shift in energy of the extremum is, substituting eq 3 into eq 2

$$V'_{ex} = b - m^2/2k$$

It can be seen from eq 3 that at constant m the shift of bond length is greater for smaller absolute values of k . Also the curvature or force constant is given by the second derivative of V with respect to X and can be seen to be unchanged (k) on going from the unperturbed to the perturbed curve. It can be seen that if the perturbation were given by a smooth curve rather than a straight line, the curvature of the perturbed curve V' would be different from k , but that the *direction* of the shift X_{ex} would depend only on the slope (positive or negative) of the perturbation at $X = 0$, the position of the unperturbed extremum, even though the perturbation were nonlinear.

Since it is known that real molecules have potential curves that are fairly well represented by parabolas, and since molecular anharmonicities are always in the same direction, the perturbation P is likely to be a very nearly linear function. It then seems interesting to see

(15) A striking example of such a "cutoff" procedure's having negligible effects upon kinetic isotope effect calculations is given by M. Wolfberg and M. J. Stern, *Pure Appl. Chem.*, **8**, 225, 325 (1964).

results if P is linear but the potential function V is somewhat anharmonic, as the next better approximation to substituent effects. In this case an anharmonic potential proportional to X^3 should be added, giving

$$V = \frac{1}{2}kX^2 + gX^3$$

$$P = mX + b$$

$$V' = \frac{1}{2}kX^2 + gX^3 + mX + b$$

where g is the anharmonicity constant. Now setting the derivative of V' with respect to X equal to zero, the maximum of the perturbed curve can be seen to be at

$$X_{\text{ex}} = [-k + (k^2 - 12mg)^{1/2}]/6g$$

for positive k and at

$$X_{\text{ex}} = [-k - (k^2 - 12mg)^{1/2}]/6g$$

for negative k . The force constant for both curves is V' is given by $k + 6gX$ and is thus a function of X . For the unperturbed extremum ($X = 0$), the force constant is k . For the perturbed extremum ($X = X_{\text{ex}}$), the force constant is $(k^2 - 12mg)^{1/2}$ for positive k and $-(k^2 - 12mg)^{1/2}$ for negative k . This model predicts a shorter bond for positive m and k , just as the usual harmonic model did. The anharmonic model is more realistic, at least for bond stretching vibrations, predicting a smaller absolute value of force constant for greater X (since g is negative for bond stretching). It is expected that longer bonds (positive X_{ex}) will both be weaker and have weaker force constants.

A very interesting point is that, apparently, anharmonicity of V should be more important in determining the change of force constant upon substitution than the nonlinearity of the perturbation, for the following reason. It can be expected that the nonlinearity of P in the direction that it will drop off more slowly as X increases (for bond stretching reaching an asymptotic value at the separated atoms, *i.e.*, complete bond rupture. But this direction is such that it would tend to increase the force constant for positive X_{ex} (negative m , for positive k) and decrease the force constant for negative X_{ex} (positive m , for positive k). This direction is opposite to what is usually expected, that longer bonds are in general weaker and have weaker force constants. It must, therefore, be concluded that the anharmonicity represented by g will usually override the possible effect of nonlinearity of P !

Another point that should be justified is that the total effect of the substituent can be obtained by summation of the effects predicted for individual (harmonic) normal coordinates. By definition the individual P effects contribute additively to the energy.

$$V' = \sum_i (\frac{1}{2}k_i X_i^2 + m_i X_i + b_i)$$

The extremum of a function of more than one variable is found by setting the partial derivative of the function with respect to each variable equal to zero

$$m_i + k_i X_i = 0 \text{ (for all } i\text{)}$$

the perturbed extremum is at the position

$$(X_i)_{\text{ex}} = -m_i/k_i$$

each normal coordinate (neglecting anharmonicity), and at the point of the potential energy hyperspace with

"coordinates" $(V'_{\text{ex}}, (X_1)_{\text{ex}}, (X_2)_{\text{ex}}, \dots, (X_{3N-6})_{\text{ex}})$, since a nonlinear molecule has $3N - 6$ normal vibrations. The position in hyperspace can be reached by vector addition of the displacements $(X_i)_{\text{ex}}$. For example, with two normal coordinates (as in Figure 1) the perturbed extremum is reached by moving along X_1 to $(X_1)_{\text{ex}}$ and then perpendicular to X_1 (*i.e.*, in the direction of X_2) to a distance of $(X_2)_{\text{ex}}$, or equivalently along X_2 first, then perpendicular to X_2 . The result of such a movement to the new extremum in hyperspace can be described in three-dimensional space, of course, since the $(X_i)_{\text{ex}}$ are known functions of the $3N$ coordinates of the N nuclei. The effects of each normal coordinate shift upon each of the three coordinates of each nucleus can be simply added together to produce the total shift of that coordinate of that nucleus.

For the harmonic approximation, the normal coordinates associated with the perturbed extremum are exactly the same as the X_i (for the unperturbed extremum). This must be so, because all masses and force constants are unchanged. It can easily be shown that if new normal coordinates are defined as

$$X'_i = X_i - (X_i)_{\text{ex}}$$

then

$$V' - V'_{\text{ex}} = \sum_i \frac{1}{2}k_i (X'_i)^2$$

and, therefore, the X'_i are indeed normal coordinates (an alternative definition of normal coordinates being that the potential energy is proportional to the squares of the coordinates, with no cross-terms proportional to $X_i X_j$).

Rule for Predicting Geometric Changes. The predictions of this theory can be stated concisely. Any substituent change which makes an increase (decrease) in the normal coordinate X of a molecule or transition state more difficult will lead to a perturbed equilibrium geometry in which X is decreased (increased) if the force constant for X motion is positive, but in which X is increased (decreased) if the force constant for X motion is negative.

It remains to decide whether a given substituent change will make the increase or the decrease of a given normal coordinate X more difficult. Qualitatively, it would appear reliable to consider the individual bonds which are being stretched or compressed in motion X ; further, the major effect should be upon those reacting bonds which are closest to the substituent. Nonreacting bonds which are close to the substituent could, of course, be considered but will usually be ignored in practice, and the reacting bonds will be singled out for study, as discussed in the previous section.

The valence-bond concept pictures bonds with varying amounts of covalent and ionic character. It is found, at least for diatomic molecules, that bonds between unlike atoms show greater bond energy than might be expected for "homonuclear-type" covalent bonds¹⁶ (*e.g.*, as calculated for bond A-B from the geometric mean of the A-A and B-B bond energies). This "excess" bond energy can be attributed to ionic character, tending to stabilize bonds between unlike atoms, and has been used as a definition of electro-

(16) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, Chapter 3.

negativity.¹⁶ A reasonable extrapolation suggests that any substituent change which makes a given bond "more homonuclear", i.e., lessens ionic character, will tend to make that bond more difficult to compress (and weaker). For example, in the molecule



where the atom of group B which is bonded to group A is assumed to be more electronegative than the atom of group A to which the former is bonded, it is predicted that an electron-supplying substituent would (a) if in group B tend to make both B and A more negative but have a larger effect on B than A, thus increasing ionic character and making the A-B bond more difficult to extend (and, of course, easier to compress), or (b) if in group A tend to make both B and A more negative but have a larger effect on A than B, thus decreasing ionic character and making the A-B bond more difficult to compress (and, of course, easier to extend). There is one point where electronegativities of the free atoms may not give proper results: if the substituent change also changes the charge type. The electronegativity of the atom "in the molecule" is what is needed. For example, the following substituent change



where the C-Cl and C-N bonds are reacting bonds and where Cl and N both have electronegativity 3.0 as elements, is a case where one would have to be very careful in making predictions. The charge distribution changes from the Cl substituent's being negative relative to carbon to the $\text{N}^+(\text{CH}_3)_3$ substituent's being positive relative to carbon, even though the positive nitrogen should be more electronegative than 3.0. In such a case, it is probably best to use the acid-base properties ($\text{N}(\text{CH}_3)_3$ being a stronger base than Cl^- in usual types of solvents), as discussed in the next paragraph. Obviously the solvent effect will be quite strong here, for polar solvation will affect little the basicity of neutral bases and decrease the basicity of negatively charged bases. The substituent effect in the gas phase could be different—even opposite—from the effect at the other extreme, say extrapolated to infinite dielectric constant. The effects for real solvents would be between the extremes, but difficult to predict theoretically. The experimental criterion of basicity can be tentatively used, but its reliability can and should be tested experimentally. Such problems as this arise only when the substituent change is unusually drastic, almost never unless one of the atoms of a reacting bond is changed.

Acid-base concepts lead to the same predictions. In the above example, B would be pictured as the basic group since it is more electronegative than A; A would be pictured as the acidic group. Supply of electrons to B should make it more basic and make the A-B bond more difficult to extend, while supply of electrons to A should make it less acidic and make the A-B bond more difficult to compress. Basicity toward a proton seems to be a good criterion⁸ and has the advantage of simplicity: e.g., absence of steric effects. Other workers have concluded¹⁷ that leaving group ability is a more appropriate criterion, on the basis that leaving group ability, measured for the reaction in ques-

(17) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, **87**, 1553 (1965).

tion, takes account of steric effects. However, the theory described in the present paper takes account of steric effects directly by consideration of their effects on normal vibrations; it is thus more appropriate to have a measure of electrical effects which includes as little steric component as possible.

It is important to keep separate the two aspects of this theory. The first, the idea of estimating the perturbation and adding it to the unperturbed curve, is a rigorously correct approach because the perturbation (though the correct perturbation may not be linear) is by definition the difference between the unperturbed and the correct perturbed curve. The second aspect, the ideas that the perturbation may be considered nearly linear and that the slope of the perturbation may be estimated from ordinary bonding concepts, may have exceptions. The crucial question in the latter case is probably whether the bonding concepts which are reasonably reliable for stable molecules can also be applied to transition states. We believe and assume that they can, because as long as one is considering differences between substituents, there seems to be no theoretical reason that transition-state effects should differ from stable molecule effects. The only source of difficulty would seem to be if the usually long, weak reacting bonds in a transition-state structure were sufficiently different from the usually shorter, stronger bonds in stable molecules that certain predictions were made incorrectly. All indications are that there is a continuous change in bonding with bond distance,¹⁸ however.

One other point should be mentioned, that the predictions made are for changes in transition-state structure, while most experimental information (rates, solvent effects, Brønsted coefficients, kinetic isotope effects) refers to the difference between reactant(s) and transition state. The correct approach would be to make predictions for all normal coordinates of both reactant(s) and transition state. However, it can be expected that substituent effects on nonreacting bonds will be small and also nearly the same for reactant and transition state. Evidence that this is so comes from studies of substituent and solvent effects on secondary deuterium isotope effects;¹⁹ such effects are quite small. These effects could nevertheless be estimated by the present theory provided the perturbations for reactant and transition state could be predicted accurately. It is the reacting bonds which differ greatly from the bonds of the reactant(s),²⁰ being much weaker in the transition state (for bonds being broken) or much stronger in the transition state (for bonds being made). Also, since the transition-state reacting bonds will be weak in most cases, substituent effects on geometry are expected to be much larger than for ordinary, strong bonds because the curvature k of the potential

(18) For example, it has been shown that Badger's rule for predicting force constants from bond lengths is reliable not only for ground states of molecules, but also for excited states and even van der Waals interactions: R. M. Badger, *J. Chem. Phys.*, **2**, 128 (1934); **3**, 710 (1935); *Phys. Rev.*, **48**, 284 (1935); D. R. Herschbach and V. W. Laurie, *J. Chem. Phys.*, **35**, 458 (1961); H. S. Johnston, *J. Am. Chem. Soc.*, **86**, 1643 (1964).

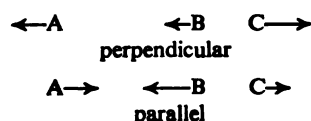
(19) W. E. Buddenbaum, Ph.D. Thesis, University of Indiana, 1964; V. J. Shiner, Jr., and G. S. Kriz, Jr., *J. Am. Chem. Soc.*, **86**, 2643 (1964); G. J. Frisone and E. R. Thornton, *ibid.*, **86**, 1900 (1964).

(20) Unless the transition state is exceedingly reactant-like, in which case no substituent effect difference between reactant(s) and transition state is predicted.

function will be less for normal coordinates of weak bonds (cf. eq 3). To the extent that substituent effects on reactant bonds are very small,²¹ this should be true except when the substituent change involves changes one of the atoms of the bond being considered (e.g., comparison of C-Br with C-Cl), the effects observed experimentally will be predicted by the inclusion of substituent effects on the transition state.

Examples. The above method of predicting substituent effects is in agreement with Hammond's postulate in all cases where the substituent effect is expected to develop largely along the reaction coordinate—which are the only cases for which the Hammond postulate has been developed—but also, upon inclusion of perpendicular effects, is in agreement with all reasonably known experimental evidence on substituent effects. An important example is SN2 nucleophilic displacement.

A displacement reaction is illustrated in Figure 1. It can be seen that the normal coordinates of the transition state are approximately



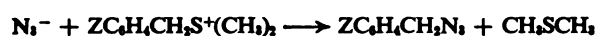
stretching of the reacting bonds. Bending will be considered in a later paragraph; it should be included in cases where the activated complex is made nonlinear by steric effects.²² The theory predicts, for substituents at A, that electron supply will make the perpendicular normal vibration shown (A-B bond extended) more difficult and the parallel normal vibration shown (A-B bond compressed) less difficult. The substituent effect should be determined by the bond, because it is closer to the site of substitution. The perturbation should therefore decrease the normal coordinate corresponding to the perpendicular vibration, i.e., shorten the A-B and B-C bonds (since the constant is positive), and decrease the normal coordinate corresponding to the parallel vibration, lengthen the A-B bond and shorten the B-C bond (since the force constant is negative). In a concerted displacement, it is probable that the curvature of the potential energy surface is considerably smaller parallel than for perpendicular motion;²³ the geo-shift is then expected to be determined largely by parallel motion (cf. eq 3), and the A-B bond will be lengthened while the B-C bond should be shortened by electron supply at A.²⁴ The same result should be predicted for the reverse reaction, where electron supply to A, which is then the leaving

group: that the parallel motion ought to lengthen the A-B bond and shorten the B-C bond. For substitution in entering or leaving group, the effects of parallel and perpendicular vibrations are predicted to oppose one another with respect to the bond closest to the substituted group (A-B in the above example) and to reinforce one another with respect to the bond once removed from the substituted group (B-C in the above example). It is not now possible to predict what experimental effect this interesting prediction should have, because the opposed effects occur upon the bond which should inherently be the more sensitive to substituents since it is closer to the site of substitution. It would also be possible to substitute B in the SN2 displacement reaction. In this case electron supply to B should make the perpendicular vibration shown less difficult and have a small effect on the parallel vibration. The effect on the parallel vibration should be small because it should be approximately equal but opposite for the two bonds involved in the parallel normal coordinate (making compression of A-B more difficult and stretching of B-C less difficult). If the reaction were a perfectly symmetric, concerted displacement, $A + BA$, the parallel effect would be exactly zero by symmetry. The substituent effect should, therefore, be determined by the effect on the perpendicular motion (and is for this reason opposite to Hammond postulate extensions), at least for fairly symmetrical transition states. For nonsymmetrical SN2 transition states, it seems likely, in analogy with Brønsted catalytic effects, that the effect would be greater on the stronger of the A-B and B-C bonds, so that the parallel motion could become important. A theoretical study of the symmetrical and nonsymmetrical cases would be very interesting. The perturbation for the former case of fairly symmetrical transition states should, therefore, increase the normal coordinate corresponding to the perpendicular vibration, i.e., lengthen the A-B and B-C bonds, and this should be the most important substituent effect. This latter effect may be quite small relative to the parallel effects in cases such as substituents at A, because the curvature of the potential energy is likely to be relatively large for perpendicular motion. The predicted pattern of substituent effects is consistent with the experimental data. For example, the chlorine kinetic isotope effect k_{35}/k_{37} for reaction of cyanide ion (1.0060), thiosulfate ion (1.0058), and water (1.0078) with *p*-chlorobenzyl chloride in 80% aqueous dioxane at 30° was found²⁵ to be largest for the weakest base water. It might be expected that the cyanide isotope effect would be smallest since it is the strongest base; however, this reaction was complicated by concurrent hydrolysis (did not exhibit precisely second-order kinetics) and the isotope effect is, therefore, an average containing some contribution from the high water isotope effect. The solvent isotope effects for CH_3Cl and CH_3Br in H_2O vs. D_2O indicate that O-C bond making is more complete for CH_3Cl .²⁶ This is a case where the substituent change involves an atom of one of the reacting bonds. The prediction for the change from Cl to Br is, in the case of the reactants, that C-X bond stretching will be made easier, i.e., that the C-Br bond will be longer than the C-Cl bond, as is known to be the case

²¹ For example, C. G. Swain, R. F. W. Bader, R. M. Esteve, Jr., V. Griffin, *J. Am. Chem. Soc.*, **83**, 1951 (1961).
²² See C. K. Ingold, *Quart. Rev.* (London), **11**, 1 (1957).
²³ The ratio of curvatures is ca. 3-5 for typical surfaces for H_2 , probably the only three-center transition state for which moderate surfaces are available; see F. S. Klein, A. Persky, and R. M. Jones, Jr., *J. Chem. Phys.*, **41**, 1799 (1964). Also, it should be noted that the success of transition-state theory itself probably rests in the relative flatness of the top of the barrier for parallel motion. If it is true that the H_2 surface really has a shallow basin (cf. H. Eyring and B. L. Bruner, *J. Chem. Phys.*, **42**, 4047 (1965)) giving two asymmetric transition states rather than a single symmetrical one, perpendicular curvature could be considerably weaker than parallel curvature, which gives a different prediction than the symmetrical case. Study of substituent effects in $A + BA$ displacement reactions might, therefore, provide experimental evidence for the presence of a basin.

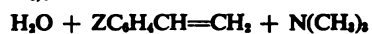
(25) J. W. Hill and A. Fry, *J. Am. Chem. Soc.*, **84**, 2763 (1962).
 (26) C. G. Swain and E. R. Thornton, *ibid.*, **84**, 822 (1962).

(1.94 vs. 1.78 Å, respectively). For the transition states, it is predicted that C-X bond stretching will be easier, which implies shorter C-X and longer C-O for methyl bromide resulting from the parallel effect, and longer C-X and C-O resulting from the perpendicular effect. The parallel effect is expected to dominate, so that C-X will be slightly shorter and C-O considerably longer for methyl bromide than for methyl chloride. The transition state is expected to be more reactant-like with respect to C-O for methyl bromide and also more reactant-like for C-Br. The latter prediction was reached by comparison with the rather large substituent effect in the reactant: although C-Br is predicted to be little different in length from C-Cl in the transition state, the reactant C-Br is a great deal longer than the reactant C-Cl, and thus the methyl bromide transition state is a great deal more reactant-like, with respect to the C-Br bond, than the methyl chloride transition state is with respect to the C-Cl bond. The reaction

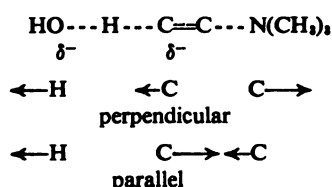


appears to have a shorter N-C bond for electron-withdrawing Z, since the solvent sensitivity of the rate of reaction is greater for electron-withdrawing Z (indicating greater charge destruction).²⁷ With HO⁻ as the nucleophile instead of N₃⁻, the C-S bond is indicated to be shorter for electron-withdrawing Z since the sulfur kinetic isotope effect decreases as Z becomes more electron withdrawing.²⁸

Another example is E2 bimolecular elimination. If only the two reacting bonds closest to the substituent are considered (and others are assumed to "follow along"), the effect of substituents Z in the elimination from a species such as β-phenylethyltrimethylammonium ion



should be predictable from the two approximate normal coordinate motions



The true normal coordinates (in particular, that for reaction coordinate motion) will involve more than three atoms, but this merely means that there will be more than one perpendicular motion involving these atoms. A better analysis of such a complex transition state would be arrived at by calculating approximately the true normal coordinates using reasonable guesses for the transition-state force constants.²⁹ The only real necessity in qualitative application of the theory is to separate the reaction coordinate motion from all perpendicular motions, since substituent effects are opposite for positive and negative force constants. In the present approximation it would be predicted that

(27) C. G. Swain, T. Rees, and L. J. Taylor, *J. Org. Chem.*, **28**, 2903 (1963).

(28) C. G. Swain and E. R. Thornton, *ibid.*, **26**, 4808 (1961).

(29) Such calculations are feasible, even for complex molecules, using a computer program such as that developed by J. H. Schachtschneider and R. G. Snyder, *Spectrochim. Acta*, **19**, 117 (1963); R. G. Snyder and J. H. Schachtschneider, *ibid.*, **21**, 169 (1965).

electron-supplying Z would make the perpendicular motion as shown more difficult and make the parallel motion as shown more difficult with respect to the C-H bond and less difficult with respect to the C-C bond. We can expect, however, that in contrast to the S_N2 case the effect on the parallel motion will not be zero. The effect on the C-H bond is expected to control the parallel motion because it is a σ bond; the C-C incipient π bond is not expected to change much in this motion because of the presence of the already formed C-C σ bond. It is reasonable to assume that substituent effects will always be larger on σ reacting bonds than on π reacting bonds which are equidistant from the substituent. The perturbation should, therefore, decrease the normal coordinate corresponding to the perpendicular vibration, i.e., shorten the H-C and C-C bonds, and increase the normal coordinate corresponding to the parallel vibration, i.e., lengthen the C-H bond and shorten the C-C bond. If it is assumed that the parallel shift is the more important, the C-H bond should be lengthened and the C-C bond shortened by electron supply at the central C. Since the parallel motion is expected to dominate, and since in this motion compression of the C-C bond is accompanied by extension of the C-N bond, electron supply at the central C is predicted to lengthen slightly the C-N bond. Similarly to the S_N2 mechanism, increased electron supply at the base (HO⁻ in the above example) is predicted to lengthen the O-H bond, i.e., make the transition state more reactant-like, while increased electron supply at the leaving group (-N⁺(CH₃)₃ in the above example) is predicted to lengthen the C-N bond, i.e., make the transition state more product-like. These predictions are in agreement with the fairly extensive experimental evidence,³⁰ which is discussed in detail in an accompanying report.³¹

The S_N1 mechanism presents difficulty. The evidence is that in the solvolysis of substituted cumyl chlorides, which presumably proceeds by rate-determining ionization



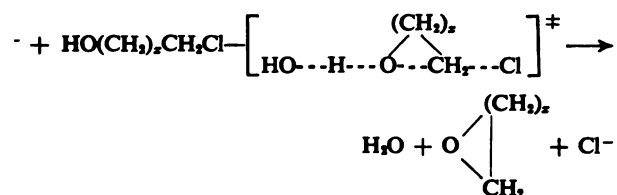
the solvolysis rates are more sensitive to solvent polarity (at 25°, methanol, ethanol, 2-propanol) for Z = *m*-methyl- and *p*-phenyl- and less for Z = *p*- or *m*-chloro-, *p*-carbomethoxy-, or *p*-trifluoromethyl- than for Z = H.³¹ The data imply that the transition state occurs with more complete ionization for electron-supplying substituents. On the other hand, the present theory predicts that if the reaction coordinate motion is the stretching of the C-Cl bond, electron-supplying Z should make this motion less difficult, i.e., the C-Cl bond shorter at the transition state. It seems likely that the theory is giving a correct prediction and that the sensitivity to solvent polarity (which is very small, barely outside experimental error) does not indicate that electron supply produces a more product-like transition state. One possibility is that the transition state is made more reactant-like in geometry but has more ionic character. There is no reason why geometry and charge separation need parallel one another precisely.³² The prediction of the present theory is in

(30) C. W. H. Saunders, Jr., in "The Chemistry of Alkenes," S. Patai, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, pp 149-201; L. J. Steff and E. R. Thornton, *J. Am. Chem. Soc.*, **85**, 2680 (1963).

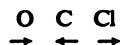
(31) Y. Okamoto, T. Inukai, and H. C. Brown, *ibid.*, **80**, 4975 (1958).

agreement with that of the Hammond postulate and intuitive reasoning that the very large rate increases associated with electron-supplying substituents suggest a more reactant-like transition state. The possibility that the direction of the perturbation was predicted correctly, *i.e.*, that electron supply actually makes C-I bond stretching more difficult, seems unlikely, although some rationalization of such a possibility has been previously given⁸ by arguing that reacting bonds are exceedingly electron deficient in the transition state. Electron deficiency of this magnitude now seems very unlikely, and the present theory rejects the possibility assuming that substituent effects in transition states can be predicted from the same rules which apply to stable molecules. Finally, there is the possibility that the rate-determining step is not simple ionization of the C-I bond. An alternative is that the transition state is practically, or even completely, ion-pair-like, with involvement of some nucleophilic center in the rate-determining step.²³ The nucleophile could be solvent even the π -electrons of the phenyl group (an "internal" nucleophile). The mechanism would then become SN2-like and, if the perpendicular motion were to determine the substituent effect, the C-Cl bond would be predicted to be lengthened by electron-supplying Z. A more detailed discussion of the SN1-type mechanism is in preparation.^{2b}

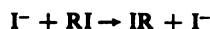
Very little definitive information is available about steric effects upon transition-state structure. It has been shown¹⁷ that the transition state for reaction of hydroxide ion with ethylene chlorohydrin ($x = 1$) is more product-like than that for tetramethylene



chlorohydrin ($x = 3$). Actually proton transfer to hydroxide ion appears to be complete (prior equilibrium) for ethylene chlorohydrin. The reaction coordinate motion would be approximately

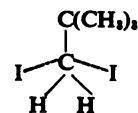


if the proton transfer were not part of this motion.¹⁷ The ring strain introduced in the compression of the C-Cl bond is predicted to make the above motion more difficult, giving a more product-like transition state, for the three-membered ring formation. The calculations of steric effects in transition states of SN2 reactions²² can be understood in terms of perpendicular motions. Larger alkyl groups, in the reaction



are calculated²² to give longer I-C bonds (both equal symmetry) at the transition state. In the reaction coordinate motion one I-C bond is compressed while the other is stretched; increased steric size of R should have no effect on this motion. In the perpendicular symmetric stretching motion, compression of both

bonds simultaneously should be made more difficult by increased size of R, which should, therefore, make both I-C bonds longer. Also, the calculation showed that the ICI bond angle was bent when R was not symmetric, in a direction away from the bulkiest part of R. For example, if R is neopentyl a 17.6° deviation



from 180° is predicted.²² The ICI bending motion is a perpendicular motion, so it is predicted that, in comparison with the symmetric case $\text{R} = \text{CH}_3$, introduction of one bulky *t*-butyl substituent should make bending of the iodine atoms toward that substituent more difficult and bending away easier, giving a transition state with the I-C-I bonds bent away from the bulky substituent.

Solvation. In making predictions about reactions in solution, one must be concerned about the possibly large effects of the solvent upon the transition state. It cannot be doubted that in many types of reaction mechanism the solvation effect is very large; most ion-forming reactions (*e.g.*, SN2 reactions between uncharged nucleophile and substrate; SN1 reactions) do not proceed in the gas phase, and it can be shown from studies of gas-phase ions that the energy requirements for such reactions are enormous unless very strong stabilization of product ion(s) by solvation occurs. According to the present theory, solvation effects should, if strong, simply make the solvent molecule(s) a part of the transition state.

The theory proposed here assumes that the structure of the unperturbed transition state and the nature of its reaction coordinate are approximately known. It is of fundamental importance, therefore, to provide reliable criteria—experimental and theoretical—for predicting the structures of transition states. The latter is very difficult, especially for reactions involving proton transfer; the position of the proton and the timing of its transfer are difficult to decide because protons tend to be very mobile. "Solvation"¹⁷ and "anthropomorphic"²⁴ rules have been proposed to help in such predictions. It should be emphasized that these rules apply to the prediction of transition-state structure, which is a completely separate (though related) problem from prediction of substituent effects.

If one accepts the predictive validity of such rules or of the present theory, they can be applied in reverse, *i.e.*, predicted substituent effects can be used to determine transition-state structure or reaction coordinate motion. Such predictions have been used to decide on the mechanism of general acid catalyzed addition of amines²⁵ and thiols²⁶ to carbonyl compounds.

It has been suggested¹⁷ that proton transfers between atoms which have unshared pairs of electrons occur rapidly either before or after the transition state, so that the proton "should lie in an entirely stable potential at the transition state and not form reacting bonds nor give rise to primary hydrogen isotope effects."²⁷

(34) J. E. Reimann and W. P. Jencks, *ibid.*, **88**, 3973 (1966).

(35) C. G. Swain and J. C. Worosz, *Tetrahedron Letters*, 3199 (1965).

(36) G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982 (1966).

(37) Cf., however, R. L. Schowen, H. Jayaraman, L. Koshner, and

(1) Cf. A. Streitwieser, Jr., *Chem. Rev.*, **56**, 638 (1956).

(2) Cf. R. A. Snee and J. W. Larsen, *J. Am. Chem. Soc.*, **88**, 2593 (1966), for direct evidence that attack of solvent on an ion pair can be rate determining.

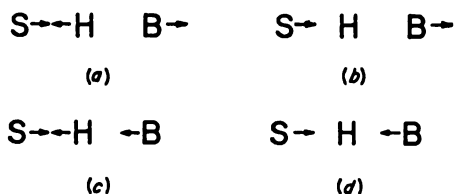


Figure 3. Approximate reaction coordinate motions for extreme types of proton transfer. (a) Concerted, unstable potential; (b) concerted, stable potential; (c) nonconcerted, unstable potential; (d) nonconcerted, stable potential. Note that motion b could not preserve the center of gravity and therefore could not be a normal coordinate for a triatomic system, but could be a normal coordinate if other atoms in the transition state also moved in such a way as to keep the center of gravity fixed.

Others have suggested²⁶ that general acid or general base catalyzed reactions should be thought of as concerted. These superficially conflicting viewpoints actually represent different mechanistic properties: the proton is in an entirely stable potential only if it does not move (relative to the center of gravity of the transition state) in the reaction coordinate motion. The proton may or may not be in a reactant-like or product-like position in the transition state; the determining factor is not the extent of proton transfer, but rather whether the reaction coordinate motion of the transition-state structure, once the transition state is reached, involves or does not involve motion of the proton. If the proton does not move in the reaction coordinate motion, it must move in one or more of the perpendicular motions, *i.e.*, in an entirely stable potential. On the other hand, a concerted, rate-determining proton transfer is one where the proton is actually bonded to a different atom in the first intermediate (or product) on the reaction path after the rate-determining transition state than it was bonded to in the first intermediate (or reactant) on the reaction path before the rate-determining transition state. Though a concerted proton transfer would be expected to involve motion of the proton in the reaction coordinate motion, it is conceivable that the other nuclei could move while the proton did not.

The extreme possibilities are illustrated in Figure 3 for a proton transfer from BH to S.

Extremes b and c seem relatively improbable, but mechanisms approaching these extremes must be considered among the spectrum of possible transition states.

Perturbations According to the Hellmann-Feynman Theorem. The Hellmann-Feynman theorem²⁸ gives the force acting on any nucleus of a system of electrons and nuclei as the sum of the *classical* repulsions by the other nuclei and attractions by the electrons. It therefore provides a good framework for discussing the qualitative ideas presented in previous sections and may eventually provide a quantitative estimate of perturbations. The force on nucleus α in direction x

G. W. Zuorick, *J. Am. Chem. Soc.*, **88**, 4008 (1966); J. P. Klinman, Ph.D. Dissertation, University of Pennsylvania, 1966, for evidence that this may not be so in certain cases.

(38) H. Hellmann, "Einführung in die Quantenchemie," Deuticke and Co., Leipzig, 1937; R. P. Feynman, *Phys. Rev.*, **56**, 340 (1939); *cf.* also: J. O. Hirschfelder, C. F. Curtiss, and R. B. Bird, "Molecular Theory of Gases and Liquids," John Wiley and Sons, Inc., New York, N. Y., 1964, pp 932-937; A. C. Hurley, *Proc. Roy. Soc. (London)*, **A226**, 170, 179, 193 (1954); **A235**, 224 (1956); T. Berlin, *J. Chem. Phys.*, **19**, 208 (1951); R. F. W. Bader, *Can. J. Chem.*, **38**, 2117 (1960); L. Salem and E. B. Wilson, *J. Chem. Phys.*, **36**, 3421 (1962).

is given by

$$F_{ax} = \frac{\partial}{\partial x_\alpha} \sum_{(\beta \neq \alpha)} \frac{Z_\alpha Z_\beta e^2}{r_{\alpha\beta}} - e \int \rho E_{ax} dr$$

where Z_α is the nuclear charge of nucleus α , $r_{\alpha\beta}$ the distance between nuclei α and β , e the electronic charge, ρ the total electron density, and E_{ax} the electric field (in the x direction) of nucleus α at the position of the electron, *i.e.*

$$E_{ax} = (Z_\alpha e \cos \theta_\alpha) / r_\alpha^2$$

where θ_α is the angle between a line connecting nucleus α with the electron and the x direction, and r_α is the distance between nucleus α and the electron. The density ρ is given by the sum of the squares of the wave functions for individual electrons, in the one-electron approximation

$$\rho(x, y, z) = \sum_i \psi^*(x, y, z_i) \psi(x, y, z_i)$$

By the definition of an equilibrium, all F_{ax} (and F_{ay} and F_{az}) must be zero at the equilibrium geometry of any system, and this includes transition states, where the equilibrium geometry is at the energy maximum, as well as stable molecules, where the equilibrium geometry is at the energy minimum. It is interesting to consider one special case. If two systems, a perturbed and an unperturbed one, both have exactly the same nuclei and differ only in their electron densities ρ , the difference between the forces for the perturbed and unperturbed systems, both forces being evaluated at the unperturbed equilibrium geometry, is (since the unperturbed force F_{ax}^{UP} is zero)

$$F_{ax}^P = F_{ax}^P - F_{ax}^{UP} = -e \int (\rho^P - \rho^{UP}) E_{ax} dr = -e \int \Delta \rho E_{ax} dr \quad (4)$$

The electric field of the nucleus, E_{ax} , is the same for both systems, and the nuclear repulsion part of the force difference exactly cancels since both forces are evaluated at the same geometry. Note that $\Delta \rho$ is a function of three spatial coordinates, not a constant.

The above expression (eq 4) is expected to be a good approximation to the force upon nuclei involved in reacting bonds if a substituent change is made far from the reaction site. In this case the substituent change will change nuclei which are so distant from nucleus α that the nuclear repulsion term will still cancel; E_{ax} of course does not change unless nucleus α is changed. Equation 4 is expected to be a worse approximation in cases where a nucleus close to nucleus α is changed, since the nuclear repulsion terms will change. Also, if nucleus α itself is changed, both the nuclear repulsion terms and E_{ax} will change. However, such an approximation may still be rather good in many cases, if "similar" nuclei replace one another (*e.g.*, chlorine and bromine), because of the fact that inner shell electrons are largely localized around a single nucleus. The inner shell electrons can be thought of as simply shielding the nucleus, *i.e.*, the nuclear repulsion terms and E_{ax} attractions practically cancel for inner shell electrons and the corresponding number of nuclear charges. Approximate calculations can therefore be made using eq 4, but using only the valence-shell electron densities and the (shielded) net valence-shell nuclear charges.

the very simple electrostatic expression derived for must be summed in order to derive the force for displacement according to normal coordinates, as required in the theory under discussion (cf. eq 1 and 2).

To simplify notation, let the nuclear coordinates, referred to the equilibrium geometry x_0, y_0, z_0 for each nucleus, be numbered consecutively, $q_1, q_2, q_3, \dots, q_i$, where q_1, q_2, q_3 are $(x - x_0), (y - y_0), (z - z_0)$ for nucleus 1; q_4, q_5, q_6 are $(x - x_0), (y - y_0), (z - z_0)$ for nucleus 2; etc. Then the normal coordinates can be written

$$X_j = \sum_i \ell_{ij}^{-1} q_i \text{ or } q_i = \sum_j \ell_{ij} X_j \quad (5)$$

each cartesian coordinate of each nucleus

$$\frac{\partial V}{\partial q_i} \equiv \frac{\partial V}{\partial (x - x_0)} = \frac{\partial V}{\partial x}$$

$$F_i = - \frac{\partial V}{\partial q_i} = - \frac{\partial V}{\partial x} = - e \int \Delta \rho E_i dr \quad (6)$$

In eq 4. The force for displacement according to normal coordinate X_j is

$$= - \frac{\partial V}{\partial X_j} = - \sum_i \frac{\partial V}{\partial q_i} \frac{\partial q_i}{\partial X_j} = \sum_i F_i \ell_{ij} = - e \int \Delta \rho \left(\sum_i E_i \ell_{ij} \right) dr$$

According to eq 5 and 6. Since all normal coordinates of the unperturbed system are by definition zero at the unperturbed equilibrium geometry, eq 2 gives, for the slope m of the perturbation P (eq 1)

$$m = \frac{\partial V'}{\partial X_j} = -F_{X_j} \quad (7)$$

The assumption of the present theory is that P is linear, that the slope m does not change much between the unperturbed equilibrium geometry (all X_j zero) and the perturbed equilibrium geometry; if so, eq 7 gives an expression applicable to all geometries, not just the unperturbed equilibrium geometry. In fact, eq 7 applies to all geometries since eq 4 gives the difference between the perturbed and unperturbed forces for any nuclear geometry, and (cf. eq 2)

$$-F_i^{UP} = - \frac{\partial V^P}{\partial q_i} + \frac{\partial V^{UP}}{\partial q_i} = - \frac{\partial (V + P)}{\partial q_i} + \frac{\partial V}{\partial q_i} = \frac{\partial P}{\partial q_i}$$

It can then be seen that the quantities F_{X_j} can be defined at any geometry as long as one uses the ℓ_{ij} which apply at an equilibrium geometry (necessary since normal coordinates, and therefore ℓ_{ij} , are not defined except at geometry extrema). The net result is that the quantities

$$m = -F_{X_j} = e \int \Delta \rho \left(\sum_i E_i \ell_{ij} \right) dr \quad (8)$$

are constant between the unperturbed equilibrium and the perturbed equilibrium geometries if the assumption that the perturbation P is linear is correct, but will otherwise change somewhat.

Equation 8 not only gives a physical picture in terms of an easy-to-visualize quantity, the change in electron

probability distribution $\Delta \rho$, but also may provide an approximate means of estimating m values from "classical" electron density approximations, or, better, from approximate wave functions.³⁹

A better expression for m can be written in terms of a power series for small displacements from the unperturbed equilibrium geometry ($X_j = 0$)

$$m = (F_{X_j})_U + \left(\frac{\partial F_{X_j}}{\partial X_j} \right)_U X_j + \frac{1}{2} \left(\frac{\partial^2 F_{X_j}}{\partial X_j^2} \right)_U X_j^2 + \dots \quad (9)$$

where the subscript U means the derivatives are evaluated at the unperturbed equilibrium geometry. Hellmann-Feynman type expressions could be written for the successive terms in eq 9; e.g.

$$\frac{\partial F_{X_j}}{\partial X_j} = - e \int \Delta \rho \left(\sum_i \ell_{ij}^2 \frac{\partial E_i}{\partial q_i} \right) dr$$

where i is summed over all coordinates of all nuclei.

In a theoretical discussion of substituent effects, it might seem as if the results would be quite different depending upon whether electron density were being supplied to (or withdrawn from) a bonding or an antibonding orbital. It might, therefore, be concluded that such simple ideas as "homonuclear character" and acid-base properties, used in previous sections for predicting substituent effects, would break down in many cases. However, the distinction between bonding and antibonding orbitals is not completely clear-cut, since the usual definition includes nuclear repulsions which are not electron energies at all. In fact, by defining "binding" orbitals as those which, when occupied, produce an attractive force tending to pull nuclei together (even though the nuclear repulsion may more than counterbalance this attractive force), and "antibinding" orbitals as those which produce a force tending to push nuclei apart, Bader and Jones⁴⁰ have concluded that essentially all orbitals are binding except at very small internuclear distances.

Since the Hellmann-Feynman theorem holds for all geometries of a system of electrons and nuclei, it must hold for transition states. The above arguments show that the primary assumption of the present theory, that transition states can be treated just like ordinary molecules in evaluating substituent effects, is in fact completely correct if one is calculating effects according to the Hellmann-Feynman theorem. Qualitative arguments concerning the direction of substituent effects are strongly indicated to apply in the same way to transition states as to ordinary molecules, though the validity of such qualitative arguments is not absolutely proven.

From eq 8, it is not immediately obvious why m should be nearly constant with geometry, i.e., why the perturbation should be nearly linear, for it would appear as if E_i , which changes with geometry, must produce large changes in the integral. The reason why such large changes do not occur (at least in diatomic molecules; see following section) is, of course, that $\Delta \rho$ also changes with geometry. Though the individual densities ρ^{UP} and ρ^P must probably be redistributed a good deal upon changing the nuclear geometry, it is

(39) For an interesting discussion of the hydrogen bond and hydrogen-transfer reactions using simple wave functions with the Hellmann-Feynman theorem, see R. F. W. Bader, *Can. J. Chem.*, **42**, 1822 (1964).
(40) R. F. W. Bader and G. A. Jones, *ibid.*, **39**, 1253 (1961).

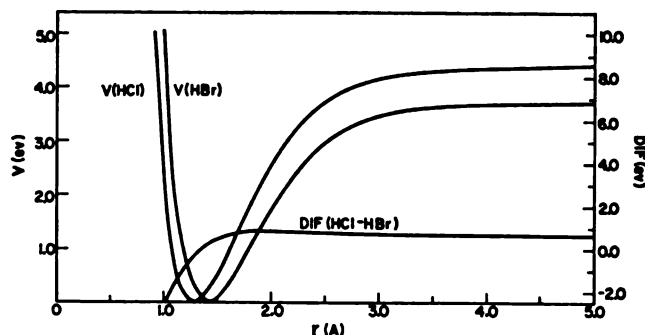


Figure 4. Potential curves for HCl and HBr as calculated from the Hulburt-Hirschfelder equation, along with the difference between the curves (DIF) showing strong curvature of the DIF curve over large changes in r (though DIF is very nearly a straight line between 1.2746 and 1.4138 Å, the r_e values for HCl and HBr, respectively). It should be noted that the choice of the potential energy scale as zero for each molecule at its r_e affects only the vertical placement, and not the shape, of DIF. DIF gives the quantity which, when added to the curve for HBr, gives the curve for HCl.

entirely possible that the electron densities are polarized toward a given nucleus α as it is moved away from other nuclei in nearly the amount required to offset the increased distance of nucleus α by leaving the actual difference distribution $\Delta\rho$ nearly unchanged relative to nucleus α . In other words, at least two opposing effects can be expected, which will tend to make m constant with geometry (for small changes in geometry).

Substituent Changes in Diatomic Molecules. In order to investigate the validity of the assumption that perturbations are linear, the actual differences between potential energy curves for some diatomic molecules have been calculated and these differences checked for linearity. A computer program⁴¹ has been written which calculates the energy of a diatomic molecule for interatomic distances from 0 to 5 Å at 0.1-Å intervals, and at 0.02-Å intervals between any specified pair of interatomic distances, from the potential function of Hulburt and Hirschfelder.⁴² The experimental parameters ω_e , $\omega_e x_e$, D_e , B_e , α_e , and r_e , along with the reduced mass, are used to give a (supposedly) rather good prediction of the potential energy curve. The program then calculates the energy differences between all possible pairs (up to eight molecules may be examined in one computation) of molecules at the above geometries and computes the slope, intercept, and standard deviation of points for the best straight line through only the differences taken at 0.02-Å intervals. Also, the program gives the differences, calculated according to the above best straight line, for all geometries from 0 to 5 Å, along with the differences between the experimental and calculated differences.

Calculations have been made for H_2 , H_2^+ , HCl, HCl^+ , HBr, HI, and CH, from which some tentative conclusions can be drawn. The spectroscopic constants from Herzberg's table^{43b} were used.

The differences are reasonably linear but tend to be concave upward, as mentioned in a previous section. These differences must, physically, approach (probably

asymptotically) constant values as the internuclear distance approaches infinity (separated atoms) and (not counting nuclear repulsions) zero (combined atoms). The former is reproduced by the program; the equation does not give correct energy results as the distance approaches zero anyway.⁴³

The differences are precisely linear for molecules with the same nuclei, *i.e.*, H_2 vs. H_2^+ and HCl vs. HCl^+ . For example, the slope for HCl minus HCl^+ is 1.129 eV Å⁻¹, and the standard deviation of points from the line (1.10 to 1.62 Å) is 0.004 eV (the equilibrium internuclear distances are 1.27 and 1.31 Å, respectively). For H_2 minus H_2^+ , the slope is 5.799 eV Å⁻¹, and the standard deviation (0.74 to 1.06 Å) is 0.035 eV (equilibrium internuclear distances 0.74166 and 1.060 Å, respectively). This discovery indicates that, for merely electronic changes, without change of nuclei, the perturbations considered for substituent effects ought to be precisely linear. For complex molecules where the substituent change is made relatively far from any reacting bonds, the only effect on the reaction center should be a small change in electron density, which can be expected to produce perturbations that are much more nearly linear than the change from HCl to HCl^+ .

The differences are considerably less linear for molecules of different types. For example (a particularly bad case), the slope for HI minus CH is -15.17 eV Å⁻¹, and the standard deviation (1.10 to 1.62 Å) is 0.85 eV (equilibrium internuclear distances 1.60 and 1.12 Å, respectively). The slope changes from 46.5 to 3.5 eV Å⁻¹ between 1.10 and 1.62 Å. This is a case where the equilibrium nuclear distances are quite different, and it can be expected that such drastic changes of "substituent" will be likely to produce large deviations from linearity. A case more typical of the type of closely related structures that might be compared experimentally is HCl minus HBr (*e.g.*, where Cl and Br are compared as leaving groups), giving: slope, 4.131 eV Å⁻¹ (1.10 to 1.62 Å), standard deviation, 0.17 eV; equilibrium internuclear distances, 1.27, 1.41 Å. The computer-calculated curves for HCl and HBr, along with their difference curve, are plotted in Figure 4.

Linearity is much better for the latter pair if the data between 1.26 and 1.40 Å are used (*i.e.*, approximately between the equilibrium internuclear distances): slope, 4.238 eV Å⁻¹; standard deviation, 0.016 eV. Furthermore, in cases where one of the atoms of a reacting bond is changed, transition-state perturbations must be considered relative to rather large reactant perturbations. In principle, the deviations from linearity would be expected to be of similar magnitude for reactant and transition state, and would, therefore, tend to cancel in considering, *e.g.*, changes in reactant-like vs. product-like character in transition states.

Of course, another possible source of nonlinearity is the approximate nature of the Hulburt-Hirschfelder equation,⁴² since the differences are taken at points fairly far removed from the equilibrium internuclear distance of at least one of each pair of molecules. The calculated energies for H_2 agree with the "most likely" values from vibrational energy level analysis⁴³ to within *ca.* ± 0.01 eV between 0.5 and 1.4 Å, but at larger internuclear distances, agreement becomes worse:

(43) D. Steele, E. R. Lippincott, and J. T. Vanderslice, *Rev. Mod. Phys.*, **34**, 239 (1962).

(41) Written in FORTRAN IV for the IBM 7040 computer of the University of Pennsylvania Computer Center.

(42) (a) H. M. Hulburt and J. O. Hirschfelder, *J. Chem. Phys.*, **9**, 61 (1941); note an error of sign in the definition of the parameter b , where the first plus sign should be a minus sign. (b) This error is also reproduced in G. Herzberg, "Spectra of Diatomic Molecules," 2nd ed, D. Van Nostrand Company, Inc., Princeton, N. J., 1950, p 102.

12 eV at 2.0 Å. The energies from the Hulburt-Heller equation have been compared with those from precise vibrational analysis for a series of electronic states of several diatomic molecules,⁴³ the average per cent difference between these values relative to the dissociation energy, $(V_{H-H} - D_0)$, is only about 1.5%, over the entire range of energies for which vibrational data are available for molecules studied. Additional complications conceivably arise from irregularities in potential curves, e.g., if there is configuration interaction involving excited states;⁴⁴ even in this case, however, effects might be expected to cancel in considerable difference between unsubstituted and substituted molecules or transition states, provided the substituent change is not too drastic.

The linearity of the difference between species containing the same nuclei is surprisingly precise,⁴⁵ and can be further explored, especially in relation to the Hellmann-Feynman theorem (e.g., eq 4).

Limitations of Theory. The major problem in applying the theory qualitatively to large organic molecules is finding the reaction coordinate. It would be highly desirable to have "rules" (cf. ref 17 and 34) to aid in finding the correct reaction coordinate.

The nature of the perturbation could be a problem, as results with diatomics indicate that, for "small" substituent changes, large curvature is unlikely. Also, the problem's existence could be investigated by studying several substituents in the same reaction; if the results fall in a rational order dependent on electronic or

steric properties of the substituents, large curvature, or at least reversal of slope, could be ruled out.

For qualitative predictions, it is difficult to decide precisely about effects which may nearly cancel, i.e., where opposite effects on the same bond are predicted from two different normal vibrations. Associated with this problem is the question whether (or when) it is justifiable to assume that the curvature of the potential energy surface in the reaction coordinate (parallel) direction is considerably less than in the perpendicular directions.

Interpretation of experiments is another type of difficulty. It is not easy to design experiments which unambiguously indicate whether a certain bond is lengthened or shortened, in the transition state, by a substituent change. Solvation effects must be considered as well as effects associated with ordinary bonds. This problem is especially important in the case of the S_N1 mechanism, which will be an important test for this theory.

Conclusion. The theory appears to give reliable qualitative predictions based on an approximate knowledge of the reaction coordinate for a reaction. It can be understood theoretically in terms of the Hellmann-Feynman theorem, and it seems justified on various qualitative grounds. We hope to explore the idea further by trying to refine the qualitative predictions (including study of substituent effects on molecular vibrations), further justify it and make quantitative predictions, and carry out experimental tests designed to uncover and explain any exceptions that may exist.

Acknowledgment. The author is grateful to Professors C. G. Swain and R. L. Schowen for helpful discussions.

43. S. Mulliken, *J. Am. Chem. Soc.*, **88**, 1849 (1966).

44. This tends to justify the approach to excited-state geometry presented (Malrieu¹⁷).

Acetolyses of 6-Substituted *syn*-9-Benzonorbornenyl and 9-Methylbenzonorbornen-9-(*anti*- and -*syn*)-yl Arenesulfonate *anti-syn* Rate Ratios as a Test for Participation. Substituent Effects and Variation from Secondary to Tertiary Systems

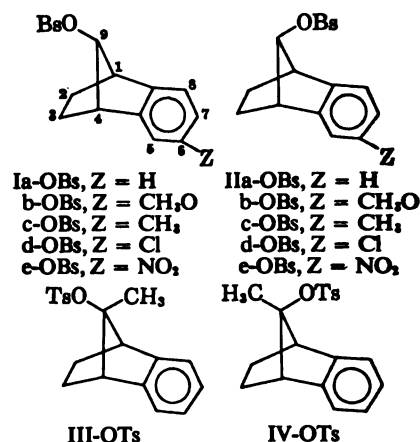
Hiroshi Tanida, Yoshiteru Hata, Shiro Ikegami, and Hiroyuki Ishitobi

Contribution from Shionogi Research Laboratory, Shionogi Company, Ltd., Fukushima-ku, Osaka, Japan. Received January 3, 1967

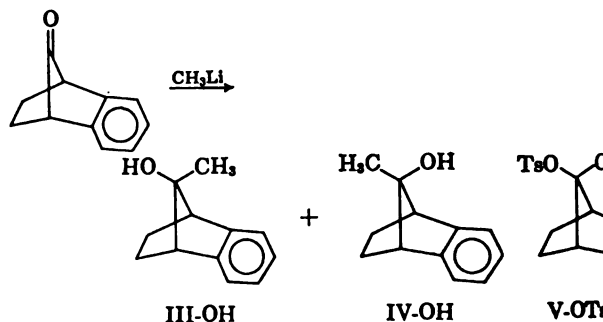
Abstract: Rates in the acetolyses of 6-substituted *syn*-9-benzonorbornenyl brosylates were determined, and their substituent effects ($k_{\text{CH}_3\text{O}}/k_{\text{NO}_2} = 43$) were compared to those of the *anti* brosylates ($k_{\text{CH}_3\text{O}}/k_{\text{NO}_2} = 386,000$). The factor of 43 indicates the absence of homobenzylic conjugation by the aromatic ring, as demonstrated in the *anti* series, as well as efficient transmission of polar effects by the benzene moiety. The *anti-syn* rate ratios obtained by the combination of data in both series are well correlated by the modified Hammett relationship, $\log(k/k_0) = \rho(\sigma_p^+ + \sigma_m^+)$, with $\rho = -3.57$. 9-Methylbenzonorbornen-9-(*anti*- and -*syn*)-yl tosylates were prepared, and the products and rates of acetolysis were determined. Acetolysis of the tertiary *anti* tosylate led to the acetate with 98% retention and the olefin (9-methylenebenzonorbornene, 2%), while that of the *syn* led to the acetate with 67% inversion and 10% retention and the olefin (21%). The variation of *anti-syn* rate ratios from the secondary to the tertiary system is discussed in terms of participation effects.

The large effect of 6 substituents in the acetolyses of *anti*-9-benzonorbornenyl brosylates (I-OBs) (a factor of 386,000 was found between the rates of the methoxy and the nitro derivatives)^{1,2} provides one of the most important evidences for the homobenzylic participation in these derivatives and also for the homoallylic participation in the norbornenyl derivatives, which were originally suggested by Bartlett³ and Winstein,⁴ respectively. Furthermore, our observation that the effects of the 6 substituent and the 7 substituent are additive indicates a symmetrical transition state (one of the most powerful supporting data for the 7-norbornenyl nonclassical ion).^{2c,5} This paper deals with the rates and products in the acetolyses of 6-substituted *syn*-9-benzonorbornenyl brosylates (II-OBs) and 9-methylbenzonorbornen-9-(*anti*- and -*syn*)-yl tosylates (III-OTs and IV-OTs). Combined treatment of these results makes the Hammett approach possible for the *anti-syn* rate ratio and provides an experimental evaluation for an important suggestion in the participation theory:⁶ tertiary carbonium ions should be stable enough to require little or no participation. Both are well-defined tests for the existence of nonclassical transition states, but not direct evidence for nonclassical ions.

Preparations. The syntheses and properties of the various types of II-OH used in this study were already reported.^{2b} Their brosylates II-OBs were prepared



by standard procedures and gave satisfactory analytical data. Addition of methyllithium to 9-benzonorbornenol produced a mixture composed of 88% III-OH : 12% IV-OH. These were isolated in the pure state



by a combination of recrystallization and chromatography. The structural characterization was made by comparison of the chemical shifts of the 9-methyl group (τ 8.96 in III-OH and 8.73 in IV-OH) and also by presence of an internal interaction between the hydroxyl group and the π electrons of the benzene ring in infrared spectrum of IV-OH. Since the *p*-nitro tosylates of the tertiary III-OH and IV-OH were formed

(7) H. Tanida, H. Miyazaki, and H. Ishitobi, *Can. J. Chem.*, **4** (1966).

(1) The numbering used in the papers of this series is shown in the charts.

(2) (a) H. Tanida, *J. Am. Chem. Soc.*, **85**, 1703 (1963); (b) H. Tanida, T. Tsuji, and H. Ishitobi, *ibid.*, **86**, 4904 (1964); (c) H. Tanida and H. Ishitobi, *ibid.*, **88**, 3663 (1966).

(3) P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960).

(4) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955), and the subsequent papers.

(5) Footnote 12 in M. Brookhart, A. Diaz, and S. Winstein, *ibid.*, **88**, 3135 (1966).

(6) (a) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 135-136; *Chem. Rev.*, **56**, 707 (1956); (b) C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Co., New York, N. Y., 1963, p 62; (c) refer to H. C. Brown, *et al.*, *J. Am. Chem. Soc.*, **86**, 1246, 5006 (1964); P. von R. Schleyer, *et al.*, *ibid.*, **86**, 2722 (1964), and references cited therein.

Acetolyses of *syn*-9-Benzonorbornenyl Brosylates^a

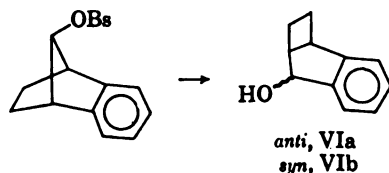
Subst	Temp, °C ^b	k_1 , sec ⁻¹	Calcd at 77.60°			Rel rate	k_1 , sec ⁻¹ (77.6°), of <i>anti</i> brosylates ^c	Rate ratio, <i>anti</i> : <i>syn</i>
			ΔH^\ddagger , kcal	ΔS^\ddagger , cal/deg	k_1 , sec ⁻¹			
I ₂ O	170.0	3.05×10^{-4}	31.4	-4.5	2.07×10^{-4}	1.6	8.08×10^{-4}	3.9×10^4
	135.0	1.32×10^{-5}						
I ₃	170.1	3.03×10^{-4}	31.4	-4.6	2.04×10^{-4}	1.6	8.44×10^{-4}	4.1×10^4
	135.0	1.32×10^{-5}						
	170.0	2.01×10^{-4}	31.6	-4.8	1.28×10^{-4}	1	1.49×10^{-4}	1.2×10^4
	161.5	9.85×10^{-5}						
	135.0	8.62×10^{-6}						
I ₄	170.1	6.81×10^{-5}	31.9	-6.3	3.89×10^{-5}	0.31	6.63×10^{-7}	1.7×10^4
	135.0	2.82×10^{-6}						
	170.1	1.43×10^{-5}	33.8	-5.3	4.73×10^{-10}	0.037	2.07×10^{-9}	4.4
I ₅ (norbornyl brosylate ^d)	149.9	2.23×10^{-6}						
	187.3	8.10×10^{-5}	34.6	-2.9	4.49×10^{-10}	0.035		
	172.2	2.00×10^{-5}						
	150.2	2.70×10^{-6}						

ried out in glacial acetic acid containing equivalent amounts of sodium acetate. ^b Controlled to $\pm 0.05^\circ$ for runs below 150° and to $\pm 0.1^\circ$ for runs from 160 to 190° . ^c Cited from ref 2b. ^d For the tosylate, S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955), have reported k_1 (205°) = 8.40×10^{-5} sec⁻¹, ΔH^\ddagger = 35.7 kcal, ΔS^\ddagger = -3.5 cal/deg. With the ratio $k_{OTs} = 2.90$, k_1 of the brosylate at 77.6° is calculated as 1.86×10^{-10} sec⁻¹.

very inert under solvolysis conditions, the *syn*-isomers of their tosylates were undertaken. Reactions of 7-norbornyl tosylate with the lithium salts of III-OH and in tetrahydrofuran (prepared by treatment with lithium) were successful for this purpose. As a reference compound, 7-methylnorborn-7-yl tosylate (I₅) was similarly prepared from 7-methylnorborn-7-ol.⁸

Acetolysis of *syn*-9-Benzonorbornenyl Brosylates and Stereoelectronic Effects on the *anti*-*syn* Rate Ratios. The rates of acetolysis were determined by standard procedures, and in each case the theoretical infinity titer was obtained. Table I summarizes the rates from the acetolyses of IIa-e-OBs and, for comparison, the rates of acetolysis of I₂O calculated by Arrhenius plots, the rates of acetolysis of I₃-OBs, and the *anti*-*syn* rate ratios.

Acetolysis of II-OBs leads to completely rearranged, stereospecific, products. The reaction in a mixture of acetone (40:60 vol. %) with added NaHCO₃ for 1 week yielded a mixture consisting of 98.6% *anti*-2-benzo[3,4]bicyclo[3.2.0]heptenol (VIa) and 1.4% *syn* isomer VIb. The structural determination of



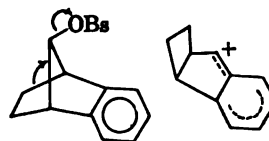
products and their acid-catalyzed rearrangements have been separately reported.⁹ However, since a control experiment showed that VIb epimerized slowly to the less hindered VIa¹⁰ under the hydrolysis conditions, it is not clear whether the above product ratio is complete kinetic control. It is theoretically anticipated that, despite the absence of rate enhancement for 7-norbornyl brosylate, the acetolysis of IIe-OBs showed predominant rearrangement; a rough vpc showed the absence of the retention

K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

Tanida, Y. Hata, and H. Ishitobi, *Tetrahedron Letters*, 361

by LiAlH₄ reduction of 2-benzo[3,4]bicyclo[3.2.0]heptenone; a mixture of VIa and VIb.

product. In contrast, acetolysis of 7-norbornyl brosylate yields a mixture containing 91% unrearranged acetate, 7% *anti*-2-bicyclo[3.2.0]heptanol, and 2% bicyclo[3.2.0]hept-2-ene.¹¹ Therefore, it should be considered that the formation of a stabilized benzylic carbonium ion, probably with participation of the 1,2-carbon bond,¹² provides a strong driving force for the rearrangement in the reaction of IIa-e-OBs.



Compared to a factor of 386,000 in the I series, the rate range from the methoxy to the nitro in the II series was only 43. This substantiates the fact that significant participation (homobenzylic conjugation) such as in the acetolysis of I is absent in that of II. However, the factor of 43 is too large for a simple electrostatic interaction. An example of similar reactions involving only inductive effects is the acetolysis of 5-substituted 2-indanyl brosylates. These materials were synthesized¹³ and solvolyzed. The rate constants are listed in Table II. The corresponding rate factor is only 8. This value is normal, because the inductive effect should decrease rapidly when going through saturated bonds.¹⁴ Therefore, it may be argued by the factor of 43 (the *syn* effect) that polar effects of the benzene ring are transmitted with considerable efficiency by the π cloud to the reaction center. Consequently, the rate change in the I series involves two factors: participation by the aromatic π system and this *syn* effect. By eliminating

(11) S. Winstein, F. Gadiant, E. T. Stafford, and P. E. Klinedinst, Jr., *J. Am. Chem. Soc.*, **80**, 5895 (1958).

(12) A referee pointed out the possibility of this effect. We appreciate his comment and infer on this basis that, if the difference in steric factors between II-OBs and 7-norbornyl-OBs could be neglected in controlling the departure of the brosyl groups, the absence of the participation would result in a rate of IIe-OBs considerably slower than that of 7-norbornyl-OBs because of polar effects by the nitrobenzene moiety in IIe-OBs.

(13) Syntheses and properties will be reported in N. Inamoto, S. Masuda, K. Tori, K. Aono, and H. Tanida, *Can. J. Chem.*, in press.

(14) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter 1.

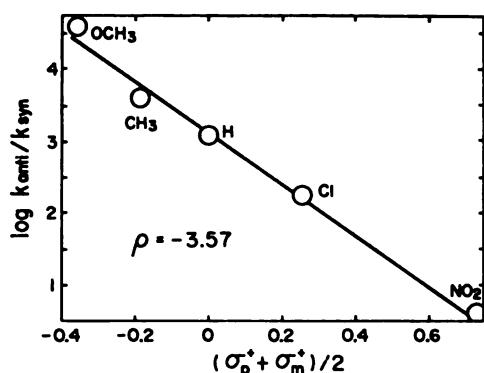
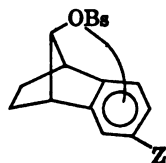


Figure 1. The ρ - σ treatment of *anti-syn* rate ratios in acetolyses of 9-benzonorbornenyl brosylates.

this effect, the *anti-syn* rate ratio should represent the rate change due only to the participation. Table I shows that the ratio changes from a factor of 3.9×10^{-4} for the methoxyl derivative to 4.4 for the nitro



derivative. The plots of $\log (k_{anti}/k_{syn})$ vs. $1/2(\sigma_p + \sigma_m)$ yield a reasonably good correlation with $\rho = -3.57$ (Figure 1). This is similar to the correlation of $\log k_{anti}$ by $1/2(\sigma_p + \sigma_m)$ where $\rho = -5.10$.^{2b,c} By simple σ^+ plots the chloro and nitro derivatives are

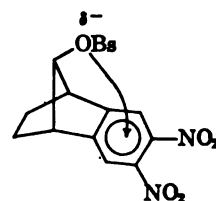
Table II. Acetolyses of 5-Substituted 2-Indanyl Brosylates

Subst	Temp, °C ^a	k_1 , sec ⁻¹	Rel rate at 77.60°
C ₂ H ₅	77.60	1.51×10^{-4}	1.4
CH ₃ O	77.60	1.39×10^{-4}	1.3
H ^b	92.87	5.28×10^{-4}	
	77.60	1.09×10^{-4}	1
	75.81	9.35×10^{-5}	
	62.78	2.06×10^{-5}	
CH ₃ CO	100.02	3.68×10^{-4}	0.36
	77.60	3.89×10^{-5}	
NO ₂	100.02	1.31×10^{-4}	0.15
	77.60	1.63×10^{-5}	

^a Controlled to $\pm 0.03^\circ$. ^b The product is quantitatively 2-indanol acetate.

distinctly below the line defined by the methoxy, methyl, and hydrogen points. Other Hammett plots attempted in a previous paper^{2b} provided unsatisfactory correlations. The large negative ρ value (-3.57) thus obtained indicates unequivocally that the amount of participation and the magnitude of the *anti-syn* rate ratio increase as activating substituents are introduced into the aromatic ring, whereas they reverse by introducing deactivating substituents. Figure 1 also suggests that, with a more positive σ^+ value than the nitro, the rate of a *syn* derivative would be greater than that of the corresponding *anti*. This was proven by the rates of 6,7-dinitro derivatives where $k_{anti} = 1.40 \times 10^{-5}$ and $k_{syn} = 9.21 \times 10^{-5}$ sec⁻¹ at $198.5 \pm 0.4^\circ$ in a water-acetic acid (20:80 vol. %) mixture. It is conceiv-

able that the highly electron-deficient group (dinitrobenzene) electrostatically attracts the leaving sulfonyl-oxy anion on the same side.



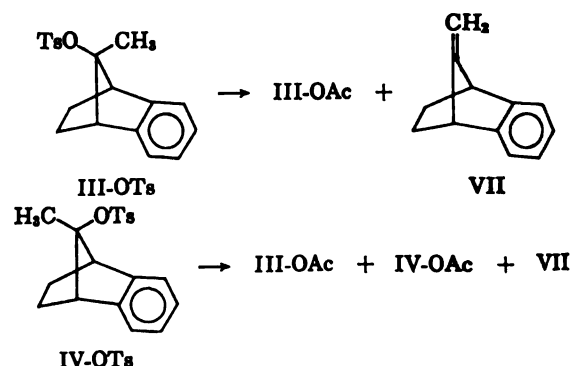
Acetolysis of 9-Methylbenzonorbornen-9-(*anti*- and -*syn*)-yl Tosylates (III-OTs and IV-OTs) and Variation of the *anti-syn* Rate Ratios from Secondary to Tertiary Systems. Table III lists the rates from acetolysis of III-OTs, IV-OTs, and V-OTs, with other pertinent data.

Table III. Rates of Acetolysis and *anti-syn* Rate Ratios for Secondary and Tertiary 9-Benzonorbornenyl Arenesulfonates

Compd	Temp, °C ^a	k_1 , sec ⁻¹	Rate ratio at 50°	
			<i>anti:syn</i>	Me:H ^b
	18.7	4.97×10^{-5}		
	37.3	6.39×10^{-4}		
	50.0	3.12×10^{-3}	493	18,000
	50.0	6.33×10^{-5}		86,700
	37.3	2.05×10^{-5}		
	50.0	1.15×10^{-4}		5.1×10^7
7-Norbornenyl-OBs	50.0	6.48×10^{-12}		
<i>anti</i> -9-Benzonorbornenyl-OBs	50.0	5.01×10^{-7}	2400	
<i>syn</i> -9-Benzonorbornenyl-OBs	50.0	2.12×10^{-10}		

^a Controlled to $\pm 0.03^\circ$. ^b Calculated with the rate ratio ROBs: ROTs = 2.90. ^c Calculated by Arrhenius plots. ^d Calculated from the observed rates in Table I. ^e Calculated from the observed rates in ref 2b.

The acetolysis of III-OTs resulted in a mixture consisting of 98% III-OAc and 2% 9-methylenebenzonorbornene (VII). In contrast, the reaction with IV-OTs



yielded a mixture consisting of 67% III-OAc, 10% IV-OAc, and 21% VII. These products were recovered unchanged under the reaction conditions and were verified to be the products of kinetically controlled solvolyses. Absence of the IV-OAc (inversion product) from III-OTs was demonstrated by vpc in amounts

ter than 0.3% yield. It should be noted that this rate and the formation of VII less than that from OTs, with the *anti-syn* rate ratio by a factor of 493, indicate some amounts of participation in the acetolysis of I-OTs.

Without firm experimental supporting evidence, it has been widely suggested that,^{6,15-18} as a cationic center made more and more stable by changing a secondary system into a tertiary system, both the amount of participation and the magnitude of the *anti-syn* (or *exo-endo*) rate ratio in the norbornyl derivatives, which has been attributed to carbon participation,¹⁹ should be expected to drop. Following this suggestion, Brown and his associates extensively studied the solvolysis of the secondary and tertiary esters or halides of the 2-norbornyl^{15a-c} and 2-benzonorbornenyl¹⁷ systems and observed no significant changes in the *exo-endo* rate ratios between the secondary and tertiary derivatives. These results have been interpreted in an alternative way as the absence of significant participation (Brown^{15,17,20}), or a fortuitous cancellation of increasing steric assistance in the primary systems with decreasing carbon participation (eyer²¹). Since participation of the π electrons of *anti*-7-norbornenyl and *anti*-9-benzonorbornenyl systems is the greatest on record and its existence is supported by even nonclassical nonsupporters,^{20b} the present rate results should help to clarify this problem.

As shown in Table III, the *anti-syn* rate ratios changed by a factor of 2400 to 493 with the transformation from the secondary to the tertiary system. This change in the rate ratio would be predicted for a major decrease in carbon participation accompanied by increasing stability of the cationic center. However, the change between both systems is only a factor of 4.9. Accordingly, it should be concluded that, even though chemically sound, the above suggestion is too insensitive as a test of participation when compared with the effect of substituent effects as mentioned above.

The methyl group at a carbonium center stabilizes the electron-deficient species because of its ability to supply electrons to the electron-deficient center. The greater the electron deficiency, the greater the contribution of the substituent. Brown has observed a relatively constant factor of 55,000 for the effect of CH_3 :H (the contribution of methyl) in many representative isopropyl *t*-butyl systems

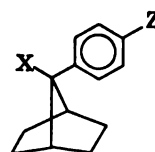
$$(\text{CH}_3)_3\text{CX}:(\text{CH}_3)_2\text{CHX} = 55,000 \text{ at } 25^\circ$$

$$\text{C}_6\text{H}_5(\text{CH}_3)_2\text{CX}:\text{C}_6\text{H}_5(\text{CH}_3)\text{CHX} = 1800$$

a factor of 1800 in *t*-cumyl chloride and α -phenyl-*t*-butyl chloride. This indicates that the methyl substituent is making a much smaller contribution to the

resonance-stabilized α -phenylethyl transition state than to the less stable isopropyl transition state.^{15d,22} Therefore, the small CH_3 :H factor of 18,000 relative to 86,700 (Table III) is in line with the presence of participation of the *anti* series (I and III), but the difference is, here again, too small to demonstrate this procedure as a competent test for participation.

The CH_3 :H factor of 5.1×10^7 for the 7-norbornyl cation is very large. This reveals that the cation makes an enormous demand on substituents for further stabilization. The existence of great participation in this system is consistent with this finding. We are currently investigating the substituent effects on the solvolysis of 7-phenylnorborn-7-yl derivatives, with the expectation that an extraordinarily large ρ value will be obtained as a semiquantitative expression of the enormous electron demand.



Experimental Section²³

Kinetic Measurements. The acetolysis conditions and procedure were the same as previously reported.^{2b}

9-Methylbenzonorbornen-9-(*anti*- and -*syn*)-ol (III-OH and IV-OH). A. Methyl iodide (8.52 g) in 20 ml of ether under a nitrogen atmosphere was added to a suspension of 830 mg of lithium metal in 30 ml of boiling ether. After stirring for 1 hr, a solution of 6.32 g of 9-benzonorbornenone in 40 ml of benzene was added and the mixture refluxed for 1 hr. The mixture was poured into a saturated NH_4Cl solution, extracted with ether, and dried. Evaporation of the ether gave 6.93 g of a 88:12 mixture of III-OH and IV-OH. Recrystallization from *n*-hexane yielded pure III-OH with mp 108–108.5°. Elution chromatography of the mother liquor on Florisil gave a second yield of III-OH as well as IV-OH with mp 92–93.2°. The yields were 4.67 g of III-OH and 0.62 g of IV-OH.

Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$: C, 82.72; H, 8.10. Found for III-OH: C, 82.62; H, 8.05. For IV-OH: C, 82.59; H, 8.08.

B. Treatment of 9-benzonorbornenone with methylmagnesium iodide in ether resulted in the exclusive formation of III-OH. The yield was 88%.

Tosylates of III-OH and IV-OH. A. **III-OTs.** To a solution of 1.05 g of III-OH in 30 ml of tetrahydrofuran, a solution of 4.4 ml of 15% *n*-butyllithium-*n*-hexane solution was added dropwise at 5–10° under a nitrogen atmosphere. After stirring for 30 min, a solution of 1.34 g of tosyl chloride in 10 ml of tetrahydrofuran was added at 5–7° and the mixture stirred for 3 hr. The tetrahydrofuran was evaporated; the residual syrup was dissolved in ether, washed with water, dried, and evaporated. The crystals obtained were recrystallized from *n*-hexane to yield 1.57 g (80%) of III-OTs with mp 90–91°.

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$: C, 69.48; H, 6.14. Found: C, 69.27; H, 6.35.

B. **IV-OTs**, mp 74.8–75.8°, was similarly obtained.

Anal. Found: C, 69.56; H, 6.15.

7-Methylnorborn-7-yl tosylate, mp 48–49°, was similarly prepared from 7-methylnorbornan-7-ol, mp 98–99° (lit.⁹ 97–98°).

Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2\text{S}$: C, 64.25; H, 7.19. Found: C, 64.44; H, 7.21.

9-Methylenebenzonorbornene. Methyltriphenylphosphonium bromide (7.14 g) was added to a stirred solution of 12.6 ml of 15% *n*-butyllithium-*n*-hexane in 60 ml of ether at approximately 23° over a 15-min interval. The mixture was stirred for an additional

(a) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1246, 1247, 1248 (1964); (b) H. C. Brown and M.-H. Rei, *ibid.*, **86**, 5004 (1964); (c) H. C. Brown and H. M. Bell, *ibid.*, **86**, 5006 (1964); (d) H. C. Brown and M.-H. Rei, *ibid.*, **86**, 5008 (1964).

¹ References cited in ref 15.

² H. C. Brown and G. L. Tritle, *J. Am. Chem. Soc.*, **88**, 1320 (1966).

³ G. D. Sargent, *Quart. Rev. (London)*, **20**, 301 (1966).

⁴ S. Winstein, A. H. Lewin, and K. C. Pande, *J. Am. Chem. Soc.*, **85**, 24 (1963); S. Winstein, *et al.*, *ibid.*, **87**, 376, 378, 379, 381 (1965), references cited therein.

⁵ (a) M.-H. Rei and H. C. Brown, *ibid.*, **88**, 5335 (1966); (b) H. C. Brown and K. Takeuchi, *ibid.*, **88**, 5336 (1966).

⁶ See footnote 2 in ref 20a.

(22) A private communication from Professor H. C. Brown.

(23) Melting points were taken by capillary and are corrected. Boiling points are uncorrected. Infrared spectra were determined with a Nippon Bunko IR-S spectrometer in carbon tetrachloride and carbon disulfide; nmr spectra were determined at 60 Mc with a Varian A-60 spectrometer using tetramethylsilane as an internal standard.

2 hr until a dark orange solution was obtained. To this a solution of 3.16 g of 9-benzonorbornenone in 50 ml of tetrahydrofuran was added and the mixture refluxed for 10 hr. The tetrahydrofuran was evaporated; the residue was extracted with ether, washed with water, dried, and evaporated, leaving an oil. Distillation of the oil followed by elution chromatography over Florisil yielded 1.1 g (35%) of 9-methylenebenzonorbornene, bp 76–78° (5 mm), n_D^{20} 1.5680.

Anal. Calcd for $C_{12}H_{12}$: C, 92.26; H, 7.74. Found: C, 92.44; H, 7.88.

6,7-Dinitrobenzonorbornen-9-anti-ol. To a solution of 656 mg of 6-nitrobenzonorbornen-9-anti-ol acetate^{2b} in 8 g of 98% H_2SO_4 was added a mixture containing 225 mg of fuming HNO_3 (d 1.5) and 450 mg of 98% H_2SO_4 at about 0°. The usual work-up gave 480 mg of the crude dinitro acetate. This compound was hydrolyzed by heating for 4 hr on a steam bath in a solvent composed of 70 ml of 20% H_2SO_4 and 30 ml of dioxane. The work-up yielded 6,7-dinitrobenzonorbornen-9-anti-ol, mp 130–131°.

Anal. Calcd for $C_{11}H_{10}O_4N_2$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.96; H, 4.26; N, 10.81.

The brosylate was prepared by the standard procedure and had mp 195°.

Anal. Calcd for $C_{17}H_{14}O_7SBrN_2$: C, 43.51; H, 2.79; N, 5.97. Found: C, 43.54; H, 2.85; N, 6.03.

6,7-Dinitrobenzonorbornen-9-syn-ol, mp 148–149°, was similarly prepared by the nitration of 6-nitrobenzonorbornen-9-syn-ol acetate,^{2b} followed by hydrolysis.

Anal. Calcd for $C_{11}H_{10}O_4N_2$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.88; H, 4.09; N, 11.03.

The acetate had mp 216–217°.

Anal. Calcd for $C_{11}H_{12}O_6N_2$: C, 53.43; H, 4.14. Found: C, 53.42; H, 4.02.

The brosylate had mp 204–205°.

Anal. Calcd for $C_{17}H_{14}O_7SBrN_2$: C, 43.51; H, 2.79. Found: C, 43.46; H, 2.84.

Vpc analyses of solvolysis products were carried out on a Hitachi gas chromatograph Model F-6, equipped with a 1 × 3 mm stainless steel column packed with 10% SE 30 on 60–80 mesh Chromosorb W. Helium was used at a pressure of 1 kg/cm² as a carrier gas. Retention times of *anti*- and *syn*-2-benzo[3,4]bicyclo[3.2.0]heptenol at 150° were 20.2 and 23.1 min, respectively. Those of 9-methylenebenzonorbornene, III-OAc, and IV-OAc at 120° were 9.5, 38.4, and 35.3 min, respectively.

Proximity Effects. XLVI. Stereospecific Synthesis of *cis*- and *trans*-4-Phenylcyclooctanol¹

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Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. Received January 25, 1967

Abstract: The stereospecific synthesis of *cis*- and *trans*-4-phenylcyclooctanol via transannular reactions involving oxygen-bridged ring precursors is described. A number of alternative paths involving cyclizations with lead tetraacetate, mercuric acetate, and mercuric oxide and iodine have been investigated and several products have been identified. An improved synthesis of *cis*-5-phenylcyclooctanol is described.

Previous papers in this series describe the synthesis of cyclooctane derivatives as part of a general study of proximity effects and transannular reactions in medium-ring compounds.⁴ Our interest in such systems includes the use of transannular reactions to develop convenient stereospecific routes to the less accessible phenylcyclooctanols. The general approach was to synthesize cyclooctyl compounds with suitably constituted oxygen bridges which could subsequently be severed by hydrogenolysis. Thus, in principle, bridge scission⁵ of 1-phenyl-9-oxabicyclo[4.2.1]nonane (**1a**) and 1-phenyl-9-oxabicyclo[3.3.1]nonane (**1b**) at the benzylic carbon-oxygen bonds would give rise to 4-phenylcyclooctanol and 5-phenylcyclooctanol, respectively. The utility of this approach depends on the hydrogenolysis occurring exclusively at the benzylic position and on the ring-opening process being stereo-

specific. There was ample evidence that the former condition would hold; the latter condition appeared less certain. As an initial exploration of this idea this paper describes the synthesis and hydrogenolysis of the cyclic ethers **1a** and **b**.

Many examples of the formation of cyclic ethers on treatment of steroidal alcohols with lead tetraacetate have been reported.⁶ The reaction has been extended to saturated acyclic,⁷ unsaturated acyclic,⁸ and saturated bicyclic⁹ alcohol systems. The cyclic ethers formed usually have been five membered rather than six membered although in some cases mixtures of the two have been isolated. For example, treatment of cyclooctanol with lead tetraacetate in benzene gave 9-oxabicyclo[4.2.1]nonane; no detectable amount of the 1,5 isomer could be found in the product.¹⁰ Under similar conditions, 1-methylcyclooctanol gave a mixture (1:3) of 1-methyl-9-oxabicyclo[4.2.1]nonane and 1-methyl-9-oxabicyclo[3.3.1]nonane.¹⁰ Thus, introduction of a methyl group may alter the conformation of the cyclooctane ring so as to favor the formation of the 1,5 over

(1) Supported in part by Research Grant GP-1587 from the National Science Foundation.

(2) Deceased, June 4, 1966.

(3) (a) To whom enquiries may be addressed at the Department of Chemistry, Queens University, Belfast, Ireland. (b) National Institutes of Health Fellow 1965–1966.

(4) For a general discussion see A. C. Cope, M. M. Martin, and M. A. McKervey *Quart. Rev.* (London), 20, 119 (1966).

(5) Removal of the carbonyl bridge in compounds containing the bicyclo[3.3.1]nonan-9-one system offers a promising method for the synthesis of a variety of substituted cyclooctanes and cyclooctapolyenes. See A. C. Cope, F. S. Fawcett, and G. Munn, *J. Am. Chem. Soc.*, 72, 3399 (1950); A. C. Cope, E. S. Graham, and D. J. Marshall, *ibid.*, 76, 6159 (1954); A. C. Cope and D. M. Gale, *ibid.*, 85, 3743 (1963); G. L. Buchanan, M. McKillop, and R. A. Raphael, *J. Chem. Soc.*, 833 (1965).

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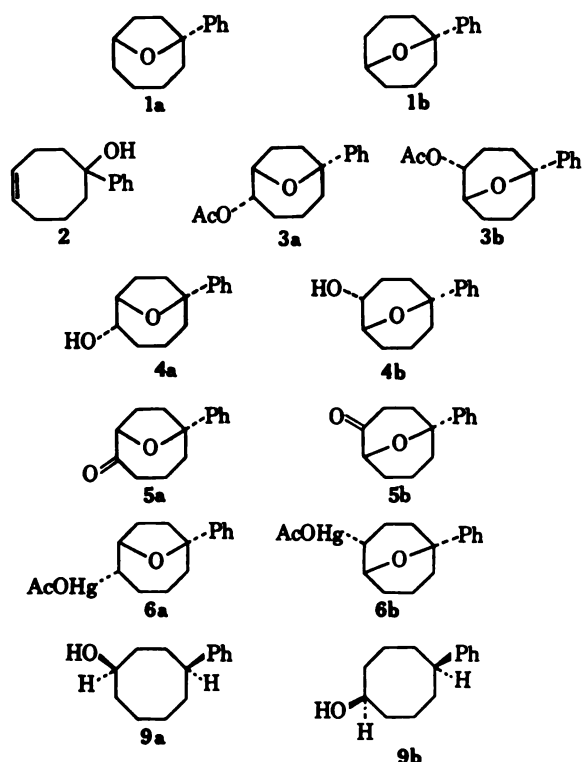
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(9) K. Kitahonoki and A. Matsuura, *Tetrahedron Letters*, 2263 (1964).

(10) A. C. Cope, M. Gordon, S. Moon, and C. H. Park, *J. Am. Chem. Soc.*, 87, 3119 (1965).

the 1,4 oxide. Other reagents which effect cyclic ether formation from monohydric alcohols include mercuric oxide and iodine, lead tetraacetate and iodine, silver oxide and bromine, and N-iodosuccinimide. These reactions have been reviewed by Heusler and Kalvoda.¹¹ Bordwell¹² has described the mercuration of 4-cycloocten-1-ol with mercuric acetate in the presence of sodium acetate. Reduction of the resulting 5-acetoxymercuri-9-oxabicyclo[4.2.1]nonane with sodium borohydride gave 9-oxabicyclo[4.2.1]nonane uncontaminated by the [3.3.1] isomer.

In the present study, 1-phenyl-4-cycloocten-1-ol (2), prepared from 4-cycloocten-1-one and phenylmagnesium bromide, was treated with lead tetraacetate in boiling chloroform for 10 hr. Gas chromatographic and infrared analysis of the crude product indicated the



presence of a saturated acetate (97%) in addition to two minor components (3%). One of the minor components¹³ appeared to be a mixture of phenylcyclooctadienes formed presumably by dehydration of the starting alcohol during the reaction or during the gas chromatographic analysis. The saturated acetate fraction, which could be obtained pure by distillation, had significant infrared absorption¹⁴ at 1730, 1070, and 1025 cm^{-1} . It was further resolved by gas chromatography into the isomers 3a and b (present in about equal amounts). It was not necessary at this stage to determine the stereochemistry of the acetoxy substituent since the asymmetry at this position was to be removed in a subsequent step. It follows however from analogy with a similar reaction with 4-cycloocten-1-ol.¹⁵ The

acetate mixture was reduced with lithium aluminum hydride to give a mixture of the secondary alcohols 4a and b (approximately equal amounts). Oxidation with chromium trioxide in pyridine gave the corresponding ketones 5a and b. Wolff-Kishner reduction of the ketone mixture afforded the ethers 1a (60%) and b (40%) in 95% yield. Partial separation of the ether mixture was achieved by crystallization from pentane at -78° . Isomer 1b separated as a crystalline solid, mp $47-47.5^\circ$, and the filtrate, which was enriched (70-75%) with isomer 1a, could be further purified by chromatography on alumina. In this way 1a was obtained 90% isomerically pure.

The method of oxymercuration followed by reduction is of synthetic value for ethers, alcohols, and lactones.^{12,16} This route was chosen in an attempt to increase the amount of the [4.2.1] isomer initially present in the mixture. Addition of the mercuri group was also chosen in the hope that a crystalline product would be obtained. Mercuration of 1-phenyl-4-cycloocten-1-ol with mercuric acetate in the presence of sodium acetate proceeded rapidly at room temperature to give a mixture of 1-phenyl-5-acetoxymercuri-9-oxabicyclo[4.2.1]nonane (6a) and 1-phenyl-4-acetoxymercuri-9-oxabicyclo[3.3.1]nonane (6b) as a crystalline solid. The isomeric composition could not be determined directly but sodium borohydride reduction¹² of the mixture gave the ethers 1a (70%) and b (30%). In addition it was found that fractional crystallization of 6 gave the [4.2.1] isomer 6a as the less soluble fraction and in this way the purity of this isomer was increased to >95%. Reduction of 6a with sodium borohydride gave 1a in 62% yield. The formation of the acetoxymercuri ethers 6a and b indicates that a functional group such as hydroxyl can participate in a transannular reaction as an internal nucleophile. The stereochemistry of the oxymercuration products was not determined but the relative configurations of the oxygen atom and the acetoxymercuri substituent in the product will be *trans* as shown on the basis of the normal *trans* addition to the olefinic bond.^{12,16-18}

We also undertook a study of the photochemically induced reaction of 1-phenylcyclooctanol with mercuric oxide and iodine to determine whether the 1-phenylcyclooctyloxy radical would undergo a transannular rearrangement of the type observed in the photochemical decomposition of 1-methylcyclooctyl hypochlorite.¹⁹ The action of such reagents as mercuric oxide and iodine or mercuric acetate and iodine on monohydric alcohols may also involve transannular hydrogen abstraction through the decomposition of the *in situ* produced hypiodites. Unlike hypochlorites, these hypiodites have not been isolated or characterized.²⁰ A complex mixture of products was obtained on ir-

yield. The configuration of the acetoxy substituent in both isomers was established to be as shown: A. C. Cope and M. A. McKervey, unpublished results.



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(12) F. G. Bordwell and M. L. Douglass, *J. Am. Chem. Soc.*, 88, 993 (1966).

(13) Comparison based only on retention time on gas chromatography.

(14) 9-Oxabicyclo[4.2.1]nonane and 9-oxabicyclo[3.3.1]nonane have distinguishing infrared bands at 1065 and 1022 cm^{-1} , respectively.

(15) We observed initially that the reaction of 4-cycloocten-1-ol with lead tetraacetate gave a mixture of the acetoxy ethers i and ii in high

ditional 1.5 hr and was then treated cautiously with cold water. Precipitate was separated and the ether solution evaporated to give 16.8 g (100%) of a viscous oil which partially solidified on cooling. The infrared spectrum of this material showed strong carbonyl absorption and the absence of acetate absorption. Gas chromatographic analysis (10-ft, 10% XF-1150 column at 198°C) showed that 4a and b were present in about equal amounts. A sample was recrystallized several times from benzene-pentane and then sublimed at 70°C (0.1 mm). The highest melting point observed was 73–74.5°C; gas chromatography showed that this material still contained both isomers.

Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.84; H, 8.46.

1-Phenyl-4-oxabicyclo[4.2.1]nonane (5a) and 1-Phenyl-4-oxabicyclo[3.3.1]nonane (5b). A solution of the alcohol 4a and b (23.3 g) in pyridine (50 ml) was added to the mixture prepared from chromium trioxide (25 g) and pyridine (50 ml). The resulting brown mixture was stirred at room temperature for 15 hr and was then diluted with ether (200 ml). The mixture was removed by filtration through Celite, and the filtrate washed with cold water (1 l.) and the organic layer separated. The aqueous layer was extracted five times with ether (total volume 1 l.), and the combined organic extracts were washed repeatedly with dilute hydrochloric acid. The dried ether solution was concentrated to give an oil (22.5 g). Distillation gave 18.1 g (78.5%), bp 139°C (0.55 mm). Gas chromatographic analysis on a 10-ft, 10% XF-1150 column at 220°C showed the presence of the two isomers in unequal amounts (ca. 37:63). A sample collected from the rubber at 200°C was analyzed.

Calcd for $C_{14}H_{18}O_2$: C, 77.75; H, 7.46. Found: C, 77.44; H, 7.44.

1-Phenyl-9-oxabicyclo[4.2.1]nonane (1a) and 1-Phenyl-9-oxabicyclo[3.3.1]nonane (1b). The above ketone mixture (18 g), 95% hydrazine (8.7 g), potassium hydroxide (35 g), and ethyl alcohol (200 ml) were heated at 130°C for 1 hr. The temperature was slowly raised to 175°C and maintained for 2.5 hr. The mixture cooled and diluted with water (500 ml). The aqueous solution was extracted with three 150-ml portions of ether, and the combined extracts were washed with water and dried. Removal of the solvent gave 5.8 g (95%) of a colorless oil which was shown by gas chromatography on a 5-ft 5% XF-1150 column at 175°C to contain 95% mixture of the [4.2.1] isomer 1a (60%) and the [3.3.1] isomer 1b (40%). Partial separation of the two isomers was achieved by distillation from pentane at –78°C. Isomer 1b separated as a fine solid. Recrystallization from pentane gave needles, mp –47.7°C.

Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.01; H, 9.05.

Filtrate from the above fractional crystallization was enriched (ca. 75%) with the isomer 1a. Further fractionation was achieved by chromatography on Merck acid-washed alumina. In this isomer 1a was obtained in about 90% isomeric purity.

1-Phenyl-5-acetoxymethyl-9-oxabicyclo[4.2.1]nonane (6a). To a stirred solution of mercuric acetate (32.2 g) and sodium (9 g) in distilled water (200 ml) was added 1-phenyl-4-cyclooctanol (2) (20.4 g) in methanol (50 ml). The solid which deposited after 1 hr was isolated by filtration and washed with water.

There was obtained 34 g of a mixture which contained 70% [4.2.1] isomer 6a and 30% of the [3.3.1] isomer 6b. Fractionation from benzene-pentane (1:1) gave 13.5 g of 6a, mp 140–142.5°C, containing 91.5% of isomer 6a. An additional 6.5 g, mp 140–141.5°C, was obtained by similar treatment of filtrate residues. These two fractions were combined and distilled from a mixture of benzene (125 ml) and pentane (75 ml) to give 15.5 g, mp 141–143°C. This material contained >95% isomer 6a.

Calcd for $C_{14}H_{18}HgO_3$: C, 41.69; H, 4.37. Found: C, 41.4; H, 4.15.

Distribution in the above organomercurials was determined by dissolving 5 mg of the solid in 0.25 ml of a sodium hydroxide solution of sodium borohydride. The mixture was shaken for a few seconds and extracted with pentane. The pentane solution was analyzed by gas chromatography on an 8-ft 20% LAC-728 column at 210°C.

1-Phenyl-9-oxabicyclo[4.2.1]nonane (1a). The mercurial 6a was suspended in 0.5 M sodium hydroxide solution (200 ml) and stirred rapidly while a solution of sodium borohydride (1 g)

in 2.5 M sodium hydroxide (30 ml) was added over 30 min. Pentane (50 ml) was added, and stirring was continued for 2 hr. The pentane layer was separated, and the aqueous layer was extracted with two 100-ml portions of pentane. The combined pentane solutions were washed with water and dried. Removal of the solvent followed by distillation gave 3.95 g (61.5%) of 1a, bp 89–92°C (0.25 mm). Gas chromatographic analysis showed that the product contained less than 3% 1b.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.01; H, 9.05.

In a similar experiment the yield was 77%. The residue from the distillation contained mostly the fragmentation product 1-phenyl-4-cycloocten-1-ol.

cis-4-Phenylcyclooctanol (9a). A solution of 1a (3.0 g) in absolute ethanol (30 ml) containing 10% palladium on charcoal (0.75 g) and two drops of perchloric acid was hydrogenated at atmospheric pressure until hydrogen uptake had ceased. The catalyst was removed by filtration, and the solvent was evaporated to leave an oil which soon crystallized. Recrystallization from hexane gave 2.25 g of cis-4-phenylcyclooctanol as needles, mp 76–78.5°C. An analytical sample, mp 79–80.5°C, was obtained by several recrystallizations from hexane. The molecular weight obtained by mass spectrometry was 202. The infrared spectrum (KBr) showed bands at 1092, 1075, 1054, 985, 897, 759, and 703 cm^{-1} .

Anal. Calcd for $C_{14}H_{18}O$: C, 82.30; H, 9.87. Found: C, 81.94; H, 9.92.

cis-4-Phenylcyclooctyl Tosylate. cis-4-Phenylcyclooctanol (5 g) was dissolved in pyridine (50 ml), and *p*-toluenesulfonyl chloride (9.3 g) was added. The solution was kept at 5°C for 16 hr. Crushed ice was added to bring the total volume to 100 ml, and an oil separated. Addition of an additional 100 ml of cold water with stirring caused the oil to crystallize. The solid was collected and dissolved in methylene chloride. After drying, the solvent was removed to leave an oil which solidified on standing. There was obtained 8.6 g (98%), mp 63–65.5°C. Two crystallizations from pentane gave an analytical sample, mp 67–67.5°C.

Anal. Calcd for $C_{21}H_{26}O_2S$: C, 70.35; H, 7.31. Found: C, 70.11; H, 7.22.

trans-4-Phenylcyclooctanol. Crude cis-4-phenylcyclooctyl tosylate (7.45 g) was added to a solution of tetraethylammonium acetate (35 g) in reagent grade acetone (300 ml) containing Linde Molecular Sieves. The mixture was heated under reflux for 24 hr, and most of the solvent was then removed under reduced pressure. The residue was dissolved in water and extracted with ether. The ether solution was washed with water and dried. Removal of the solvent gave an oil (4.0 g). Gas chromatographic analysis on a 2-ft 20% SE 30 column at 190°C showed the presence of trans-4-phenylcyclooctyl acetate (63%) and a mixture of 4- and 5-phenylcyclooctene (37%). The total reaction product was dissolved in ether (50 ml), and lithium aluminum hydride (0.5 g) was added in small portions with stirring. The mixture was heated under reflux for 1 hr and then treated cautiously with cold water and 10% hydrochloric acid. The ether layer was separated and dried. Removal of the solvent gave an oil (3.5 g). The oil was dissolved in pentane (30 ml) and was allowed to stand at –5°C for 24 hr. The crystals obtained (1.7 g) had mp 60–62°C. Crystallization from hexane gave 1.55 g (36.5%), mp 61–62°C. An analytical sample, mp 63–64.5°C, was obtained by recrystallization from hexane. The infrared spectrum (KBr) showed bands at 1049, 1035, 1010, 915, 759, and 703 cm^{-1} .

Anal. Calcd for $C_{14}H_{18}O$: C, 82.30; H, 9.87. Found: C, 82.24; H, 9.62.

4-Phenylcyclooctanone. cis-4-Phenylcyclooctanol (1.0 g) in acetone (5 ml) was oxidized with an excess of Jones reagent³³ at room temperature for 24 hr. The mixture was poured into water and extracted with three 25-ml portions of ether. The combined extracts were washed with saturated sodium bicarbonate solution and dried. Removal of the solvent gave 0.9 g (91%) of an oil which was shown by gas chromatography on a 2-ft 20% SE 30 column at 190°C to be 98% pure. A sample collected from the same column was analyzed.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.12; H, 8.97. Found: C, 82.75; H, 8.93.

The tosylhydrazone prepared in ethanol and recrystallized from the same solvent had mp 128–130°C.

Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.07; H, 7.07; N, 7.56. Found: C, 67.65; H, 7.11; N, 7.55.

(33) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemm, *J. Chem. Soc.*, 2548 (1953).

G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Soc.*, 75, 422 (1953).

cis-5-Phenylcyclooctanol (9b). A solution of 1-phenyl-9-oxabicyclo[3.3.1]nonane (1b) (3.25 g) in absolute ethanol (35 ml) containing 10% palladium on charcoal (1.0 g) and six drops of perchloric acid was hydrogenated until hydrogen uptake had ceased. The catalyst was removed by filtration through Celite, and the filtrate was treated with ten drops of saturated potassium bicarbonate solution and then concentrated at reduced pressure. The residual semisolid was dissolved in ether, and the ether solution was washed with water and dried. Removal of solvent gave a white solid (3.2 g), mp 66–68°. Two crystallizations from hexane gave crystals, mp 69.5–70.5° (lit.²⁴ mp 70–71°). The infrared spectrum of the product was identical with that of *cis*-5-phenylcyclooctanol described by Cope and Kinnel.²⁴

Lithium Aluminum Hydride Reduction of 4-Phenylcyclooctanone. Lithium aluminum hydride (100 mg) was added to the ketone (200 mg) in ether (5 ml). The mixture was allowed to stand at room temperature for 1 hr. Cold water and dilute hydrochloric acid were added, and the ether layer was separated, washed with water, and dried. Removal of solvent gave an oil (ca. 220 mg). This material crystallized in part from pentane at –5° after 6 weeks. The crystals obtained had mp 44–52°. The infrared spectrum showed that the product was a mixture of *cis*- and *trans*-4-phenylcyclooctanol.

Mixtures of *cis*- and *trans*-4-phenylcyclooctanol were prepared and their melting point ranges were determined (see Table I).

Table I

% <i>cis</i>	Mp, °C	% <i>cis</i>	Mp, °C
0.0	61.5–62.5	76.8	56.5–71.0
7.55	55.5–59.5	85.3	68.5–75.5
21.9	50.0–56.5	95.4	72.5–78.0
35.0	45.0–47.0	100.0	79–79.5
51.5	44.0–52.0		

1-Phenylcyclooctanol. The white crystalline hydrate, prepared by the method of Cope and Kinnel,²⁴ could be distilled at 125.5–127° (1.0 mm) to give the anhydrous product as a viscous oil.

Anal. Calcd for $C_{14}H_{18}O$: C, 82.30; H, 9.87. Found: C, 82.40; H, 9.83.

Reaction of 1-Phenylcyclooctanol with Mercuric Oxide and Iodine. Anhydrous 1-phenylcyclooctanol (25 g) was dissolved in cyclohexane (500 ml) in a 1-l. flask fitted with a stirrer and a condenser set for reflux. Calcium carbonate (50 g) and red mercuric oxide (150 g) were added, and the mixture was stirred and heated to boiling with a GE 274-w sunlamp. Iodine (100 g) was added in small portions through the condenser over a period of 45 min. The mixture was stirred and irradiated for an additional 3 hr. After cooling, the solids were removed by filtration, and the filtrate was washed with 10% sodium thiosulfate solution (350 ml) and

dried. Removal of solvent gave a yellow oil (35 g). The oil was dissolved in pentane and chromatographed on acid-washed alumina (350 g). Elution with pentane (1200 ml) gave an oil (11.7 g) in several fractions. Distillation afforded 7.25 g (29.3%) of a mixture of 1a and b, bp 101–115° (0.75 mm). Gas chromatographic analysis indicated that the two ethers were present in about equal amounts. The mixture was dissolved in pentane (65 ml), and the solution was cooled at –75° for 30 min. The crystals were isolated to give 2.1 g of 1b uncontaminated with 1a. The filtrate yielded an oil containing 1a (65%) and 1b (35%). The yield of the ether mixture varied from 20 to 35% in similar runs.

Further elution of the column during the chromatography yielded a third product which was shown to be 8-iodo-1-phenyloctan-1-one (8). After several recrystallizations from pentane it had a melting point of 41.5–42°.

Anal. Calcd for $C_{14}H_{19}IO$: C, 50.92; H, 5.79; I, 38.43. Found: C, 51.21; H, 5.79; I, 38.18.

Reduction of 8-Iodo-1-phenyloctan-1-one (8). The iodide (0.5 g) was dissolved in glacial acetic acid (7 ml), and zinc dust (1.0 g) was added. The mixture was heated on a steam bath with occasional stirring for 20 min. The solution was decanted, and the residual solid was washed several times with pentane. Water was added to the acetic acid-pentane mixture, and the organic layer was separated. The pentane solution was washed several times with saturated sodium bicarbonate solution and dried. Removal of the solvent gave an oil (300 mg) which was 90% pure by gas chromatography. The infrared spectrum of a sample collected from a 2-ft 20% SE 30 column at 200° was identical with that of heptyl phenyl ketone described below.

A portion was converted to the dinitrophenylhydrazone which had mp 113–115° after recrystallization.

Heptyl Phenyl Ketone. Octanoic acid (5.0 g) and thionyl chloride (7 ml) were heated on a steam bath for 1 hr. The excess thionyl chloride was removed at reduced pressure, and the residue was dissolved in benzene (10 ml). The benzene solution was added slowly (caution) to a suspension of aluminum chloride (10.0 g) in benzene (50 ml). When the addition was complete, the mixture was heated on a steam bath for 1 hr and then was poured onto crushed ice. The benzene layer was separated, washed with 10% sodium bicarbonate solution and water, and dried. Removal of the solvent left an oil which was purified by dissolution in pentane and addition of activated charcoal. The pentane solution was filtered and cooled to –10°. The crystals which could be obtained by rapid filtration melted at room temperature. A pure sample of heptyl phenyl ketone (a band appeared in the infrared at 1685 cm^{-1}) was obtained by preparative gas chromatography on a 2-ft 10% SE 30 column at 200°.

The 2,4-dinitrophenylhydrazone had mp 113–116° after recrystallization from ethanol. It showed no melting point depression when mixed with the 2,4-dinitrophenylhydrazone of heptyl phenyl ketone prepared by reduction of the iodide described above.

Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.18; H, 6.33; N, 14.84.

The "Charge" Effect in Nucleophilic Displacement Reactions

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Abstract: A previous study on the reactivity of isopropyl methylphosphonofluoridate with various anions of hydroxybenzenes indicated that the incorporation of a cationic site into the benzene nucleus increased the reactivity of the anion relative to its basic strength. In this work, the reactivities of different cationically substituted nucleophiles have been determined. One class of nucleophiles, called " α " nucleophiles because they possess an unshared electron pair on the (α) atom adjacent to the attacking atom, showed no (anions of hydroxamic acids) or only a slight (anions of keto oximes) "charge" effect, i.e., their reactivities were equal to or only slightly greater than would be expected for a nucleophile of the same class of the same basic strength but possessing no cationic group in the molecule. A second class of nucleophiles, the anions of hydrated aldehydes, similar to the hydroxybenzenes in that the atom adjacent to the attacking atom contained no unshared electron pair, exhibited a "charge" effect qualitatively and quantitatively similar to that shown by the hydroxybenzenes. An explanation for the different responses to the "charge" effect shown by the " α " and "non- α " nucleophiles is offered. The "charge" effect studies are not only useful practically, but also may be used in separation of factors in nucleophilicity. These studies support the designation of a separate classification for " α " nucleophiles when discussing reactivity.

recent studies² it has been observed that anions of hydroxybenzenes containing cationic groups are more reactive than other hydroxybenzenes of the same protonicity in displacement of fluoride ion from isopropyl methylphosphonofluoridate (GB) in aqueous solution. It was also shown that the magnitude of the increase in reactivity was related to (a) the distance between the cationic and anionic sites, the difference increasing as the distance between the loci of the charges decreases, (b) to the number of cationic groups in the nucleophile, each cationic site contributing independently in accordance with its distance from the anionic site. For example, it was shown that the monoanion of protonated 3-aminomethylcatechol was approximately five times as reactive as the monoanion of a catechol of the same proton basicity but possessing no cationic group, whereas the monoanion of 4-aminomethylcatechol was less than twice as reactive as a cationic monocatecholate anion of comparable basicity. Also, the monoanion of the protonated 3-ethylaminomethylcatechol was approximately six times as reactive as the monoanion of the diprotonated, 3,6-bis(dimethylaminomethyl)catechol 38, and the monoanion of the 6-tris(dimethylaminomethyl)catechol 75 times as reactive as their noncationic-bearing, but same protonicity, analogs.^{2b} The enhanced reactivity shown by a nucleophile containing a cationic site ("charge" effect) has been explained on the basis that pK_a of the conjugate acid is a true measure of the basicity of the nucleophile toward neutral substrates; that the basicity of a cation-bearing nucleophile is greater than a neutral substrate than would be predicted from the pK_a of the conjugate acid, since the Coulomb repulsion factors operative in ionization phenomena are absent in reaction with a neutral substrate.

(a) Edgewood Arsenal, Md. (b) University of Delaware, Newark,

(a) J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Billington, Jr., and G. R. List, *J. Am. Chem. Soc.*, **86**, 3075 (1964); (b) J. Epstein, H. O. Michel, D. H. Rosenblatt, R. A. Stephani, and E. Cook, *ibid.*, **86**, 4959 (1964).

While the effect of a cationic group on the reactivity of the hydroxybenzenes in displacement reactions of the phosphonyl ester, GB, has been established, the effect of cationic substitution in nucleophiles other than the hydroxybenzenes in this displacement reaction has not been assessed. In this paper, we report on the effect of cationic substituents on the reactivity of the anions of hydroxamic acids, keto oximes, and hydrated aldehydes in displacement of fluoride ion from GB in aqueous solution.³

Experimental Section

Materials. Picoline, isonicotinic acid, nicotinehydroxamic acids, and the corresponding methiodides were synthesized according to the directions of Hackley, *et al.*⁴ *o*-Diethylaminoethoxybenzohydroxamic acid was kindly supplied by Dr. R. E. Plapinger. Chloral, pyruvic aldehyde (as an aqueous solution), and 2-, 3-, and 4-pyridine carboxaldehydes were obtained from commercial sources. The 2- and the 4-pyridine carboxaldehydes were converted to their methiodides according to the procedure of Steinberg, Poziomek, and Hackley.⁵ The methiodide of 1,1-dimethyl-2-dimethylamino-propionaldehyde was prepared from the commercially available free base by reaction with methyl iodide in diethyl ether, mp 230°. *Anal.* Calcd for $C_8H_{18}INO$: C, 35.4; H, 6.6. Found: C, 35.5; H, 6.8. Compounds 1, 2, 3, and 11 in Table III were kindly supplied by Dr. G. M. Steinberg.⁶ The other compounds were prepared according to published procedures.⁶ All compounds were of high purity using elemental analyses, neutralization equivalents, and sharpness of melting point criteria except pyruvic aldehyde which was determined to be 49.6% by analysis.

Determination of pK_a Values. The compounds were made up to be approximately 0.01 *M* with the ionic strength adjusted to 0.1 with KCl. A 3-ml aliquot, adjusted to the desired temperature and maintained at that temperature to $\pm 0.1^\circ$, was titrated potentiometrically with a microsyringe (total volume 0.5 ml) cali-

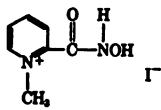
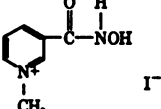
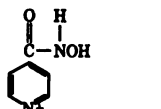
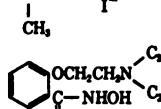
(3) For studies on the chemistry and mechanisms of the reaction between GB and hydroxamic acids, see (a) R. Swidler and G. M. Steinberg, *ibid.*, **78**, 3594 (1956); GB and keto oximes: (b) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956); GB and hydrated aldehydes: (c) G. M. Steinberg, E. J. Poziomek, and B. E. Hackley, Jr., *J. Org. Chem.*, **26**, 368 (1961).

(4) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 3651 (1955).

(5) G. M. Steinberg and J. Bolger, *J. Am. Pharm. Assoc.*, **46**, 188 (1957).

(6) For pertinent references on the preparation of compounds 4, 5, 6, 7, 8, 9, and 10 (Table III) see O. Toussier, *Org. Reactions*, **7**, 371 (1953).

Table I. pK_a and k_2 (Reaction with GB) for Charged Hydroxamic Acids at 30°

Compd	pK_a	k_2 , l. mole ⁻¹ min ⁻¹
	5.25	2.11 ± 0.08 ^a
	6.41	20.94 ± 0.37 ^b
	5.95	8.09 ± 0.09 ^b
	8.42	630 ± 10 ^{c,d}

^a Average of three determinations. ^b Average of four determinations. ^c Average of two determinations. ^d Experiments on this compound run at 25°.

brated in units of 0.005 ml, and estimable to 0.0005 ml with 0.1 *N* CO₂-free NaOH solution. (A Radiometer automatic titrator was used.)

Determination of Reaction Velocities and Rate Constants. The general procedure for determination of reaction velocities and methods for calculation of the bimolecular rate constants has been previously described.^{2a,7}

In all cases the nucleophiles were in sufficient excess so that their concentrations remained, to all intents and purposes, constant, resulting in first-order kinetics.

For the hydroxamic acids and the hydrated aldehydes, the reaction velocities were determined by analyzing the GB concentrations with time, enzymatically, taking advantage of the anticholinesterase properties of GB.

The reaction velocities for the α -keto oximes were determined manometrically from the CO₂ produced upon reaction of the acidic products of GB oxime reaction with sodium bicarbonate. The half-time of the reaction was taken as the time required to produce 50% of the total CO₂ produced. The bimolecular rate constants were calculated from the first-order rate constants and the concentration of the anions according to the equation

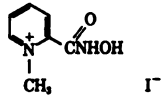
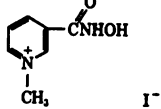
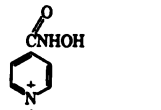
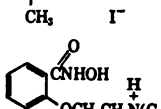
$$k_2 = k_{\text{obsd}}([H^+] + K_a)/K_a[C_0]$$

where k_2 is the bimolecular rate constant in l. mole⁻¹ min⁻¹, k_{obsd} is the first-order rate constant in min⁻¹, K_a is the ionization constant of the hydroxamic acid, oxime, or hydrated aldehyde, and $[C_0]$ is the initial concentration of the acid.

Results

Table I gives the pK_a values of four cationic-bearing hydroxamic acids and the bimolecular rate constants of their anions with GB. Table II contains the data by which one can compare the reactivities of the anions of the above hydroxamic acids with the anions of noncationic-bearing hydroxamic acids. The values listed under the heading "Log k_c " have been calculated from the equation^{8,9} relating the log of the bimolecular rate

Table II. "Charge" Effects in Hydroxamic Acids^a

Compd	pK_a	Log k_2	Log k_c	Log k_2/k_c
	5.29	0.36	0.32	-0.04
	6.41	1.26	1.32	+0.06
	5.95	0.89	0.91	+0.02
	8.42	2.87	2.80	-0.07

^a Calculated from the equation $\log k_2 = 0.80pK_a - 3.87$ at 30° (see Table I).

constant with the pK_a for the nucleophile, viz., $\log k_c = 0.80pK_a - 3.87$; those under the heading "Log k_2 " are the experimentally determined values. Log k_2/k_c then, denotes the deviation of the experimental value from that predicted from the equation of the "normal" nucleophiles of the class under study.

The almost negligible (within experimental error) difference between the logarithms (<0.1, see ref 2a) of bimolecular rate constants of the cationic hydroxamic acids (k_2) and the hydroxamic acids containing no cationic groups (k_c), considering that the distance of separation between the cationic and anionic sites and the type of group producing the charge (i.e., pyridine, aliphatic amine) has been varied over rather wide limits, is strong evidence that there is no "charge" effect on the hydroxamic acid anion similar to that found for the hydroxybenzenes.

The data (Table III) were used to determine the effect of "charge" on the nucleophilicity of the anions of keto oximes.

A plot of the data in Table III is shown in Figure 1, the circles representing values of noncationic-bearing oximes, whereas the x's are for compounds containing a positive charge. The equation of the line drawn through the circular points ("base" line) is

$$\log k_c = 0.642pK_a - 3.25$$



Table IV lists the relevant data for assessing the "charge" effect. As in the previous instance, the values listed under the heading "Log k_c " have been calculated from the equation of the "base" line relating the bimolecular rate constant of the anion of keto oximes with GB and the pK_a of the keto oximes, viz., $\log k_c = 0.642pK_a - 3.25$. Again, $\log k_2/k_c$ is the deviation of the experimental value from that predicted from the equation of the "normal" keto oximes. These data suggest that there is an effect of charge on the reactivity of the anions of keto oximes although, perhaps, not as pronounced as in the case of the hydroxybenzenes. A similar conclusion can be drawn from

(7) T. Wagner-Jauregg and B. E. Hackley, Jr., *J. Am. Chem. Soc.*, **75**, 2125 (1952).

(8) G. F. Endres and J. Epstein, *J. Org. Chem.*, **24**, 1497 (1959).

(9) R. W. Swidler, R. E. Plapinger, and G. M. Steinberg, *J. Am. Chem. Soc.*, **81**, 3271 (1959).

Table III. Data for Keto Oximes at 30°

$\begin{array}{c} \text{O} \quad \text{R}' \\ \parallel \quad \\ \text{R}-\text{C}-\text{C}=\text{NOH} \end{array}$				
Compd	R	R'	pK _a	k ₂ , l. mole ⁻¹ min ⁻¹
1	CH ₃	$\begin{array}{c} \text{CH}_2\text{N}^+(\text{C}_2\text{H}_5)_2 \\ \\ \text{CH}_3 \end{array}$	6.95	15.9
2	CH ₃	$\begin{array}{c} \text{H} \\ \\ \text{CH}_2\text{N}^+(\text{CH}_3)_2 \end{array}$	7.05	29.0
3	CH ₃	$\begin{array}{c} \text{CH}_2\text{N}^+(\text{cyclohexyl}) \\ \\ \text{H} \end{array}$	7.15	35.9
4	CH ₃	COOC ₂ H ₅	7.20	19.0
5	CH ₃	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CCH}_3 \end{array}$	7.50	37.7
6	$\begin{array}{c} \text{H} \\ \\ \text{C}=\text{NOH} \end{array}$	H	7.65	49.8
7	$\begin{array}{c} \text{O} \\ \parallel \\ \text{HON}-\text{C}-\text{NOH}^b \end{array}$		7.95	(69.6) ^a
8	CH ₃	H	8.35	127
9		H	8.40	127
10		H	8.45	149.4
11	CH ₃	$\begin{array}{c} \text{CH}_2\text{CH}_2\text{N}^+(\text{C}_2\text{H}_5)_2 \\ \\ \text{CH}_3 \end{array}$	8.60	248.6
12	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2 > \text{C}=\text{CH} \end{array}$	H	8.90	275.0

^a (69.6) value corrected for first oxime dissociation. ^b Complete structure.

Table IV. "Charge" Effects in Keto Oximes

Compd	Compd structure	pK _a	Log k ₂ ^a	Log k ₂	Log k ₂ /k _c
1	$\begin{array}{c} \text{O} \quad \text{CH}_2\text{N}^+(\text{C}_2\text{H}_5)_2 \\ \parallel \quad \\ \text{CH}_3\text{C}-\text{C}=\text{NOH} \\ \\ \text{CH}_3 \end{array}$	6.95	1.21	1.20	-0.01
2	$\begin{array}{c} \text{O} \quad \text{CH}_2\text{N}^+(\text{CH}_3)_2 \\ \parallel \quad \\ \text{CH}_3\text{C}-\text{C}=\text{NOH} \\ \\ \text{H} \end{array}$	7.05	1.27	1.46	0.19
3	$\begin{array}{c} \text{O} \quad \text{CH}_2\text{N}^+(\text{cyclohexyl}) \\ \parallel \quad \\ \text{CH}_3\text{C}-\text{C}=\text{NOH} \\ \\ \text{H} \end{array}$	7.15	1.34	1.55	0.21
11	$\begin{array}{c} \text{O} \quad \text{CH}_2\text{CH}_2\text{N}^+(\text{C}_2\text{H}_5)_2 \\ \parallel \quad \\ \text{CH}_3\text{C}-\text{C}=\text{NOH} \\ \\ \text{CH}_3 \end{array}$	8.60	2.27	2.40	0.13

^a Calculated from the equation $\log k_2 = 0.642\text{pK}_a - 3.25$, temperature 30°.

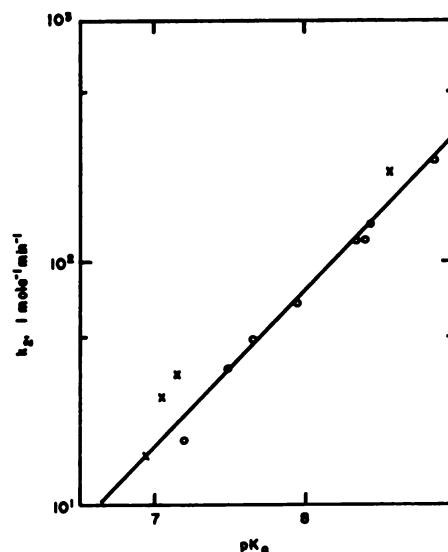


Figure 1. Plot of $\log k_2$ vs. pK_a for reaction of 12 keto oximes with GB at 30°: x, charged keto oximes; O, uncharged keto oximes.

an analysis of the data of Green, *et al.*,¹⁰ on the rate constants of oximes with GB.

Data on seven aldehydes, three of which contain cationic groups, and ninhydrin are shown in Table V. That the effect of a cationic substituent in a hydrated aldehyde on the nucleophilicity of its anion is marked can be seen by comparison of the reactivities of the anions of chloral and 2-formyl-1-methylpyridinium iodide, and pyruvic aldehyde and 4-formyl-1-methylpyridinium iodide. The pK_a values of the first two compounds are almost identical, *viz.*, 9.94 and 9.95, yet their reactivities differ by almost an order of magnitude [$k_2(\text{chloral}) = 32$ l. mole⁻¹ min⁻¹; $k_2(2\text{-formyl-1-methylpyridinium iodide}) = 215$ l. mole⁻¹ min⁻¹]. Similarly, the bimolecular rate constant for the reaction between GB and the anion of pyruvic aldehyde (pK_a of conjugate acid = 11.0) is 102 l. mole⁻¹ min⁻¹; the bimolecular rate constant for the reaction between GB and the anion of 4-formyl-1-methylpyridinium iodide, whose conjugate acid pK_a is less than that of pyruvic aldehyde, *viz.*, 10.72, and hence may be expected to be less than 102 l. mole⁻¹ min⁻¹, is 302 l. mole⁻¹ min⁻¹.

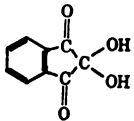

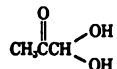
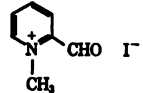
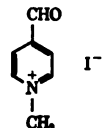

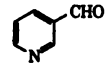
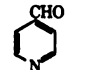
Moreover, the effect of charge appears to be quantitatively similar in the hydrated aldehydes and the hydroxybenzenes. It was shown in the latter series that $\log k_2/k_c$ (where k_2 is the bimolecular rate constant of the anion of "charged" hydroxybenzene with GB and k_c is the bimolecular rate constant of an anion of hydroxybenzene of the same proton basicity but possessing no cationic group) could be estimated from the relationship

$$\log k_2/k_c = c/d^2$$

where c , a proportionality constant, equals 12.7 and d is the distance between the cationic and anionic sites in Angstrom units. The distance between the cationic and anionic sites in the anion of 2-formyl-1-methylpyridinium iodide is estimated from Dreiding models to be 2.64 or 3.64 Å depending upon whether the anionic site is assumed to reside on the oxygen atom

(10) A. L. Green, G. L. Sainsbury, B. Saville, and M. Stanfield, *J. Chem. Soc.*, 1583 (1958).

Table V. Summary of Data for Reaction of Hydrated Aldehydes and Ninhydrin with GB at 25°

Compd	p <i>K</i> _a	<i>k</i> ₂ , l. mole ⁻¹ min ⁻¹
	8.82	13.3 ± 0.1 ^a
	9.95	32.0 ± 0.4 ^a
	11.0	102 ± 5 ^b
	9.94	214 ± 2.5 ^{a,d}
	10.72	302 ± 6 ^{a,d}
	13.6	8450 ± 350 ^a
	13.0	960 ± 112 ^a
	12.05	459 ± 37 ^a

^a Two determinations. ^b Three determinations. ^c Five determinations. ^d Data obtained with the cooperation of Dr. George M. Steinberg.

closest to or farthest from the nitrogen atom. If the latter value is chosen, then, from data on the hydroxybenzenes, it would be predicted that the reactivity of 2-formyl-1-methylpyridinium iodide with GB would be 12.7/3.642² or 0.96 log unit higher than that of chloral (hydrated aldehyde of the same p*K*_a but possessing no cationic group). The actual difference is 0.83 log unit.

Also, the bimolecular rate constant of the reaction between GB and the anion of a hydrated aldehyde (containing no cationic substituent) whose conjugate acid has a p*K*_a equal to 10.72 may be expected to be¹¹ approximately 87 l. mole⁻¹ min⁻¹. Hence the enhancement in rate shown by the 4-formylpyridinium methiodide over that which might be expected from its p*K*_a is 0.54 log unit (log 302 - log 87). The distance between the anionic and cationic sites in the 4-formylpyridinium methiodide from Dreiding models is 4.88 Å. Using this value for *d*, and *c* = 12.7, one would predict from the data on hydroxybenzenes a logarithmic increase in rate of 0.53 log unit, in very good agreement with the value of 0.54 obtained above.

Although of doubtful quantitative significance because of the high probability of error in extrapolation of the

(11) The least-squares equation of the line using the data for chloral, pyruvic aldehyde, 3- and 4-formylpyridine, and ninhydrin is: log *k*₂ = 0.465p*K*_a - 2.95. The bimolecular rate constant for the reaction between a noncationically substituted hydrated aldehyde of p*K*_a = 10.22 would be expected to be ca. 87 l. mole⁻¹ min⁻¹.

data to pH 13.6, it is nevertheless of qualitative value that the anion of a hydrated aldehyde containing no cationic group whose conjugate acid has a p*K*_a of 13.6 may be expected to have a *k*₂ value of ca. 1800 l. mole⁻¹ min⁻¹. The value found for the cation-bearing anion of the aldehyde, 2,2-dimethyl-3-trimethylammonio-propanol iodide (p*K*_a of the conjugate acid = 13.6), was considerably higher, viz., 8450 l. mole⁻¹ min⁻¹.

Table VI lists the distances of separation between the cationic and anionic sites in anions of hydroxamic acids, keto oximes, and hydrated aldehydes, the expected deviations from "normal" that these nucleophiles would show if their behavior were similar to that of the hydroxybenzenes, and the deviation calculated as the logarithm of ratio of the experimentally determined bimolecular rate constants with GB to the bimolecular rate constants of a nucleophile in the same class and of the same proton basicity.

The values of *d* shown in Table VI for the keto oximes require explanation. The distance of separation of the charges in the keto oximes and hydroxamic acids is difficult to estimate due to free rotation of groups; Dreiding models indicate that the distance of separation of charge in the keto oximes designated as compounds 2 and 3 in Table III can vary from 2.8 to 4.4 Å. However, with the larger value there is no steric crowding of the oximino group by the alkyl groups on the amine. That there should be no steric obstruction is suggested by the almost identical deviations from the "base" line shown by compounds 2 and 3 in Figure 1, even though the groups attached to the nitrogen are different. The model having a distance of separation of ca. 4 Å was one in which substitution of ethyl groups for a hydrogen and a methyl (conversion of compound 2 to compound 1 in Table III) produced a structure in which the oxygen of the oximino group was slightly sterically hindered. Steric hindrance in compound 1 is suggested by kinetic data (see Figure 1 and ref 2a). Similar considerations led to a value of ca. 5 Å for the distance of charge separation in compound 11.

In all cases the locus of positive charge was assumed to reside on the pyridinium or amino nitrogens; the site of high electron density was assumed to be on the oximino oxygens in the case of the anions of the hydroxamic acids¹² and keto oximes and on the alcoholic oxygen in the case of the hydrated aldehydes.

Discussion

From the data in Tables II, IV, V, and VI, one concludes that a cationic substituent greatly enhances the reactivity of anions of hydrated aldehydes (relative to their proton basicities), enhances only slightly the reactivity of the keto oximate anion, and has negligible effect upon the reactivity of anions of the hydroxamic acids. Furthermore, the response of the hydrated

(12) The choice of the locus of high electron density is obviously arbitrary; in the anions of the hydroxamic acids and keto oximes, the sites of high electron density can be assumed to reside on either of two oxygens or the oximino nitrogen. O. Exner and B. Kakac [Collection Czech. Chem. Commun., 28, 1965 (1963)] conclude from ultraviolet absorption studies on hydroxamic acids and their anions that the site of electron density in the anion is on the carbonyl oxygen; G. M. Steinberg and R. W. Swidler, *J. Org. Chem.*, 30, 2362 (1965), and R. E. Flapinger, *ibid.*, 24, 802 (1959), argue that the anion exists in at least two and possibly three forms.

Table VI. Predicted and Actual Deviations from "Normal" for Anions of Hydroxamic Acids, Keto Oximes, and Hydrated Aldehydes

Compd	<i>d</i> , Å	<i>c/d</i> ^a (predicted) ^a	Log <i>k</i> ₂ / <i>k</i> ₀ (actual) ^b	Compd	<i>d</i> , Å	<i>c/d</i> ^a (predicted) ^a	Log <i>k</i> ₂ / <i>k</i> ₀ (actual) ^b
Hydroxamic acids				Hydrated Aldehydes			
	4.4 ^c 2.2 ^f	0.65 2.62	-0.04		3.64 ^c 2.64 ^f	0.96 1.82	0.85
	6.0 ^c 3.5 ^f	0.35 1.00	0.06		4.88	0.532	0.54
	6.0 ^c 4.4 ^f	0.35 0.65	0.02		5.0 ^d	0.51	0.68
	8.6 ^c 0.0 ^f	0.17 ...	0.07 ...				
Keto Oximes							
	4.0 ^c	Ca. 0.79	-0.01				
	4.0 ^c	Ca. 0.79	0.19				
	4.0 ^c	Ca. 0.79	0.21				
	5.0	Ca. 0.51	0.13				

^a Calculated from the fraction c/d^2 , where $c = 12.7$, d = distance of separation of charges in Angstrom units. ^b k_2 = experimental bimolecular rate constant of the reaction between GB and the anion of compound listed; k_0 is the bimolecular rate constant calculated from the following equations: hydroxamic acids: $\log k_0 = 0.80pK_a - 3.87$; keto oximes: $\log k_0 = 0.642pK_a - 3.25$; hydrated aldehydes: $\log k_0 = 0.456pK_a - 2.95$, where pK_a is the negative logarithm of the acid dissociation constant of the compound listed. The equations relating $\log k_2$ with pK_a are from ref 3 (hydroxamic acids), Figure 1 of this paper (keto oximes), and Table V of this paper (data on the reactivity of the anions of chloral, pyruvic aldehyde, 3- and 4-formylpyridine, and ninhydrin with GB). ^c This distance can vary from approximately 2.8 to 4.4 Å, depending upon the configuration adopted, a "stretched out" configuration giving a value of 4.4. ^d "Stretched out" configuration. ^e The positive charge is assumed to reside on the nitrogen; the negative, on the oxygen. The value of superscript f is the smallest distance of separation; that of e , the largest.

aldehydes to the "charge" effect is quantitatively similar to that of the hydroxybenzenes.

The reactivity of the anions of compounds with GB increases in the order: hydrated aldehydes ~ phenols < oximes < hydroxamic acids whereas the effect of introduction of a charged substituent decreases in the same order. One is tempted to relate the "charge" effect with reactivity, the "charge" effect becoming less important as the intrinsic reactivity of the nucleophile increases. However, the anions of hydroxybenzenes of the catechol and pyrogallol type respond to the "charge" effect equally as well as the anions of phenol or of the hydrated aldehydes do, and yet have re-

activities of the same order as those of the anions of the oximes and hydroxamic acid.¹³ Correlation of "charge" effect with the reactivity is not justified. Nor does there appear to be any correlation between the magnitude of the effect caused by introduction of a cationic substituent and the value of the slope (a measure of the degree of bond formation in the transition state) in the equation relating the logarithm of the bimolecular rate constant with the pK_a of the

(13) Compare, for example, the equation of the line relating the bimolecular rate constants of the anions of pyrocatechols with GB, viz., $\log k_2 = 0.76pK_a - 3.70$, with that of the anions of hydroxamic acids and GB, viz., $\log k_2 = 0.80pK_a - 3.87$.

conjugate acid of the reacting nucleophile for different classes of nucleophiles. The slopes for the anions of phenols,^{2a} catechols, and pyrogallols^{2b} (which show marked "charge" effects) are 0.59, 0.80, and 0.76; those of keto oximes and hydroxamic acids are 0.64 and 0.80.

It is, however, perhaps of some significance that of the classes of nucleophiles studied, those which appear to respond only slightly (keto oximate anion) or not at all (anions of hydroxamic acids) to the "charge" effect are " α " nucleophiles,¹⁴ that is, the atom adjacent to the nucleophilic one contains an unshared pair of electrons, whereas those which show marked "charge" effects (anions of hydrated aldehydes, hydroxybenzenes) are "non- α " nucleophiles.¹⁵

Because the anions of the keto oximates are partially affected by a cationic substituent, they may be classified as " α " nucleophiles possessing some "non- α " character. In fact, if one assumes that the keto oximate anion possesses 68% " α " character and 32% "non- α " character (the rationale for the assignment of 68 and 32% is given below) and that the "charge" effect acts only on "non- α " nucleophiles, then it can be shown that the predicted $\log k_2/k_c$ for compounds 2 and 3 (distance of separation of charged groups is approximately 4 Å) is 0.25 and for compound 11 (distance of separation is approximately 5 Å), 0.16, in good agreement with the values of $\log k_2/k_c$, viz., 0.19, 0.21, and 0.13, found for the three compounds (Table VI).

The values of 68 and 32% were arrived at by treating the free energy of activation as a sum of independent contributions¹⁶ attributable to the " α " and "non- α " characters of the nucleophile. Thus, one may write

$$\log k_2 = \log k_\alpha + \alpha_n \log k_{\alpha n} \quad (1)$$

where k_2 is the bimolecular rate constant for the nucleophile in question with a given substrate at a given temperature; k_α and $k_{\alpha n}$ are the bimolecular rate constants due to " α " and "non- α " contributions for a given basicity of the nucleophile; and α and α_n are constants ranging from 0 to 1 with $\alpha + \alpha_n = 1$.

For reactions with GB, it can be assumed that values of k_α and $k_{\alpha n}$ can be obtained from data on the reactivity of the anions of hydroxamic acids (pure " α ") and phenols (pure "non- α "). If the nucleophile in question is the keto oximate anion, the $\log k_2$ can be calculated from the equation

$$\log k_2 = 0.642pK_a - 3.25$$

Thus for a keto oximate anion whose conjugate acid has a $pK_a = 7.5$,¹⁷ $\log k_2 = 1.57$; $\log k_\alpha = 2.13$ (calcu-

(14) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

(15) Conceivably, the hydroxybenzenes may be considered to be partial " α " nucleophiles inasmuch as the α atom is conjugated with the β atom and hence partially "owns" an unpaired set of electrons. However, the hydroxybenzenes are classed as "non- α " nucleophiles because of the similarities in the nucleophilicities of their anions and the anions of alcohol and the hydrated aldehydes, whose classification as "non- α " nucleophiles is unequivocal. For example, Bruice, *et al.*, *Biochemistry*, **1**, 7 (1962), found in displacement of *p*-nitrophenol from *p*-nitrophenylacetate that phenols and aliphatic alcohols fall on the same line in a Brønsted plot; in displacement of fluoride ion from GB, anions of phenols and hydrated aldehydes of similar basicity have equal reactivities (cf. phenol $pK_a = 9.78$, $k_2 = 34$ l. mole⁻¹ min⁻¹; with chloral, $pK_a = 9.95$, $k_2 = 32$ l. mole⁻¹ min⁻¹ (Table V)).

(16) For other examples of such treatment see R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965.

(17) An anion, whose conjugate acid has a $pK_a = 7.5$, has been selected since these calculations will be used to determine "charge"

lated from the equation relating the bimolecular rate constants of the reaction between GB and hydroxamic acid anions, viz., $\log k_\alpha = 0.80pK_a - 3.87$, where $pK_a = 7.5$; and $\log k_{\alpha n} = 0.390$ (calculated from the equation relating the bimolecular rate constants of the reaction between GB and phenolate anions at 25°, viz., $\log k_{\alpha n} = 0.598pK_a - 4.172$, and correcting to 30° using an Arrhenius activation energy value of 12.0 kcal/mole¹⁸).

Substituting the values for $\log k_2$, $\log k_\alpha$, and $\log k_{\alpha n}$ into eq 1 gives α_n equal to 0.32. Thus, by this line of reasoning the keto oximate anion possesses 68% " α " character and 32% "non- α " character.

Although other factors are doubtless of importance in nucleophilic reactivity, the success in quantitatively predicting the effect of charge in the keto oximates lends support to the treatment given herein and to the conclusion that the "charge" effect is applicable only to "non- α " nucleophiles. Also, the "charge" effect is useful in distinguishing between two effects, both related to proton basicity, in displacement of fluoride ion from GB. The lack of response of the " α " nucleophiles to the "charge" effect is considered evidence for (as Edwards and Pearson suggest¹⁴) an independent source in nucleophilicity.

Although one can state that there is a difference in the effectiveness of a cationic group on the reactivity of " α " and "non- α " nucleophiles, the reason for the difference is not immediately apparent. One can speculate that since the reactivity of an anion of a charged hydroxamic acid to a neutral substrate is reflected in the pK_a of its conjugate acid, whereas the reactivities of "non- α " nucleophiles are not, that the processes affecting ionization in the conjugate acids of the two nucleophiles are different. It has recently been suggested, for example, that the so-called "inductive" effect in the base-weakening effects of the trimethylammonio group on aniline may be a field effect.¹⁹ The fact that *m*-aminophenyltrimethylammonium chloride is a weaker base than the *para* isomer is cited as evidence²⁰ that the trimethylammonio group does not exert a π -inductive effect. Likewise, in the phenol series, *m*-trimethylammoniumphenol is a stronger acid than the corresponding *para* isomer, suggesting that in the phenols also, the trimethylammonio group does not exert its effect *via* π induction. In contrast, the methiodide of isonicotinehydroxamic acid is a stronger acid than the methiodide of nicotinehydroxamic acid (Table I). It is therefore reasonable to postulate that the trimethylammonio group exerts a field effect in the phenols and a " π -inductive" effect in the hydroxamic acids.

Thus the trimethylammonio group will act as an electron sink in the hydroxamic acids; that is, there will be no electrostatic contribution by repulsion of the dissociating proton in the ionization of " α " acids. The cationic group, therefore, is no different in its action from any other electron-withdrawing group,

effects in the keto oximes on compounds having pK_a values between 7 and 8.5 (Table IV).

(18) The Arrhenius activation energies for the reaction between GB and the anions of *m*-nitrophenol, *p*-nitrophenol, and *m*-hydroxybenzaldehyde are 11.3, 12.0, and 12.6, respectively (J. Epstein, Ph.D. Thesis, University of Delaware, 1966).

(19) M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3548 (1962).

(20) J. D. Roberts, R. A. Clement, and J. J. Drysdale, *ibid.*, **73**, 2181 (1951).

e.g., NO₂, CN, etc. In the case of the acids of the nucleophiles of the phenol type, on the other hand, a substantial contribution to the ionization constant is made by electrostatic interaction of the cationic site and the proton, a repulsion of the latter assisting in its removal by the water molecules. Hence the basicity of the "α" nucleophile possessing a cationic charge to a neutral species will be reflected in its basicity to a proton (pK_a) and the reactivity of a "charged α" nucleophile is predictable from its pK_a.

Finally, it appears desirable to point out the implications of these conclusions on the general factors affecting nucleophilicity^{14,21,22} and especially on the high reactivity shown by "α" nucleophiles.¹⁴ In the anions of phenols and hydrated aldehydes, it is thought that the site of high electron density is highly localized in the nucleophile's oxygen,²³ whereas in the "α"

nucleophiles, it is felt that the electrons are highly mobile and distributed over several of the electronegative atoms.²⁴ The lack of mobility of the highly localized electrons is responsible for the relatively low slope (β) values²¹ in the correlation equations of rate and pK_a of the "non-α" nucleophiles in their reactions with organophosphorus esters. (Higher slopes are obtained with such nucleophiles if other factors, such as H bonding, contribute to the formation of the transition state, e.g., in catechol.) In contrast, the highly mobile electrons in the "α" nucleophile are much more available for transition-state bond formation and show generally higher slopes. It is interesting, too, in this connection that β for the anions of keto oximes, which it is postulated contain some "non-α" character, lies between that of the anions of phenols and those of hydroxamic acids.

(21) R. F. Hudson, *Chimica (Aarau)*, 16, 173 (1962).

(22) J. F. Bunnett, *Ann. Rev. Phys. Chem.*, 14, 271 (1963).

(23) In apparent contradiction to the postulation that the electron density is localized on the phenolic oxygen, it is well known that phenols react with many electrophiles at ring positions rather than at the phenolate oxygen, indicating that there is a high electron density at the ring

positions. It is our feeling, however, that the high ring electron density results from the approach of the electron-deficient reactant; that in the presence of a localized substrate the distribution of electrons in the phenolate anions will be localized on the phenolic oxygen.

(24) See ref 12.

Secondary Deuterium Isotope Effects on a Cyclic Allylic Rearrangement¹

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Abstract: Secondary α- and γ-deuterium isotope effects on the cyclic intramolecular rearrangement of allyl thionbenzoate to allyl thiolbenzoate have been measured. The α effect (1.06) is significantly smaller than that observed for (1.10–1.12) carbonium ion, carbanion, or radical pathways. With the γ effect (0.97), this result indicates that these effects are useful mechanistic criteria for allylic rearrangements. These results also indicate that the transition state structurally resembles reactant more than product, suggesting that this type of study will be useful in characterizing the position of a transition state along a reactant–product coordinate in such reactions.

Intramolecular allylic rearrangement reactions have occupied a position of considerable importance in the development of organic reaction mechanism theory.² Many of these reactions have been important in the study of carbonium ion processes³ and others have been resistant enough to ordinary mechanistic probes to earn the sobriquet "no mechanism" reactions.⁴

It has long been recognized that a continuum of merging carbonium ion pair and cyclic mechanisms may connect these two classes of allylic rearrangements.⁵ Since examples of carbanion and homolytic intramolecular allylic rearrangements are now known,^{2,6} this

mechanistic continuum may be generalized to include, at the noncyclic limit, reactions of all three charge types, carbonium ion, radical, and carbanion, each merging with a cyclic reaction scheme at the other end of the continuum.

No satisfactory method for characterizing the mechanism of an intramolecular allylic rearrangement in terms of such a general cyclic to noncyclic continuum is presently available. A mechanistic criterion suited to this purpose should be insensitive to medium effects to permit its use in a wide variety of environments including the gaseous state. Methods for qualitatively placing a particular reaction along a carbonium ion cyclic continuum have been developed⁷ and depend primarily on estimation of the polarity of the kinetically important transition state by means of kinetic solvent or substituent effects; reactions which are sensitive to polar effects are considered to involve carbonium ion pair mechanisms, and those which are insensitive are assigned cyclic mechanisms. The interpretation of

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) For a recent review, see P. B. D. de la Mare, "Molecular Rearrangements," P. DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 2.

(3) H. L. Goering, *Record Chem. Progr.*, 21, 109 (1960), and later papers in this series.

(4) For a recent review, see S. J. Rhoads, ref 2, Chapter 10.

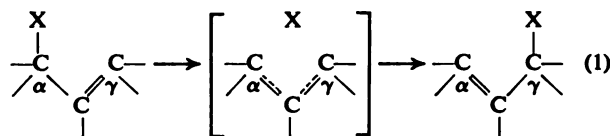
(5) S. Winstein, *Nature*, 173, 898 (1954).

(6) G. S. Hammond and C. D. DeBoer, *J. Am. Chem. Soc.*, 86, 899 (1964).

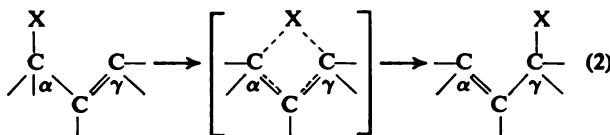
(7) S. G. Smith, *ibid.*, 83, 4285 (1961).

these effects rests on a large body of empirical evidence concerning the magnitudes of polar solvent and substituent effects on carbonium ion reaction rates;⁸ these methods are not directly applicable to the merging carbanion cyclic or homolytic cyclic continua.

The fundamental difference between mechanisms for cyclic and noncyclic reactions is one of timing. In an extreme noncyclic reaction mechanism, the bond between the migrating group and carbon atom to which it was originally attached (α -carbon) is essentially completely broken before the onset of bonding between the migrating group and the migration terminus (γ -carbon), as indicated in eq 1. In contrast, the transition state



for a cyclic reaction is characterized by significant bonding between the γ -carbon and the migrating group *before* completion of bond breaking between the α -carbon and the migrating group (eq 2). Thus a cri-



terion capable of distinguishing between synchronous and stepwise bond-breaking and bond-making processes should be capable of distinguishing between cyclic and noncyclic mechanisms, or, more subtly, of placing a reaction on a general continuum between these extremes.

Recent investigations have shown that the study of secondary α -deuterium isotope effects ("effects of the first kind," in Halevi's terminology⁹) are valuable probes in studying the timing of bond-making and bond-breaking processes.¹⁰ For our purposes, such effects have several valuable characteristics. First, Seltzer¹¹ has pointed out that the magnitude of the rate retardation associated with the substitution of one deuterium atom for a hydrogen atom α to the leaving group is remarkably constant at 10–12%, regardless of the charge type (carbanion, free radical, or carbonium ion) of the reaction. Second, inverse isotope effects have been observed upon substitution of deuterium for hydrogen at doubly bonded carbon atoms for a variety of reactions in which these carbons undergo a trigonal to tetrahedral conversion, similar to that envisioned for the γ -carbon in a cyclic allylic rearrangement transition state.⁹ Third, since secondary deuterium isotope effects are basically substituent effects and appear to be unaffected by reaction medium effects, their use as mechanistic criteria in studying allylic rearrangement reactions should be restricted only by the availability of kinetic or other means of measuring the deuterium isotope effect with adequate precision and the ability to introduce deuterium atoms at the α - and γ -carbons of the appropriate allylic system.

(8) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, Book Co., Inc., New York, N. Y., 1962, pp 42–49.

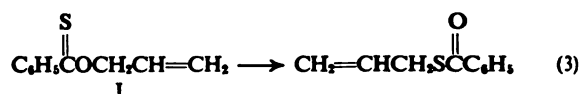
(9) E. H. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963).

(10) S. Seltzer and F. T. Dunne, *J. Am. Chem. Soc.*, **87**, 2628 (1965); S. Seltzer, *ibid.*, **87**, 1534 (1965).

(11) S. Seltzer, *ibid.*, **83**, 2625 (1961).

In this framework, cyclic allylic rearrangement transition states should exhibit smaller than normal rate retardations due to α -deuterium substitution and significant rate accelerations due to γ -deuterium substitution, in keeping with the synchronous nature of bond-making and bond-breaking processes. In contrast, noncyclic rearrangements should exhibit normal α -deuterium isotope effects, since bond breaking at the transition state should be about as complete in their reactions as it is in the examples of carbonium ion, carbanion, and radical reactions for which deuterium isotope effects have been measured. The magnitude, even the direction, of γ -deuterium isotope effects in noncyclic reactions is less readily predicted, and a definite answer to this question awaits experimental evidence.

With this background, we have initiated a program to evaluate these effects as mechanistic criteria for intramolecular allylic rearrangements by measuring the kinetic effect of α - and γ -deuterium substitution on a reaction of known cyclic character. We chose to study the rearrangement of allyl thionbenzoate (I) to allyl thiolbenzoate (eq 3). Smith, who discovered this reac-



tion, showed that it was extremely insensitive to polar, solvent, and substituent effects and must, therefore, involve a cyclic rather than a carbonium ion mechanism.⁷ Other considerations render carbanion or free radical reactions unlikely. For our purposes, this reaction also offered ready synthetic accessibility and a convenient method for kinetic determinations.

Results

The required allyl-1,1- d_2 alcohol was prepared from acrylyl chloride and lithium aluminum deuteride according to the method of Schuetz and Millard.¹² After some exploratory experiments, the following route (eq 4) was worked out for the preparation of allyl-3,3- d_2



alcohol. The lithium aluminum hydride reduction of propargylic alcohols to allylic alcohols has been studied in some detail by Bates, Jones, and Whiting,¹³ but this appears to be the first report of its use in the simplest case, propargyl alcohol itself. The deuterated allylic alcohols thus obtained were better than 99.2% homogeneous to capillary gas chromatography and had retention times undistinguishable from that of pure allyl alcohol. Their structures were further confirmed by infrared and nmr spectra. In particular in the infrared spectrum of the allyl-1,1- d_2 alcohol the α -CH₂ stretching bands at 3.41 and 3.49 μ appear as CD absorptions at 4.55 and 4.78 μ and the CH₂ deformation at 6.89 μ ¹⁴ is replaced by a new band at 8.70 μ which is probably the CD₂ deformation. In addition, the nmr spectrum of this compound differs from that of allyl alcohol in that

(12) R. D. Schuetz and F. W. Millard, *J. Org. Chem.*, **24**, 297 (1959).

(13) E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1854 (1954).

(14) H. W. Thompson and P. Torkington, *Trans. Faraday Soc.*, **42**, 432 (1946).

doublet at τ 6.00 of the α -methylene¹⁶ proton is present and the ten-line pattern of the β -vinyl proton is shifted to the four-line X portion of an ABX spectrum with J_{AX} (*trans*) = 16 Hz and J_{BX} (*cis*) = 10 Hz. 1,3,3- d_2 alcohol similarly exhibits a shift of the terminal methylene absorptions at 3.25, 3.35, 7.10, 10.90 μ (CH) to 4.31, 4.51, 9.63, and 13.70 μ (CD) in the infrared. The nmr spectrum of this compound showed the absence of the 4.67–5.10 multiplet of the terminal methylene in allyl alcohol; the weak perturbations of the α -CH₂ doublet at τ 6.00 (long-range coupling) were gone and the β -vinyl resonance appeared as a broad hump at τ 4.12, presumably a triplet broadened by coupling to the deuterons on the γ carbon.

These alcohols, together with unlabeled allyl alcohol, were converted to the corresponding thionbenzoates by treatment with sodium hydride followed by benzoyl chloride.⁷ The latter compound was prepared by the method of Staudinger and Siegmant¹⁶ purified by repeated distillation to constant nmr infrared spectra.

The allyl-1,1- d_2 thionbenzoate (II) thus obtained gained 1.98 D atoms per molecule and the isomeric 3,3- d_2 thionbenzoate (III) has 1.85 D atoms per molecule.¹⁷ The infrared spectrum of allyl thionbenzoate (I) was in agreement with that reported by Smith,⁷ its nmr spectrum supported the assigned structure. Perhaps worthy to note that the aromatic protons ortho to the thiocarbonyl group in this series of compounds are deshielded relative to their counterparts in aryl benzoyl compounds by about 0.3 ppm. The spectra of the deuterium-substituted allyl thionbenzoates also consistent with their assigned structures, exhibiting spectral features similar to those observed for corresponding alcohols.

The kinetic data recorded in Table I were obtained by the ampoule technique, following the disappearance of the thionbenzoate absorption at 410 μ in acetonitrile. Rate constants were calculated by the method of DeTar¹⁸ the best least-squares fit to the exponential form of the first-order rate equation (see Experimental Section). Standard errors in almost all cases were less than 0.8%, so that the 95% confidence limits for the individual rate constants are less than $\pm 1.7\%$. Isotope effects (rate ratios) are calculated for simultaneous deuterations on the three allyl thionbenzoates I–III. Isotope effects calculated for one deuterium atom at the α position are: α , 0.059 ± 0.007 and γ , 0.97 ± 0.007 . Activation parameters calculated for the rearrangement of the unlabeled compound, allyl thionbenzoate, are $\Delta H^\ddagger = 25.7 \pm 0.6$ kcal/mole and $\Delta S^\ddagger = -10$ cal/mole

the effect of temperature on the deuterium isotope effects is so small that it is within the experimental error of our determinations. The slight increase in the magnitude of the γ -isotope effect is consistent with earlier results on thiocyanate ion catalyzed isomerization of maleic to fumaric acid but is not of itself statistically significant. Attempts to calculate $\Delta\Delta H^\ddagger$

Table I. First-Order Rate Constants and Deuterium Isotope Effects for Allyl Thionbenzoate–Allyl Thiolbenzoate Rearrangement in Acetonitrile

Temp, °C	$k_I \times 10^6$, sec ⁻¹	$k_{II} \times 10^6$, sec ⁻¹	$k_{III} \times 10^6$, sec ⁻¹	$\alpha k_{II}/k_I$ (k_I/k_{II})	$\gamma k_{II}/k_I$ (k_I/k_{III})
100.0	4.29		4.50		0.945
	4.17	3.81	4.48	1.117	0.932
	4.22	3.73	4.44	1.131	0.950
	4.16	3.77	4.41	1.102	0.941
85.0	0.938	0.828	1.031	1.136	0.936
	0.909	0.841	0.977	1.128	0.937
70.0	0.186	0.168	0.201	1.111	0.926
	0.192	0.170	0.206	1.131	0.932

and $\Delta\Delta S^\ddagger$ from these data by the method of Leffek, Robertson, and Sugamori¹⁹ give values which are not statistically significant.

Samples of the reaction products, allyl thiolbenzoates, were obtained by treating samples of the allyl thionbenzoates I–III for 200 hr at 100° in sealed tubes.⁷ Allyl thiolbenzoate was obtained from I, as indicated by the correspondence of its infrared spectrum with that reported by Smith and the agreement of its nmr spectrum with the assigned structure. Allyl-1,1- d_2 thionbenzoate (II) afforded the product of clean allylic rearrangement, allyl-3,3- d_2 thiolbenzoate, most clearly indicated by the absence of the τ 4.40–5.08 terminal methylene absorption in the nmr. Similarly allyl-3,3- d_2 thionbenzoate (III) gave allyl-1,1- d_2 thiolbenzoate as indicated by the absence of the τ 4.37 doublet (α -methylene). We estimate that no more than 3–4% of unrearranged allyl moiety could have gone undetected in these experiments. These results agree with the conclusion of Smith that clean rearrangement of the allyl moiety accompanies conversion of the thion to the thiol ester.

Discussion

The strongly negative entropy of activation provides strong support for the conclusion, reached earlier by Smith⁷ on the basis of polar solvent and substituent effects, that this reaction proceeds by way of a cyclic transition state. Similar values of ΔS^\ddagger have been observed for the Claisen and Cope rearrangements.^{4,6} An alternate interpretation of large negative entropies of activation, electrostriction of solvent in a polar transition state, seems inapplicable here in view of the insensitivity of this reaction to solvent polarity.

The α -deuterium isotope effect (6–7% rate retardation) for this cyclic reaction is about one-half that observed at similar temperatures for the effect of similar deuterium substitution on reactions involving carbonium ion, carbanion, or radical pathways.^{9,11} This difference in magnitude is well beyond the experimental uncertainty involved. Since allylic rearrangements of noncyclic character can be expected to show normal α -deuterium isotope effects (many of the “normal” reactions involve benzylic systems, electronically very similar to those involved in allylic noncyclic rearrangements), this result supports the hypothesis that α -deuterium isotope effects are of real value in distinguishing between cyclic and noncyclic pathways for these rearrangements.

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Deuterium analysis by J. Nemeth, Urbana, Ill.
D. F. DeTar, *J. Am. Chem. Soc.*, **78**, 3911 (1956). We are indebted to a referee for calling this method to our attention and to the Washington State University Computing Center for invaluable assistance.

Similarly the rate acceleration (ca. 3% per deuterium) produced by deuterium substitution of the migration terminus is similar in magnitude and direction with several reactions in which some conversion of the trigonal carbon to tetrahedral has occurred at the transition state.⁹

This result may be compared to the γ -deuterium isotope effect of 1.00 (k_H/k_D) reported by Belanić-Lipovac, Borčić, and Sunko²⁰ for the solvolysis of α,α -dimethylallyl chloride. The small, but real, difference in γ -deuterium isotope effect between the cyclic reaction studied here and this carbonium ion solvolysis supports the hypothesis that this type of effect also can be useful as a mechanistic criterion in such systems, provided that further experimental work supports the generality of these effects. From an empirical point of view, these conclusions must be regarded as tentative until supported by further experimental work with both cyclic and noncyclic rearrangements.

Viewed in a more theoretical light, these conclusions do not rest on particular assumptions used with Bigeleisen's fundamental equation for deuterium isotope effects.²¹ If we adopt Streitwieser's assumptions, application of eq 5 from his early paper²² on this subject indicates that a change of -65 cm^{-1} in the bending frequencies of the allyl thionbenzoate is responsible for the γ -deuterium effect upon going to the transition state. Similarly a change of 135 cm^{-1} is associated with the α -deuterium effect. Again, adopting Streitwieser's analysis of the important isotope vibrational frequencies,²³ the terminal methylene group in allylic compounds has been assigned frequencies of 3080, 2990, 1410, and 920 cm^{-1} . Upon rearrangement these become, respectively, 2940, 2840, 1455, and 1385 cm^{-1} in the α -methylene compound, resulting in a total change of -325 cm^{-1} for the complete allyl thionbenzoate to allyl thiolbenzoate conversion. A similar change of $+325\text{ cm}^{-1}$ is obtained for the deuterium-sensitive frequencies of the α -methylene group. Insofar as these changes in vibrational frequencies reflect the structure of the transition state, the situation at both the α - and γ -carbons resembles reactants more than products, with the change in frequencies somewhat more pronounced at the α - than the γ -carbon. It is worth noting that this conclusion does not rest on a detailed correlation between vibration frequencies and bond order of the reacting bond at the transition state, but rather on the assumption that changes in bond strength are reflected in roughly proportionate changes in vibration frequency for the α -CH bending modes.

Alternatively, if one adopts the formulation of Wolfsberg and Stern²⁴ in which bending force constants rather than vibrational frequencies are used as primary structural parameters, the same conclusion may be reached. In this way, one interprets the γ effect as

reflecting a small alteration of the carbon-hydrogen bending force constants at the transition state and the α effect as involving a smaller alteration at this site than those commonly encountered or treated in Wolfsberg's model calculations. Insofar as bending force constants reflect structure, then, the same conclusion regarding placement of the transition state along the reaction coordinate is reached. The validity of this argument also does not rest on a relationship between force constants and bond order in the "reacting" bonds, although it seems reasonable to believe that the length of this bond in the transition state will influence the steric environment of the neighboring carbon-hydrogen bonds enough to alter the bending force constants.

Further, the transition state for this reaction may be described as "looser" than completely concerted in that bond breaking at the α -carbon appears to be more advanced than bond formation at the γ -carbon. This involves the assumption, reasonable but not firmly established, that the functional relationships between bond order in the bond-breaking process and the α -deuterium isotope effects are the same as those operating between the bond-making process and the γ -deuterium isotope effect. In this light, the fact that the γ -deuterium isotope effect is smaller than the α effect implies that bond making at the γ -carbon is lagging behind bond breaking at the transition state. *A posteriori*, this is reasonable since the conversion of reactant to transition state is an endothermic process and in a unimolecular reaction devoid of strong solvation effects it must involve a decrease in total bond order. This takes no account, of course, of over-all bond order changes internal to the allyl and thiocarboxyl moieties, which may well play a significant role in the activation process.

The pattern of deuterium isotope effects observed here is consistent with a transition state which more closely resembles reactant (allyl thionbenzoate) than product (allyl thiolbenzoate). This interpretation, which is consistent with Hammond's postulate²⁵ for a one-step exothermic reaction, does not depend on a particular set of approximations used in interpreting deuterium isotope effects, as discussed above, and raises the intriguing possibility that measurement of these effects in reactions of known cyclic character can lead to placement of their transition states along a reactant-product reaction coordinate. We are presently testing this hypothesis on such cyclic allylic rearrangements.

Experimental Section

Thiobenzyl Chloride. This material was prepared by the method of Staudinger.¹⁴ Repeated distillation removed impurities exhibiting absorptions at τ 2.17–2.40 in the nmr and 12.6 and $14.2\text{ }\mu$ in the infrared. The purified material was deep purple in color and had bp $53\text{--}55^\circ$ (0.2 mm); $\lambda_{\text{max}}^{\text{nm}}$ 8.07 (s), 9.56 (s), 11.93 (s), 13.18 (s), 14.81 (s), and 15.70 (s) μ ; nmr multiplets at τ 1.86–2.08 (2 H, *ortho*) and τ 2.48–3.08 (3 H, *meta* and *para*); $\lambda_{\text{max}}^{\text{cm}^{-1}}$ 527 $\text{m}\mu$ (ϵ 68).

Allyl-1,1- d_2 Alcohol. This material was prepared by the method of Schuetz and Millard,¹⁵ bp $92\text{--}95^\circ$ (690 mm); $\lambda_{\text{max}}^{\text{nm}}$ 3.00 (broad, s), 4.55 (m), 4.78 (s), 7.09 (s), 8.38 (s), 9.10 (s), 10.04 (s), 10.40 (s), and 10.80 (s) μ ; nmr absorptions at τ 3.86–4.31 (1 H, quadruplet, $J_{AX} = 16\text{ Hz}$, $J_{BX} = 10\text{ Hz}$), τ 4.67–5.10 (2 H, two overlapping AB quadruplets, J_{AX} and J_{BX} as above, $J_{AB} = -2\text{ Hz}$), and τ 5.30 (1 H, singlet); no detectable absorption at τ 6.0 (α -CH₃).

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(21) J. Bigeleisen, *J. Chem. Phys.*, **17**, 425 (1949).

(22) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958).

(23) It is recognized that this approach is somewhat deficient in the absence of a complete assignment of the vibrational frequencies of those compounds (see ref 9). However, these assignments are supported by the observed shifts in our deuterium-substituted allylic compounds and are in accord with previous work (ref 14; also, L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp 13, 34.)

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Propargyl-3,0- d_2 Alcohol. Propargyl alcohol (11.2 g, 0.20 mole) was equilibrated with 20 g of D_2O containing 6 mg of barium oxide overnight. The mixture was continuously extracted with 15 ml of ether for 6 hr, and the ether layer was stirred overnight with 20 g of fresh D_2O containing 35 mg of BaO. The latter equilibration was repeated twice more, and the final ether extract was dried and distilled in a micro spinning-band column affording 8.16 g of propargyl-3,0- d_2 alcohol, bp 108–110° (690 mm), homogeneous to capillary gas chromatography. Spectral analysis showed: nmr <1% τ 7.29 ($C\equiv CH$), ca. 10% τ 5.37 (OH), τ 5.75 (CH_2 , singlet); λ_{max}^{OH} 3.00 (OH, m), 3.86 (CD, s), 4.03 (OD, m), 5.04 (m), 7.36 (m), and 9.78 (m) μ .

Allyl-3,3- d_2 Alcohol. Propargyl-3,0- d_2 alcohol (8.0 g, 0.14 mole) dissolved in 100 ml of dry ether was added dropwise under a nitrogen atmosphere to a slurry of lithium aluminum hydride (5.7 g, 0.15 mole) in 70 ml of ether maintained at 4–6° in an ice bath. After the addition was complete (85 min), the reaction mixture was stirred at 0° for 12 hr when gas chromatographic examination of a quenched aliquot showed that the reduction was 95% complete and that less than 0.3% of propyl alcohol had been produced. Deuterium oxide (12 ml) was cautiously added, and the mixture was stirred for 14 hr when 9.6 ml of 10% aqueous NaOH solution was added. The precipitated inorganic solids were removed by filtration and washed well with ether. The combined filtrates and washings were distilled in a micro spinning-band column affording 2.88 g of allyl-3,3- d_2 alcohol, bp 92–94° (695 mm), containing less than 0.2% propyl alcohol and less than 0.6% propargyl alcohol by capillary gas chromatography. Spectral analysis showed: λ_{max}^{OH} 3.00 (broad, OH), 3.49 (CH_2 , m), 4.05 (broad, OD), 9.10 (m), 9.91 (s), 13.70 (m) μ ; nmr absorptions (in τ) at 4.12 (1 H, broad), 3.98 (2 H, doublet, $J = 5$ Hz), and 6.78 (OH, 0.6 H, singlet), negligible absorption at 4.87 ($\delta-CH_2$).

Allyl Thionbenzoate and Its Deuterated Analogs. These compounds were prepared from the appropriate allyl alcohol and thionbenzoyl chloride by the method of Smith. The spectra of all three allylic thionbenzoates had the following common features: λ_{max}^{OH} 420 $m\mu$ (ϵ 122); λ_{max}^{OH} 3.26 (w), 6.27 (w), 6.90 (w), 7.60 (s), 7.92 (s), 8.20 (s), 9.30 (m), 9.52 (m), 9.76 (m), 10.72 (m), 12.98 (m), 14.60 (s), and 15.76 (m) μ ; nmr absorptions at τ 1.75–1.98 (2 H, *ortho*, multiplet) and τ 2.62–3.02 (3 H, *meta* and *para*, multiplet). In addition, allyl thionbenzoate had λ_{max}^{OH} 10.10 (w), 10.90 (w) μ ; and nmr absorptions at τ 3.65–4.34 (1 H, β -proton, multiplet), τ 4.53–4.95 (2 H, $=CH_2$, multiplet), and τ 4.97 (2 H, CH_2 , weakly perturbed doublet, $J = 6$ Hz, overlapping $=CH_2$ peak).

Anal.²⁶ Calcd for C_8H_8OS : C, 67.38; H, 5.66; S, 17.99. Found: C, 67.63; H, 5.80; S, 17.74.

Allyl-1,1- d_2 thionbenzoate had, in addition, λ_{max}^{OH} 4.50 (w), 4.70 (w), 7.10 (m), and 10.90 (m) μ , and showed nmr absorptions at τ 4.02 (center of gravity, 4 lines, $J_{AX} = 17$ Hz, $J_{BX} = 10$ Hz, 1 H) and τ 4.54–4.95 (multiplet, 2 H, $=CH_2$). Allyl-3,3- d_2 thionbenzoate had, in addition, λ_{max}^{OH} 4.31 (w), 11.20 (w), and 13.40 (m) μ , and showed nmr absorptions at τ 4.08 (broad, 1 H, half-height width 13 Hz) and τ 5.01 (doublet, $J = 6$ Hz, 2 H).

Kinetic Measurements. Rates were followed by the ampoule technique, 13 separate observations between 10 and 85% reaction being made in most runs. Three simultaneous kinetic determinations were made on allyl thionbenzoate (I) and its deuterated analogs II and III. Solutions were made up by accurately weighing the appropriate thionbenzoate into a 50-ml volumetric flask and diluting to the mark with spectro grade acetonitrile. Aliquots (3.3 ml) were transferred to Pyrex ampoules which were immediately sealed. Care was taken to randomize the order in which ampoules were sealed and later removed from the constant temperature bath.

The ampoules were weighed with lead strips and placed in a wire mesh basket. The basket was placed in the constant temperature bath (controlled to 0.02° by a proportioning controller) and allowed to come to thermal equilibrium for 30–60 min. To start each run, other ampoules were similarly withdrawn and quenched at appropriate intervals to obtain each kinetic point. An ampoule was withdrawn and immediately quenched in ice-acetone. Control experiments showed that the temperature dropped more than 20° within 5 sec. The quenched ampoules were stored in the refrigerator at –5° until the run was completed. Infinity points were

obtained after 10–12 half-lives at 100° and were about 2% of the initial absorption.²⁷ Before measuring the absorbance the ampoules were allowed to warm to room temperature. The absorbance at 410 $m\mu$ was read from the 520 to 350 $m\mu$ spectrum of the sample determined on a Cary Model 14 spectrophotometer. Duplicate determinations were reproducible to 0.003 absorbance unit.

Following the method of DeTar,¹⁸ the rate constants were determined by fitting the data to the equation $A = a + be^{-kt}$, where A is the absorbance at time t , a is the absorbance at infinite time, and $b = A_0 - A_\infty$. The initial estimates of a and b required by this method were measured values and the initial estimate of k was obtained from a least-squares fit of the data to the equation $\ln(A - A_\infty) - \ln(A_0 - A_\infty) = -kt$. Table II contains data for a typical run, including a comparison of observed absorbances and those calculated from the parameters obtained from the exponential least-squares fit. The standard deviations of most rate constants were less than 0.8%, and calculated initial and infinity absorbances were within 0.01 absorbance unit of those observed. Temperatures were measured by a National Bureau of Standards calibrated thermometer.

Table II. Data for a Typical Kinetic Run*

Time, sec	Absorbance	
	Obsd	Calcd
0	1.131	1.134
3,555	0.970	0.971
7,210	0.829	0.828
10,800	0.708	0.708
14,430	0.606	0.605
18,005	0.519	0.519
21,605	0.443	0.445
25,155	0.383	0.383
28,800	0.330	0.329
32,400	0.283	0.283
36,000	0.243	0.244
39,605	0.212	0.211
43,200	0.181	0.183
46,755	0.161	0.159
∞	0.022	0.022

* Initial estimate: $A = 0.0220 + 1.1090 \exp(-0.000044644t)$; final parameters: $A = 0.0220 + 1.1125 \exp(-0.000044755t)$.

Reaction Products. Samples (ca. 150 mg) of allyl thionbenzoate and the two deuterium-substituted allyl thionbenzoates were sealed in small glass ampoules and immersed in the 100° oil bath for 200 hr (more than ten half-lives for the slowest reaction rate reported). The products were characterized as follows. Allyl thionbenzoate gave allyl thiolbenzoate: λ_{max}^{OH} 420 $m\mu$ (ϵ 1.2); λ_{max}^{OH} 3.27 (w), 3.41 (w), 6.02 (s), 6.32 (m), 6.91 (m), 8.30 (s), 8.51 (s), 10.14 (m), 11.00 (s), 12.97 (s), 14.56 (s), and 15.47 (s) μ ; nmr absorptions at τ 2.02–2.25 (multiplet, 2 H, *ortho*), 2.51–2.75 (multiplet, 3 H, *meta* and *para*), 3.80–4.50 (multiplet, 1 H, β), 4.40–5.08 (multiplet, 2 H, δ), and 6.37 (doublet, $J_{app} = 7$ Hz, 2 H, α). Allyl-1,1- d_2 thionbenzoate gave allyl-3,3- d_2 thiolbenzoate: λ_{max}^{OH} 420 $m\mu$ (ϵ 1.6); λ_{max}^{OH} as in allyl thionbenzoate except that the 10.14- μ band was absent; bands at 4.31 (w), 4.51 (w), and 13.60 (m) μ ; nmr absorptions as in allyl thiolbenzoate except that τ 4.40–5.08 δ -hydrogen absorption and weak perturbations of the τ 6.37 doublet were absent, and the τ 3.80–4.50 multiplet had collapsed to a broad absorption centered at τ 4.19, half-height width 14 Hz. Allyl-3,3- d_2 thionbenzoate gave allyl-1,1- d_2 thiolbenzoate: λ_{max}^{OH} 420 $m\mu$ (ϵ 1.6); λ_{max}^{OH} as in allyl thiolbenzoate except that the 3.42- μ band is absent and an absorption at 4.64 (w) μ is present; nmr as in allyl thionbenzoate except that the τ 3.80–4.50 multiplet has collapsed to a four-peak pattern centered at τ 4.17 ($J_{AX} = 16$ Hz, $J_{BX} = 10$ Hz), the τ 4.40–5.08 multiplet is simplified to an eight-line pattern centered at τ 4.92 (J_{AX} and J_{BX} as above, J_{AB} probably –2 Hz), and the τ 4.37 doublet was absent.

(26) Galbraith Laboratories, Knoxville, Tenn.

(27) S. G. Smith⁷ reported a similar observation.

Secondary Deuterium Kinetic Isotope Effects in Radical-Forming Reactions. II. The Decomposition of *t*-Butyl Perpivalate

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Abstract: Measurement of the rates of decomposition of *t*-butyl perpivalate and its deuterated analog show the secondary deuterium kinetic isotope effect on the formation of *t*-butyl radical is 1.02 per deuterium. The theories proposed to explain these isotope effects are compared using the present data and that for the formation of *t*-butyl cation.

While the effect of substitution of deuterium for hydrogen on the rates of a large number² of reactions leading to cationic intermediates have been determined, almost no attention has been given to these effects in radical-forming processes. The earliest report of such an isotope effect in a radical reaction was that for the autoxidation of cumene which indicated the magnitude of k_H/k_D to be 1.10.³ The effects have also been measured⁴ for radical addition to olefins but the interpretation in these cases is complicated by opposing α and β effects which operate simultaneously. In a study directed mainly at determining the magnitude of α isotope effects in concerted acyl peroxide cleavage, a preliminary measurement of the effect of partial β deuteration on the rate of decomposition of *t*-butyl perhydratropate was also reported.⁵ Here the isotope effect was found to be quite small ($k_H/k_D \sim 1.02$). This small⁶ isotope effect for the formation of α -phenethyl radical in the converted decomposition of the corresponding perester was at odds with that reported for the formation of cumyl radical and also at odds with some theories² of the origin of these isotope effects in general. It was thus decided to measure the β deuterium secondary kinetic isotope effect on the formation of *t*-butyl radicals in the decomposition of *t*-butyl perpivalate.

It has previously been shown⁷ that the decomposition of this compound is concerted. Therefore, *t*-butyl radical character is present in the over-all rate-determining transition state. Since nine deuterium atoms can be incorporated, a reduction in the relative error of the measurements was anticipated. In addition, a comparison of the isotope effects for formation of radicals and cations of the same formal structure should be helpful in providing a distinction between the theories proposed to account for these isotope effects. The isotope effect on the solvolysis of *t*-butyl chloride has been determined by several groups.⁸

While these studies were in progress, a report of the β isotope effect on the formation of α -phenethyl radical in the decomposition of the corresponding azo compound appeared.⁹ The isotope effect observed in this case was in agreement with that estimated for the decomposition of the perhydratropate but with greatly increased accuracy.

Results

Deuterated pivalic acid was obtained from *t*-butyl chloride-*d*₉ by a Grignard sequence. The peresters were obtained by the Bartlett⁷ method and purified by column chromatography. Their deuterium content was estimated by a quantitative nmr technique. Purity was judged by their nmr and infrared spectra and by reproducibility of the rate constants upon repurification.

The rates were measured in purified solvents by disappearance of the infrared carbonyl adsorption (k_{IR}) at 1772 cm⁻¹ and by pseudo-first-order¹⁰ and zero-order disappearance¹¹ of galvinoxyl (k_G) using its visible absorption at 770 m μ . The results of these studies are summarized in Table I.

The stated errors are for *completely reproduced* experiments in which each compound was resynthesized from a different batch of *t*-butyl chloride. Decompositions in different batches of purified solvent and the decomposition of the undeuterated perester obtained from a commercial batch of pivalic acid all showed rate behavior within the stated uncertainty. The rate constants were obtained from a linear least-squares treatment of the data.¹² All rate plots were linear for at least three half-lives.

The rate constants obtained by the infrared method were invariably higher than those observed by the galvinoxyl method. Both the presence of a good radical scavenger and the low perester concentrations used in the galvinoxyl method should tend to decrease the relative importance of any radical-induced paths for destruction of perester. The difference in the rates obtained by the two methods might, therefore, be a consequence of some induced decomposition remaining

(1) National Defense Education Act Predoctoral Fellow, 1965-1967.

(2) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963); A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(3) C. E. Boozer, B. W. Ponder, J. C. Trisler, and C. E. Wrightman, *J. Am. Chem. Soc.*, **78**, 1506 (1956).

(4) A. P. Stefani, M. Szwarc, and M. Feld, *ibid.*, **84**, 4451 (1962); W. A. Pryor, R. W. Henderson, R. A. Patsiga, and N. Carroll, *ibid.*, **88**, 1199 (1966).

(5) T. Koenig and W. Brewer, *Tetrahedron Letters*, 2773 (1965).

(6) The error in these measurements was larger than desired so that the magnitude of the isotope effect is only approximate. However, the conclusion that the isotope effect is small is a valid one.

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I. Rates^a of Decomposition of *t*-Butyl Perpivalate and *t*-Butyl Perpivalate-*d*₆

Perester	Temp, °C	$k_{1R} \times 10^4$ sec ⁻¹	k_{H_2}/k_{D_2}	$k_0 \times 10^4$ sec ⁻¹	k_{H_2}/k_{D_2}	n^a
H ₂ ^b	60.56	0.419 ± 0.010	1.16 ± 0.03	0.400 ± 0.015	1.24 ± 0.04	1.07
D ₂ ^b	60.56	0.361 ± 0.003		0.324 ± 0.005		1.14
H ₂ ^b	74.04	2.27 ± 0.056	1.14 ± 0.03	1.93 ± 0.036	1.22 ± 0.03	1.17
D ₂ ^b	74.04	1.995 ± 0.027		1.57 ± 0.032		1.16
H ₂ ^c	60.56			0.626 ± 0.021	1.25 ± 0.03	0.68
D ₂ ^c	60.56			0.505 ± 0.010		0.56
H ₂ ^d	60.56			0.650 ± 0.012	1.23 ± 0.02	
D ₂ ^d	60.56			0.527 ± 0.010		

verages of from 3 to 11 runs. Linear least-squares treatment of individual runs gives standard deviations of less than 2% for three half in all cases. Stated uncertainties are average deviations. ^b Chlorobenzene. ^c 90% Aqueous dioxane. ^d A second batch of 90% as dioxane. ^a Moles of galvinoxyl decolorized per mole of peroxide.

II. Zero-Order Rates of Decomposition of *t*-Butyl peroxide at 60.56°

[G] ₀ , $M \times 10^3$	[P] ₀ , $M \times 10^3$	n^a
3.14	4.42	0.878
3.14	8.84	0.833
3.14	26.5	0.730
3.41	32.8	0.722
3.14	35.4	0.709
3.32	58.9	0.687

suming a k_0 of 4.188×10^{-5} sec⁻¹.

the conditions of the infrared measurement. data of Table II support this interpretation. clearly defined increase in n , the moles of radicals ed/mole perester consumed, with decreasing initial ter concentration was observed by the zero-order¹¹ oxyl method. Since the products of the reaction le a large amount of polymer, the details of this al-induced path are obscured. However, we e the data of Table II establish that such a path and therefore that the galvinoxyl rates are more y correct. The intervention of such a radical- ed path would tend to decrease the isotope effect is isotopically insensitive. This would explain ver magnitude of the isotope effect obtained by frared method.

gaseous products of the decomposition were ined briefly, and the results are summarized in III.

III. Gaseous Products of Decomposition at 60.56°

Product	Yield, moles/mole	
	Chloro- benzene	90% aqueous dioxane
Carbon dioxide	0.908	0.874
Isobutane	0.134	0.381
Isobutylene	0.109	0.477
Methane	0.103	0

chlorobenzene, the yields of carbon dioxide, isone, and isobutane are comparable to those ned previously.⁷ The yields of these hydrocarbons gher in the aqueous dioxane. The *t*-butyl alcohol ned from decomposition of the deuterated perester eous dioxane was shown to contain no deuterium. indicates that none of the ionic processes such as

carboxy inversion¹³ or *t*-butyl cation formation¹⁴ are likely in this case.

Discussion

The results of the preceding section indicate that k_{H_2}/k_{D_2} for the formation of *t*-butyl radical from the corresponding perester is 1.02. This value is slightly higher than that observed for the formation of α -phenethyl radical ($k_{H_2}/k_{D_2} = 1.017$) in the decomposition of the corresponding azo compound.⁸ Though the isotope effect is small, it is much larger than effects calculated for transition states which do not involve perturbations of the C-H force constants.^{9,15} It is, however, much smaller than the effect ($k_{H_2}/k_{D_2} \sim 1.11$) observed for formation of *t*-butyl cation under a variety of conditions.⁸ The fact that the isotope effect is nearly the same in the more basic aqueous dioxane shows the polar character, necessitated for the transition state of concerted decomposition of ring-substituted *t*-butyl perphenylacetates ($P = -1.09$),¹⁶ is apparently not pronounced enough to cause carbonium ion type isotope effect to be admixed in this case. This result is in accord with the small solvent effect on the over-all rate of decomposition. The data at the second temperature in chlorobenzene indicate the small observed isotope effects are not a result of proximity to an isokinetic temperature.

Theories of the β Effect. Though these isotope effects have been known for a number of years, there is no general agreement on the details of their origin. The theories proposed to explain them include pure steric effects,¹⁷ large decrease in C-H bending frequency in the hyperconjugatively stabilized transition states,¹⁸ decreased stretching frequency in the hyperconjugatively stabilized transition states,¹⁹ hyperconjugative effects plus solvation,²⁰ and decreased zero-point energy due to hyperconjugation and anharmonicity.²¹ The latter theory is a quantitative one in which isotope effects have been identified with the loss in resonance energy due to the decrease in the average C-D bond length

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(16) P. D. Bartlett and C. Rüchardt, *J. Am. Chem. Soc.*, **82**, 1756 (1960).

(17) H. C. Brown and G. J. McDonald, *ibid.*, **88**, 2514 (1966); H. C. Brown, M. Azzaro, J. Koelling, and G. J. McDonald, *ibid.*, **88**, 2520 (1966).

(18) A. Streitwieser, R. Jagow, R. Fahey, and S. Suzuki, *ibid.*, **80**, 2326 (1958).

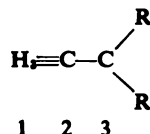
(19) E. S. Lewis, *Tetrahedron*, **5**, 143 (1959).

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(21) A. Ron, E. A. Halevi, and R. Pauncz, *J. Chem. Soc.*, 630 (1960).

and bond angle as calculated by molecular orbital methods.²²

Most of these theories have the concept of hyperconjugative stabilization of radicals and cations as a common beginning point. In order to compare the predictions of these various theories for radical- and cation-forming processes, molecular orbital calculations for the ethyl, isopropyl, and *t*-butyl radicals and cations were carried out using essentially the parameterization of Colpa and DeBoer.^{23,24} In these calculations, the three hydrogen 1s and methyl carbon atomic orbitals are transformed into pseudo-group orbitals, one of which, in each case, has the proper symmetry for linear combination with the 2p vacancy at the central carbon.



$$\begin{array}{lll} \alpha_1 = \alpha_0 - 0.5\beta_0 & S_{12} = 0.500 & \beta_{12} = S_{12}/S = 2.00\beta_0 \\ \alpha_2 = \alpha_0 - 0.1\beta_0 & S_{23} = 0.190 & \beta_{23} = S_{23}/S_0 = 0.76\beta_0 \\ \alpha_3 = \alpha_0 & & \omega = 1.41 \end{array}$$

The results of the calculations with these parameters, are summarized in Table IV.

Table IV. Molecular Orbital Results

Species	DE ^a	ΔDE^b	Den. ^c	ΔP_{12}^d	$\pi_{12,12}^e$	k/k''
C ₂ H ₅ ⁺	0.6967	216	0.592	0.072	0.454	1.96
C ₂ H ₅ ·	0.1025	54	0.860	0.025	0.077	1.11
C ₃ H ₇ ⁺	0.9190	288	0.468	0.048	0.283	2.27
C ₃ H ₇ ·	0.2020	102	0.758	0.022	0.067	1.20
C ₄ H ₉ ⁺	1.1088	330	0.404	0.037	0.203	2.38
C ₄ H ₉ ·	0.2952	144	0.678	0.020	0.055	1.26

^a The delocalization energy in units of β_0 , the bond integral for benzene. ^b Decrease in delocalization energy (in cal/mole) for the deuterated compound due to increased S_{12} assuming $\beta_0 = 60$ kcal/mole. ^c Spin or positive charge density at the central carbon for the radicals or cations, respectively. ^d Decrease in bond order per C-H bond, i.e., $1 - [(2 + P_{12})/3]$. ^e Self-polarizability of the π C=H bond. ^f Total calculated isotope effect for the fully β -deuterated intermediates at 300°K.

Ideally, these calculations should predict the resonance energy and spin density for the radicals and resonance energy and charge density for the cations. The calculated resonance energy is in fair agreement with experiment²⁷ for the radicals, but somewhat low for the cations in the gas phase assuming β_0 is 60 kcal/mole. The delocalization of both spin²⁸ and charge appears to be overemphasized when compared to esr²⁹ and nmr³⁰ results for the species in solution.³¹

(22) We are grateful to Professor Halevi for helpful discussions concerning the interpretation of his theory.

(23) J. P. Colpa and E. DeBoer, *Mol. Phys.*, **7**, 333 (1963).

(24) An excursion into the variation in parameters and methods of iteration including those of Chesnut,²⁵ Halevi,²¹ and Mulliken²⁶ indicates none of the conclusions made here would be significantly altered by a different choice.

(25) D. B. Chesnut, *J. Chem. Phys.*, **29**, 43 (1958).

(26) N. Mueller and R. Mulliken, *J. Am. Chem. Soc.*, **80**, 3489 (1958).

(27) J. Franklin and H. Tumpkin, *J. Chem. Phys.*, **20**, 745 (1952).

(28) The application of the McLachlan perturbation formula to wave functions obtained here gives an increase in calculated spin density at the central carbon which makes the agreement with the esr measurements better: A. D. McLachlan, *Mol. Phys.*, **3**, 233 (1960).

(29) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

(30) G. Olah, E. Baker, J. C. Evans, W. Tolgyesi, J. McIntyre, and I. Bartein, *J. Am. Chem. Soc.*, **86**, 1360 (1964).

The calculated changes in resonance energy for the deuterated intermediates, listed in the third column of the table, are arrived at by increasing S_{12} by 0.0025 according to the arguments of Halevi^{2,21} but without consideration of the inductive effect of deuterium. The change for the *t*-butyl radical is close to the observed isotope effect. The similarity calculated by this method for the radical- and cation-forming processes is, however, too great even without consideration of the greater electropositivity of deuterium.²²

In order to examine the molecular orbital predictions of the relative isotope effects due to changes in vibrational frequency, several assumptions are necessary. (a) Streitwieser's¹⁸ simplification of the complete equation for calculation of isotope effects in terms of vibrational frequencies is used.

$$\ln k_H/k_D = (0.187/T)\Sigma(\nu - \nu^*) \quad (1)$$

(b) The differences between transition and intermediate states and between gas phase and solution are neglected in the beginning but discussed later. (c) The drastic²² assumption is made that all of the vibrational frequencies which are important in determining the magnitude of the isotope effect will vary in proportion to the change in the C-N stretching force constant. This last assumption allows a simplification of (1) to

$$\ln k_H/k_D = (0.187/T)\Delta\gamma_{\text{eff}} \quad (2)$$

where $\Delta\gamma_{\text{eff}}$ is the effective frequency change on going from initial to transition state which is assumed to be proportional to the change in force constant for C-H stretching. The problem now becomes one of relating the molecular orbital wave functions to change in force constant for C-H stretching since

$$\Delta\gamma_{\text{eff}} = \gamma_{\text{eff}}(1 - \sqrt{F'/F_0})$$

where γ_{eff} is an effective frequency and F' and F_0 are the force constants for the C-H stretching in the transition and beginning states, respectively.

It can be seen immediately that the isotope effects for the radical- and cation-forming processes will be too similar in magnitude if one assumes the changes in force constants to be proportional to changes in bond order.³⁴ Salem³⁵ has shown, in fact, that the bond order terms for changes in force constants cancel and that the actual changes should be proportional to the self-polarizability of the bond. Adapting this method to the present problem gives

$$F'/F_0 = 1 + C\pi_{12,12}\beta_0 \quad (3)$$

(31) Application of Simpson's truncated perturbation method to these molecules, parameterizing with the measured resonance energies and estimated heats of formation of the ethyl radical and cation structures, gives charge and spin densities which are very close to those calculated here. This method, however, predicts no electronic transitions for the *t*-butyl cation below 220 mμ: W. T. Simpson and C. W. Looney, *ibid.*, **76**, 6285 (1954).

(32) A more refined version of this type of calculation gives better agreement: S. Ehrenson, private communication.

(33) In general, this is indeed a drastic assumption, but in terms of molecular orbital theory, it has some merit. For example, as the C≡H π bond weakens, the C-C π bond must strengthen. The effect also appears to be dominated by the stretching mode change.

(34) G. Berthier, B. Pullman, and J. Pontis, *J. Chim. Phys.*, **49**, 367 (1952); C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)*, **A193**, 456 (1948).

(35) L. Salem, "The Molecular Orbital Theory of Conjugated Systems," W. A. Benjamin, Inc., New York, N. Y., 1966; H. C. Longuet-Higgins and L. Salem, *Proc. Roy. Soc. (London)*, **A251**, 172 (1959).

The infrared spectrum of *t*-butyl cation in solution has recently been measured and a normal mode analysis carried out.³⁰ The set of frequencies obtained from this analysis predicts an equilibrium isotope effect for formation of the cation which is nearly identical with the kinetic isotope effect observed for the solvolysis of *t*-butyl chloride.³⁶ These data provide a method of parameterizing eq 3 so that self-polarizability can be used to predict secondary isotope effects. The F'/F_0 ratio used in this normal mode analysis is 0.885 and k_H/k_D , for solvolysis of *t*-butyl chloride at 25° is 2.38. These data give

$$\ln k_H/k_D = (482/T)(1 - \sqrt{1 - 0.572\pi\beta}) \quad (4)$$

where the constants have been taken into account and π is the self-polarizability of the $C\equiv H$, π bond. The last column of Table IV gives the calculated isotope effect of all the compounds shown using this parameterization. The observed total isotope effect for formation of the *t*-butyl radical is very close to the value calculated here.

The relatively small isotope effect now established for radical formation is thus in agreement with the extent to which hyperconjugation stabilizes such molecules. The calculated self-polarizability of the $C\equiv H$, π bond in the α -phenethyl radical is nearly identical with that for *t*-butyl and thus an identical isotope effect would be predicted by the present theory. We believe the lower value for this isotope effect observed by Seltzer is due to a decrease in the relative endothermicity of azo compound compared to perester decomposition and that the isotope effect in the perhydratropate decomposition will be closer to that observed for the pervalate. This point is being tested presently.

The good quantitative agreement for the *t*-butyl radical and cation systems should be viewed cautiously because of the assumptions made. Two complications with assumption b are apparent. One is the difference in degree of planarity of the transition states for radical- and cation-forming processes. Preliminary calculations using the extended Hückel method³⁷ indicate that the isotope effect should be reduced for nonplanar transition states. These calculations also indicate that radicals experience relatively less stabilization on planarization than do carbonium ions. The importance of this possibility is being examined by studies of bridged compounds.

Alternatively, it can be argued that the isotope effect for radical reactions should be more nearly calculable by molecular orbital theory since radical reactions in solution are not very different from the corresponding process in the gas phase. The calculated charge density on the central carbon of isopropyl cation is less than that estimated from its nmr spectrum³⁰ taken under conditions quite similar to those for the infrared measurements which in turn were fit by the normal mode analysis. Thus, calculated delocalization is greater than observed for carbonium ions so that an underestimate of the isotope effect for the radical process should have resulted from parameterization using carbonium ion data.

(36) J. C. Evans and G. Y. -S. Lo, *J. Am. Chem. Soc.*, **88**, 2118 (1966).

(37) R. Hoffman, *J. Chem. Phys.*, **39**, 1397 (1963). The program for these calculations was the one obtainable from Quantum Chemistry Program Exchange with minor modifications.

This situation is resolved if the solvent is postulated to furnish an attractive interaction with the polarized β protons of the hyperconjugatively stabilized carbonium ion. The consequent broadening of the vibrational potential for these C-H bonds would result in a lowering of the effective force constant when considering the cations as independent entities. This is essentially a restatement of the effect as described by Shiner³⁰ and one which can be tested since its logical consequence is a similar isotope effect for cation formation in the gas phase. This argument could explain the relative insensitivity of the isotope effects for *t*-butyl cation formation in different solvents.

While we favor the last hypothesis as the best single explanation for β isotope effects in cation formation, the very approximate nature of the present treatment makes the argument considerably less than compelling. A more reasonable view is that the net isotope effects can be a result of several of the postulated origins. However, we would hope that the present treatment might be useful as an empirical guide to the expected magnitudes of such isotope effects. Accordingly, Table IV contains calculated isotope effects for each species and these predictions are presently being tested.

The steric origin¹⁷ of these isotope effects has been neglected here. The argument that these effects are due to inordinately large changes in bending frequency¹⁸ has also been neglected (a breakdown of assumption c). The infrared spectrum of the *t*-butyl cation showed no particular indication of this origin.

Experimental Section

Proton nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer. Infrared measurements were made using a Beckman IR-7 instrument. Ultraviolet and visible spectral measurements were made on Cary 14 or Cary 11 spectrophotometers. Mass spectra were determined using a modified Consolidated Electrodynamic 26-614 residual gas analyzer.³⁸ Gas-liquid partition chromatography was carried out using an Aerograph Autoprep instrument.

Materials. Chlorobenzene was purified by shaking with 98% sulfuric acid, then with water, and drying over magnesium sulfate followed by a 2-hr reflux over phosphorus pentoxide. Finally, it was distilled from phosphorus pentoxide and then from potassium hydroxide, bp 130.5–130.9°.

Dioxane (reagent grade) was passed through a column of Woelm neutral alumina, refluxed over sodium for 24 hr, distilled, and passed through a column of neutral alumina. It was used immediately to prepare the 90% dioxane-water solutions which were stored in the dark, under nitrogen, at 0° until used.

t-Butyl hydroperoxide (Matheson Coleman and Bell) was distilled with the first third being discarded. The second third was retained, bp 32–35° (15 mm).

Galvinoxyl was prepared by the method of Kharasch.³⁹ Purification was by recrystallization in small amounts of absolute ethanol under nitrogen to a constant extinction coefficient of 595 at 776 m μ in benzene solution (lit.⁴⁰ 607 m μ). Pivalic acid was obtained from Matheson Coleman and Bell.

Peresters. The peresters were prepared from the corresponding acid chlorides by the method of Bartlett.⁷ Pivalic acid-*d*₄ was obtained by a Grignard sequence.⁴¹ The pivaloyl chloride was obtained by adding 90% of the calculated equivalents of thionyl chloride to the pivalic acid. After refluxing for 0.5 hr, a small aliquot was removed and the acid content determined by its nmr spectrum. Small increments of thionyl chloride were added until

(38) Funds for the purchase of this instrument were partially furnished through grants from the National Science Foundation and National Institutes of Health.

(39) M. Kharasch and B. Joshi, *J. Org. Chem.*, **22**, 1435 (1957).

(40) P. D. Bartlett and T. Funahashi, *J. Am. Chem. Soc.*, **84**, 2956 (1962).

(41) A. Streitwieser and H. S. Klein, *ibid.*, **85**, 2759 (1963).

the acid chloride/acid ratio was greater than 20. The acid chloride was then used directly for the perester synthesis.

The peresters were purified by passing them through a column of Woelm activity 1 basic alumina at 0° using ether eluent. This effectively removes all traces of *t*-butyl hydroperoxide. Before each kinetic run the compounds were rechromatographed and all traces of ether removed by pumping under high vacuum. Peroxide contents as determined by iodometric titration were not reproducible (83–92%). A purity of 100% was assumed on the basis of the nmr and infrared spectra and the reproducible kinetic behavior.

The pivalic acid-*d*₆ and pivaloyl chloride-*d*₆ were shown to contain less than 1% hydrogen using the nmr spectrum of a solution containing weighed amounts of compound and dioxane. The perester contained less than 2.6% hydrogen in the pivaloyl fragment as judged by the total nmr peak areas in the *t*-butyl region compared to dioxane in known concentration.

Kinetic Methods. The infrared method for measuring the rates utilized the disappearance of the carbonyl stretching band of the perester at 1772 cm⁻¹. The products of the reaction do not absorb at this frequency. Beer's law behavior was verified for this solvent-perester system. About 0.1-ml aliquots of about 0.1 *M* solutions of perester were added to 15 small tubes of Pyrex glass. The tubes were sealed and immersed in a constant temperature bath regulated to ±0.03°, removed at timed intervals, and quenched in ice. The tubes were stored at 0° until the infinity points were taken (ten half-lives). The analyses for duplicate runs were carried out together.

The pseudo-first-order galvinoxyl method utilized the disappearance of the galvinoxyl absorption at 767 mμ. The galvinoxyl solutions (10⁻³ *M*) containing less than a radical equivalent (*n* × perester concentration) in Pyrex culture tubes were carefully degassed and sealed under vacuum. Beer's law behavior and the effective path length were determined for each tube. The reaction

tubes were immersed in the oil baths for timed intervals, removed and quenched, read in the spectrophotometer, and reimmersed in the bath for a new time increment. Blank solutions of galvinoxyl in chlorobenzene were completely stable over the length of the runs. The blank galvinoxyl solutions in aqueous dioxane showed 14% decomposition over the eight half-life time periods. The runs in this solvent were therefore corrected, point by point, for the behavior of the blank solution. All of the rate plots were linear for more than three half-lives. The zero-order galvinoxyl studies were the same except for the initial perester concentrations.

Product Studies. The gaseous products from the decomposition were collected from breakseal flasks into a calibrated vacuum line. The total gas yield was thus obtained. The composition of the gas mixture was estimated by the sensitivities of the mass spectrometer to the components of the mixture. The *t*-butyl alcohol from the decomposition of the deuterated perester in aqueous dioxane was separated by glpc using a 30 ft × 1/8 in. column packed with 30% SE-30 on Chromosorb W. Its mass spectrum was identical with that of authentic *t*-butyl alcohol.

Acknowledgment. This work was supported by a grant from the Army Research Office, Durham. We are indebted to Dr. C. E. Klopfenstein whose computer program for molecular orbital calculations was modified to include heteroatom and overlap parameters and who assisted us in adapting the Hoffman program to the IBM 360 computer system. We are also grateful to Professor M. Schurr and Professor W. T. Simpson for many penetrating criticisms of this work and to Professor M. Sage for helpful discussions.

The Coupling Reactions of 1-Chlorocyclopentene, 1-Chlorocyclohexene, and 1-Chlorocycloheptene with Phenyllithium. The Question of Cycloallenic Intermediates¹

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Abstract: In previous work it was postulated that the coupling reactions of 1-chlorocyclopentene and 1-chlorocyclohexene with phenyllithium in ether at 150°, which yield 1-phenylcyclopentene and 1-phenylcyclohexene, proceed *via* an elimination-addition mechanism involving short-lived cycloalkyne intermediates. An alternative mechanism utilizing cycloallenic intermediates was not rigorously ruled out, however. In the present study the reactions of 1-chloro-2-methylcyclopentene, 2-chloro-3-methylcyclopentene, 1-chloro-2-methylcyclohexene, 2-chloro-3-methylcyclohexene, 1-chlorocyclopentene-2,5,5-*d*₃, 1-chlorocyclohexene-2,6,6-*d*₃, 1-chlorocycloheptene, and 1-chlorocycloheptene-2,7,7-*d*₃ with phenyllithium have been examined. In addition, isotopic rate constant ratios, *k*_H/*k*_D, were obtained from competition experiments employing 1-chlorocycloalkenes and 1-chlorocycloalkenes-2,*n,n*-*d*₃ (*n*-membered ring). Rate constant ratios for the five-, six-, and seven-membered rings were 3.36 ± 0.40, 5.34 ± 0.40, and 7.16 ± 0.40, respectively. The results of these studies provide compelling evidence that the coupling reactions of 1-chlorocyclopentene, 1-chlorocyclohexene, and 1-chlorocycloheptene with phenyllithium take place predominantly, if not exclusively, by way of an elimination-addition mechanism involving cycloalkyne intermediates.

In 1944, Wittig and Harborth³ reported that 1-phenylcyclohexene was formed in 5% yield upon heating 1-chlorocyclohexene and phenyllithium in ether at 100°. Later, it was suggested⁴ that this reaction might, in a

manner analogous to the coupling reactions of aryl halides with aryllithium reagents,⁵ proceed *via* an elimination-addition mechanism involving a cyclohexyne intermediate. In an effort to delineate the

(1) Presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965; Abstracts, p 23N.

(2) National Institutes of Health Predoctoral Fellow, 1964–1967.

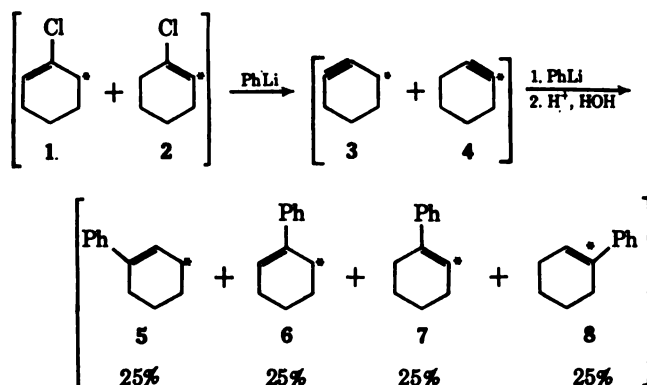
(3) G. Wittig and G. Harborth, *Ber.*, 77, 306 (1944).

(4) F. Scardiglia and J. D. Roberts, *Tetrahedron*, 1, 343 (1957).

(5) (a) G. Wittig, G. Pieper, and G. Fuhrmann, *Ber.*, 73, 1193 (1940); (b) G. Wittig, *Angew. Chem.*, 69, 245 (1957); (c) R. Huisgen and H. Rist, *Naturwissenschaften*, 41, 358 (1954); (d) R. Huisgen and H. Rist, *Ann.*, 594, 137 (1955); (e) E. Jenny and J. D. Roberts, *Helv. Chim. Acta*, 38, 1284 (1955).

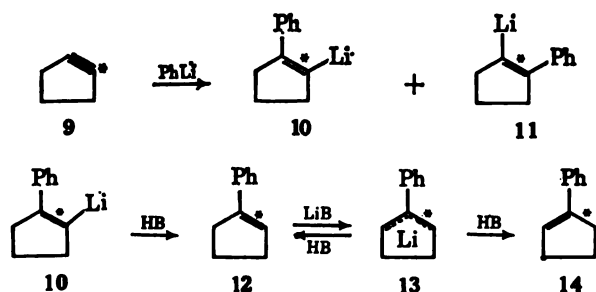
mechanism of substitution, Scardiglia and Roberts^{4,6} treated a 1:1 mixture of 1-chlorocyclohexene-6-¹⁴C (1) and 1-chlorocyclohexene-2-¹⁴C (2) with phenyllithium in ether at 150°. The 1-phenylcyclohexene which was obtained in 28% yield contained 23% (relative to the total ¹⁴C content) of the ¹⁴C label in the 1 position (8). The fact that ¹⁴C was found in the 1 position demonstrates that at least a portion of the substitution product arose from a mechanism other than direct nucleophilic displacement; the percentage of ¹⁴C in the 1 position is close to that predicted on the basis of a cyclohexyne hypothesis (Chart I).

Chart I



1-Chlorocyclopentene also reacts with phenyllithium at elevated temperatures.^{6,7} In a tracer study of this reaction, 1-chlorocyclopentene-1-¹⁴C gave rise to 1-phenylcyclopentene in which the starting ¹⁴C label was partitioned among the 1 (48.9%), 2 (36.2%), and 5 (14.9%) positions.⁶ In the absence of competing or consecutive rearrangement reactions, the ¹⁴C should have been distributed equally between the 1 and the 2 positions (10 and 11) had cyclopentyne-1-¹⁴C (9) intervened in the substitution process (Chart II). It has been proposed⁶ that a portion of the ¹⁴C in the 2 position rearranged to the 5 position by way of base-induced (phenyllithium or lithium ethoxide) allylic isomerization (10 → 14, Chart II).

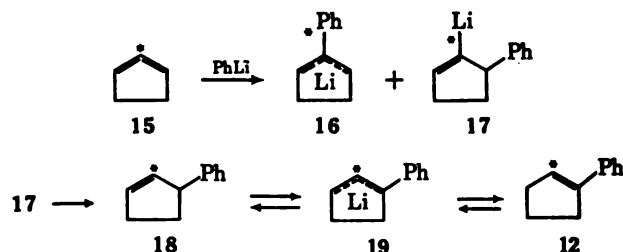
Chart II



Whereas aryl halides can give only one type of 1,2-elimination product, arynes, cyclic vinyl halides can, in principle, give either a cycloalkyne or a cycloallene. The patterns of ¹⁴C-isotope rearrangement discussed above fit a multistep cycloallenic substitution sequence almost as well as they do a cycloalkyne mechanism. To illustrate, 1,2-cyclopentadiene-2-¹⁴C (15) would yield organolithium intermediates 16 and 17 in a 1:1 ratio if one-half of the phenyllithium added to the

middle and one-half to the ends of the allenic system in 15 (Chart III). Intermediate 16 would ultimately produce 1-phenylcyclopentene-1-¹⁴C. Protonation of 17 followed by prototropic rearrangement would afford 12, which could continue on to 14. This mechanism cannot be criticized too severely for the necessity of hav-

Chart III



ing to rearrange the double bond of 17 into conjugation with the phenyl group (17 → 12), since the cyclopentyne mechanism requires similar transformations. The ¹⁴C data for 1-chlorocyclohexene can also be explained in terms of a cycloallenic mechanism, provided that the ratio of middle-to-end addition is again 1:1.

Roberts and co-workers⁸ have stated a definite preference for the cycloalkyne mechanism. Two arguments which they advanced in arriving at this preference were the following. The cycloalkyne hypothesis readily accounts for the *primary pattern* (excluding the prototropic rearrangement of 10 to 14) of ¹⁴C-isotope rearrangement, for phenyllithium should add with equal probability to the two carbons of the cycloalkyne triple bonds (kinetic isotope effects and minor steric differences neglected). It is less obvious why cycloallenes should react with phenyllithium in the manner required by the ¹⁴C data. A second objection to cycloallenic intermediates involves a selectivity argument. Were cycloallenic intermediates to intervene, they would have to display some measure of selectivity, for a nonstatistical addition of phenyllithium is called for by the results of the ¹⁴C experiments. In view of this selectivity, it is difficult to see why phenyllithium should add to both five- and six-membered ring allenic intermediates to give essentially equal portions of middle-to-end addition. These arguments, though satisfactory from the qualitative point of view, are difficult to translate into quantitative terms. For example, how much more selective should 1,2-cyclohexadiene be than 1,2-cyclopentadiene? Since they should both be highly reactive, might not the selectivity difference be undetectable?

A number of observations in the literature bear directly or indirectly on the question of the suitability of cycloallenes as intermediates in the nucleophilic substitution reactions of nonactivated cyclic olefinic halides. In an attempted synthesis of cyclononyne, Blomquist⁸ found that 1-chlorocyclononene reacted with alcoholic potassium hydroxide to give a mixture of cyclononyne and 1,2-cyclononadiene. Moore and Ward⁹ have studied acetylene-allene equilibria in C₉, C₁₀, and C₁₁-cyclic systems and found that the allene became progressively more stable relative to the isomeric alkynes as the ring size was decreased. A 1,2-cyclononadiene to cyclononyne equilibrium ratio of

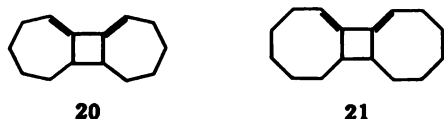
(6) L. K. Montgomery, F. Scardiglia, and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 1917 (1965).

(7) L. K. Montgomery and J. D. Roberts, *ibid.*, **82**, 4750 (1960).

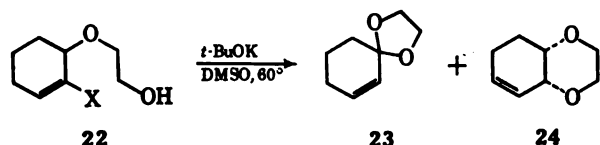
(8) A. T. Blomquist, L. H. Liu, and J. C. Bohrer, *J. Am. Chem. Soc.*, **74**, 3643 (1952).

(9) W. R. Moore and H. R. Ward, *ibid.*, **85**, 86 (1963).

about 13:1 (potassium *t*-butoxide, *t*-butyl alcohol, 100.3°) was obtained by these authors. Ball and Landor¹⁰ observed that 1-chlorocyclononene and 1-chlorocyclodecene react with sodamide in liquid ammonia to give the corresponding allenes, contaminated with about 15% of the cyclic acetylenes. Under similar reaction conditions 1-chlorocycloheptene and 1-chlorocyclooctene yielded, at least formally, allene dimers (20 and 21). Bottini and Schear¹¹ treated



2-chloro- and 2-bromo-3-(2-hydroxyethoxy)cyclohexene (22) with potassium *t*-butoxide in dimethyl sulfoxide and obtained products 23 and 24. These authors argue effectively that 23 was formed *via* an elimination-addition sequence involving a cycloallenic intermediate and, further, that cycloalkynes were not formed at all in this system. Finally, very recently Wittig¹² has



trapped 1,2-cyclohexadiene, generated through the action of potassium *t*-butoxide on 1-bromocyclohexene in dimethyl sulfoxide, using the highly reactive diene 1,3-diphenylbenzofuran. Taken as a whole, the above observations strongly suggest the need for additional research on the mechanism of the reactions of 1-chlorocyclohexene and 1-chlorocyclopentene with phenyllithium.

In the present investigation two experimental approaches have been employed in an attempt to unambiguously distinguish between the cycloalkyne and the cycloallene pathways. The first approach might be termed methyl-group blocking experiments. 2-Methylcycloalkanones, when treated sequentially with phosphorus pentachloride and base, yield mixtures of 1-chloro-2-methylcycloalkenes and 1-chloro-*n*-methylcycloalkenes (*n*-membered ring). The former halides cannot give rise to cycloalkynes, while the latter can. A simple mechanistic test is thus provided by examining the reactions, or lack thereof, of the two types of chlorides with phenyllithium. Moreover, the methyl groups of the 1-chloro-*n*-methylcycloalkenes serve as structural labels for the observation of any rearrangement which accompanies substitution. The methyl-group blocking experiments, though extremely classical in nature, prove to be an effective mechanistic tool, particularly in view of the relative ease with which they can be carried out experimentally. In a second approach, deuterium-labeled vinyl chlorides have been used to detect rearrangement and to probe the timing of the bond-breaking processes that lead to products.

Results and Discussion

General. The olefinic chlorides required for this study were prepared from appropriate ketones by way

(10) (a) W. J. Ball and S. R. Landor, *Proc. Chem. Soc.*, 143 (1961); (b) W. J. Ball and S. R. Landor, *J. Chem. Soc.*, 2298 (1962).

(11) A. T. Bottini and W. Schear, *J. Am. Chem. Soc.*, 87, 5802 (1965).

(12) G. Wittig and P. Fritze, *Angew. Chem. Intern. Ed. Engl.*, 5, 856 (1966).

of a two-step sequence. In the first, a simple ketone, a cycloalkanone- $\alpha,\alpha,\alpha',\alpha'-d_4$, or a 2-methylcycloalkanone was treated with phosphorus pentachloride in methylene chloride, affording a mixture of the desired olefinic chloride(s) and the *gem*-dichloride. The crude chloride mixtures were treated with potassium *t*-butoxide in *t*-butyl alcohol, sodium methylsulfinyl carbanion in dimethyl sulfoxide, or potassium *t*-butoxide in dimethyl sulfoxide in order to dehydrohalogenate the *gem*-dichlorides. The deuterated cycloalkanones were prepared from cycloalkanones by base-catalyzed proton-deuteron exchange with deuterium oxide. Authentic samples of possible olefinic chloride-phenyllithium substitution products were synthesized following standard procedures.

The previously reported^{4,6,7} coupling reactions of 1-chlorocyclopentene and 1-chlorocyclohexene with phenyllithium afforded 1-phenylcyclopentene and 1-phenylcyclohexene in 25–35% yields. It has been found that 1-chlorocycloheptene reacts with phenyllithium under similar reaction conditions to give 1-phenylcycloheptene; typical yields were somewhat higher. In an effort to determine whether these substitution reactions are a general reaction of olefinic chlorides, *trans*-3-chloro-2-pentene and phenyllithium were subjected to the standard reaction conditions. Analysis of the reaction products revealed that 55% of the starting chloride had been consumed, but that neither coupling products (*trans*- and *cis*-2-phenyl-2-pentene, *trans*- and *cis*-3-phenyl-2-pentene, 2-phenyl-1-pentene) nor acetylenic elimination products (1- and 2-pentyne) were present. These findings could be rationalized in a variety of ways; an extended discussion of such possibilities would seem of doubtful value. *cis*-3-Chloro-2-pentene would be a better model for the cyclic chlorides, and it is possible that an examination of its reaction with phenyllithium might be more revealing. Considering the equivocacy of the *trans* isomer results, however, additional effort was not expended on this aspect of the coupling reactions.

The C₅ Ring System. An ether solution which was 0.072 *M* in 1-chloro-2-methylcyclopentene and 0.76 *M* in phenyllithium was sealed in a stainless steel bomb and heated at 150° for 1.3 hr.¹³ The cooled reaction mixture was poured into water; the resulting organic reaction products were separated and quantitatively analyzed. A summary of products of interest is reported in Table I. Little or no (2% or less) coupled products were observed, indicating that an olefinic proton is required to achieve substitution.

Only 39% of the initial 1-chloro-2-methylcyclopentene was recovered. Independent of what the process or processes were that destroyed the starting material, it is interesting to note that a minimum¹⁴ of 40% of the chlorine in the starting olefin ended up as chloride ion in the aqueous wash solutions. About 21% of the chlorine in the initial 1-chloro-2-methylcyclopentene was not accounted for. Presumably nonvolatile, chlorine-containing products, perhaps polymer, were also formed.

(13) All of the coupling reactions in this study were conducted at (150 ± 10)° for a period of 1.3 hr. The concentrations of the reactants varied somewhat from experiment to experiment.

(14) A large quantity of bromide ion which came from the phenyllithium preparation was also present, making a precise chloride ion analysis difficult. Control experiments indicated that the chloride analyses reported here are low by several per cent (8–12% of the total chloride ion).

Table I. Reaction of 1-Chloro-2-methylcyclopentene with Phenyllithium^a

Reactant or product	Reactant, mmols	Product, mmols
1-Chloro-2-methylcyclopentene	7.23	2.80
3-Methyl-1-phenylcyclopentene and 3-methyl-2-phenylcyclopentene	0 ^b	<0.16 ^c
1-Methylcyclopentene	0 ^b	Trace
Chloride ion	0 ^b	2.85

^a Conducted in 100 ml of anhydrous ether at $(150 \pm 10)^\circ$ for 1.3 hr. ^b No analysis was made. Presumed to be absent. ^c Trace of unidentified component(s).

One final product of interest was the trace amount of 1-methylcyclopentene. Since it was not in the 1-chloro-2-methylcyclopentene, it most likely arose by way of metal-halogen interconversion.

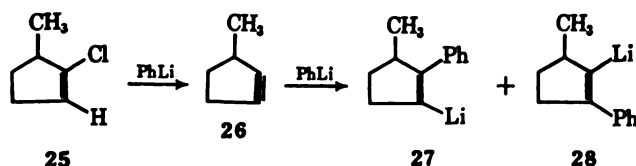
When 2-chloro-3-methylcyclopentene was heated with phenyllithium, 85% reaction occurred (Table II).

Table II. Reaction of 2-Chloro-3-methylcyclopentene with Phenyllithium

Reactant or product	Reactant, mmols	Product, mmols
2-Chloro-3-methylcyclopentene	15.9	2.4
3-Methyl-2-phenylcyclopentene	0 ^b	2.00
3-Methyl-1-phenylcyclopentene	0 ^b	2.09
3-Methylcyclopentene	0 ^b	Trace
Chloride ion	0 ^b	10.54

^a Conducted in 140 ml of ether at $(150 \pm 10)^\circ$ for 1.3 hr. ^b No analysis was made. Presumed to be absent.

Two substitution products were detected and isolated employing glpc. One was unequivocally identified as 3-methyl-2-phenylcyclopentene. The chromatographic retention time behavior of the other product was identical with that of a nonseparable mixture of 3-methyl-1-phenylcyclopentene and 4-methyl-1-phenylcyclopentene, which was prepared independently starting from 3-methylcyclopentanone. Moreover, the nmr and infrared spectra of the second substitution product were similar, though not identical, with those of the olefin mixture. One noteworthy spectral difference was that the nmr vinyl proton absorption of the coupled product was a crude doublet, while the same absorption region of the olefin mixture was broader and more complex. It would not be unreasonable to infer from this that the substitution product was predominantly one isomer, 3-methyl-1-phenylcyclopentene, the product that would be expected ($25 \rightarrow 26 \rightarrow 27 + 28$) for an elimination-addition substitution mechanism involving a 3-methylcyclopentene intermediate 26. The fact that 3-methyl-



2-phenylcyclopentene and 3-methyl-1-phenylcyclopentene were obtained in roughly equal quantities (Table II) lends additional support to the postulated intermediacy of 3-methylcyclopentene. Slight steric

differences in the transition states for the formation of organolithium intermediates 27 and 28 are probably responsible for the slight preferential formation of 3-methyl-1-phenylcyclopentene.

One aspect of the 2-chloro-3-methylcyclopentene study that is somewhat disturbing is that no allylic isomerization of the substitution products was noted. Although limited isomerization of 3-methyl-1-phenylcyclopentene to 4-methyl-1-phenylcyclopentene would not have been discerned, prototropic rearrangement of 3-methyl-2-phenylcyclopentene to 2-methyl-1-phenylcyclopentene would have been easily detected by glpc. It could be argued that base-catalyzed allylic isomerization of 3-methyl-2-phenylcyclopentene is slow owing to the fact that proton removal must occur at a tertiary carbon; such a rationalization is not entirely satisfying. Accordingly, the mechanism of coupling was probed by a second method.

The reaction of 1-chlorocyclopentene-2,5,5-*d*₃ with phenyllithium provided coupled product in only 11% yield, suggesting that a kinetic isotope effect was operative. About 65% of the starting chloride was recovered. The infrared and nmr spectra of the recovered olefin were identical with those of the starting material. Proton nmr analysis of the substitution product indicated that 0.14 ± 0.03 deuterons and 1.84 ± 0.20 deuterons resided in olefinic and saturated ring positions, respectively. In order to gain an indication as to how much of the coupled product existed as some form of an organolithium species at the end of the reaction, 1-chlorocyclopentene was treated with phenyllithium, and the resultant products were treated with deuterium oxide. An average of 0.20 ± 0.03 deuterium was incorporated into the olefinic position; a maximum of 0.2 deuterium was present in the saturated positions. Mass spectral analysis of the benzene-benzene-*d*₁ showed that about 12% of the initial phenyllithium survived the reaction. In Table III the experimental

Table III. Reaction of 1-Chlorocyclopentene-2,5,5-*d*₃ with Phenyllithium^a

Observation or hypothetical model	Deuterium ^b	
	Olefinic	Saturated
Observed	0.14 ± 0.03^c	1.84 ± 0.20^c
Cyclopentene-3,3- <i>d</i> ₂ , no isomerization	0	2.00
Cyclopentene-3,3- <i>d</i> ₂ , isomerization	0.15	1.55
1,2-Cyclopentadiene-1,3- <i>d</i> ₂ , limited isomerization	0.50	1.00
1,2-Cyclopentadiene-1,3- <i>d</i> ₂ , isomerization	0.43	0.93

^a Conducted in ether at $(150 \pm 10)^\circ$ for 1.3 hr. ^b Average number of deuterons per position per molecule. ^c Student's distribution, 99.5% confidence limit.

deuterium distribution in the 1-chlorocyclopentene-2,5,5-*d*₃ coupled product is compared to calculated distributions based on four alternative mechanistic hypotheses: cyclopentene-3,3-*d*₂ intermediate, no allylic isomerization; cyclopentene-3,3-*d*₂ intermediate, allylic isomerization as required by the ¹⁴C-tracer study;⁶ 1,2-cyclopentadiene-1,3-*d*₂ intermediate, sufficient isomerization to obtain 1-phenylcyclopentene (*vide supra*); 1,2-cyclopentadiene-1,3-*d*₂ intermediate, allylic isomer-

ization as required by the ^{14}C -tracer study.⁶ Clearly, the cyclopentene-3,3- d_2 isomerization hypothesis provides the best fit to the data. The glaring inability of the 1,2-cyclopentadiene-1,3- d_2 hypotheses to accommodate the data is also significant.

The kinetic isotope effect was examined in a competition experiment employing 1-chlorocyclopentene and 1-chlorocyclopentene-2,5,5- d_3 in a 2.7:1 molar ratio. So little deuterium was present in the coupled product that an isotope effect on coupling could not be reliably determined directly from product composition. The unreacted chlorides could be accurately assayed, however. From the initial and final quantities of 1-chlorocyclopentene and 1-chlorocyclopentene-2,5,5- d_3 , a rate constant ratio, $k_{\text{H}}/k_{\text{D}}$, for the disappearance of starting material of 3.36 ± 0.40 was calculated using the standard formula.¹⁵ In applying this formula, the usual assumptions¹⁵ were made, namely that the rate expressions for the two competing reactions were first order in substrate but otherwise differed only in the values of the specific rate constants k_{H} and k_{D} .

The value of $k_{\text{H}}/k_{\text{D}}$ is quite large, considering the temperature at which the competition experiment was conducted. If merely the zero-point energies of the CH and CD stretching vibrations were lost in going to the coupling reaction transition states, the maximum expected rate constant ratio at 150° would be about $3.8^{16,17}$. Even if $k_{\text{H}}/k_{\text{D}}$ for substitution was lower than the measured ratio, it is obvious that it was sizeable in view of the modicum of deuterium that was incorporated into the product. Consequently, the competition experiment provides valuable evidence in support of the proposed elimination-addition mechanism. The magnitude of the isotope effect and the fact that 1-chlorocyclopentene-2,5,5- d_3 was recovered unmodified make it clear that the rate-determining step in substitution is an irreversible metallation at the olefinic proton (deuteron) position or, alternatively, concerted elimination to cyclopentene (cyclopentene-3,3- d_2).

The C_6 Ring System. Preparative glpc could not be conveniently employed to separate 1-chloro-2-methylcyclohexene and 2-chloro-3-methylcyclohexene. A mixture of the two isomers was treated with phenyllithium. In Table IV a summary of reactants and products is displayed. The product distribution

Table IV. Reactions of 1-Chloro-2-methylcyclohexene and 2-Chloro-3-methylcyclohexene with Phenyllithium^a

Reactant or product	Reactant, mmols	Product, mmols
1-Chloro-2-methylcyclohexene	28.4	17.7
2-Chloro-3-methylcyclohexene	17.7	3.99
3-Methyl-2-phenylcyclohexene	0 ^b	4.00
3-Methyl-1-phenylcyclohexene	0 ^b	4.35
1-Methylcyclohexene	0 ^b	Trace
3-Methylcyclohexene	0 ^b	Trace
Chloride ion	0 ^b	23.4

^a Conducted in 210 ml of ether at $(150 \pm 10^\circ)$ for 1.3 hr. ^b No analysis made. Presumed to be absent.

(15) G. A. Russell in "Technique of Organic Chemistry," Vol. VIII, Part I, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p 343.

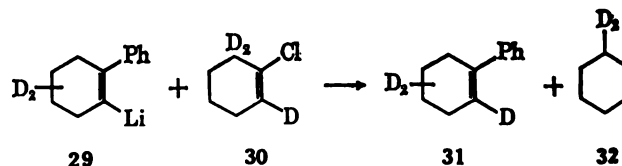
(16) L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press Co., New York, N. Y., 1960, p 20.

(17) Calculation based on CH and CD stretching frequencies (infrared data) of 3077 and 2294 cm^{-1} .

appears to be very much the same as with the methyl-labeled chlorocyclopentenes. About 38% of the 1-chloro-2-methylcyclohexene reacted. No 2-methyl-1-phenylcyclohexene was observed, implying that substitution products were not formed from 1-chloro-2-methylcyclohexene. If the coupling of 2-chloro-3-methylcyclohexene with phenyllithium followed a route involving 3-methylcyclohexyne, 3-methyl-2-phenylcyclohexene and 3-methyl-1-phenylcyclohexene should have been produced in a 1:1 ratio. A ratio close to this value was observed experimentally. As was the case with the products from 2-chloro-3-methylcyclopentene, the 1-phenyl isomer was favored slightly.

1-Chlorocyclohexene-2,6,6- d_2 and phenyllithium gave a deuterium-labeled substitution product in 13% yield. Unreacted olefinic chloride was recovered and was found to be unchanged. Analysis of the deuterium distribution in the coupled product showed, as anticipated, that an average of 1.93 ± 0.11 deuterons was located in the saturated ring positions. Quite unexpected, however, was the finding that 0.82 ± 0.09 deuteron resided in the olefinic position. Mass spectral analysis of the benzene from the reaction revealed that only 7.0 mmols of benzene- d_4 was formed. About 20.2 mmols of 1-chlorocyclohexene-2,6,6- d_2 reacted. A plausible explanation of these results would be that a large primary kinetic isotope effect retarded the rate of the elimination-addition pathway to such an extent that direct nucleophilic substitution could effectively compete for the 1-chlorocyclohexene-2,6,6- d_2 . Isotope rate constant measurements indicate that this is not the case.

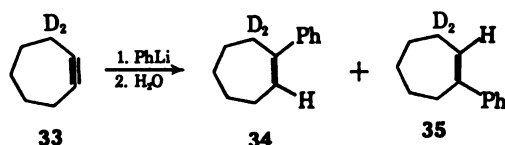
The kinetic isotope effect in the C_6 system was explored utilizing the competition method. A 3:1 mixture of 1-chlorocyclohexene and 1-chlorocyclohexene-2,6,6- d_2 afforded a substitution product possessing nmr and infrared spectra which were virtually indistinguishable from nondeuterated 1-phenylcyclohexene. A $k_{\text{H}}/k_{\text{D}}$ of 5.34 ± 0.40 was calculated, based on these observations that 1-chlorocyclohexene-2,6,6- d_2 does not react with phenyllithium by way of direct nucleophilic displacement. About the only way to bring the 1-chlorocyclohexene-2,6,6- d_2 product study and the $k_{\text{H}}/k_{\text{D}}$ measurement into compatibility is to assume that coupling takes place via a cyclohexyne-3,3- d_2 (32) intermediate and that the organolithium compounds which result from phenyllithium addition (29) react preferentially with the substrate ($29 + 30 \rightarrow 31 + 32$). If the reaction is autocatalytic, $k_{\text{H}}/k_{\text{D}}$ cannot



be calculated in the usual manner.¹⁵ Nevertheless, qualitatively it is clear that a large isotope effect operates on the coupling reaction.

The C_7 Ring System. Methyl-group blocking experiments were not carried out on a C_7 system. In order to see if substitution occurs with cycloheptenyl chlorides, 1-chlorocycloheptene-2,7,7- d_3 was heated with phenyllithium under the standard reaction con-

ons. Substitution product was obtained in 15% d, which is somewhat higher than with the C_5 and deuterated chlorides. Proton nmr analysis of the product indicated the presence of 0.17 ± 0.02 deuteron per molecule in the olefinic position and 5 ± 0.12 deuterons per molecule in the saturated positions. Since the saturated proton region of the spectrum of 1-phenylcycloheptene consisted of a complex absorption extending continuously from 1.1 to 2.9 ppm downfield from tetramethylsilane, it was possible¹⁸ to determine the position(s) of the two deuterons on the cycloheptene ring. The deuteron spectrum of the substitution product,¹⁹ however, revealed two types of aliphatic deuterons, centered at 1.5 and 2.50 ppm. The areas of the deuteron absorption peaks were approximately equal, the downfield peak being slightly the larger. These data provide excellent evidence that substitution takes place by way of cycloheptyne-3,3- d_2 (33) intermediate.



the k_H/k_D for competition between 1-chlorocycloheptene and 1-chlorocycloheptene-2,7,7- d_2 was 7.16/0.40. As in the C_5 and C_6 systems, the product contained little deuterium. At least two factors might reasonably be responsible for the unusually large magnitude of the rate constant ratio. First, it has been reported that tunneling is important in certain bimolecular elimination reactions and that k_H/k_D is increased accordingly.²⁰ Second, a variety of detailed elimination mechanisms can be envisioned which involve multicenter transition states. With such mechanisms the CH and CD stretching and bending frequencies might both be important in determining the magnitude of the isotope effect.²¹

The Question of Cycloallenic Intermediates. The experimental results presented in this paper in consort with the earlier ^{14}C -tracer studies⁶ demonstrate beyond reasonable doubt that the coupling reactions of 1-chlorocyclopentene, 1-chlorocyclohexene, and 1-chlorocycloheptene with phenyllithium proceed predominantly, if not exclusively, by way of elimination-addition mechanisms involving cycloalkyne intermediates. It is clear, nonetheless, that the olefinic chlorides enter into reactions other than substitution. For example, in no case was there a 1:1 molar correspondence between chloride consumed and coupled product formed. 1-chloro-2-methylcyclopentene and 1-chloro-2-methylcyclohexene underwent significant reaction, despite the fact that they possessed no olefinic protons. It is difficult to say whether or not cycloallenic intermediates might be involved in these side reactions.

Returning to the findings of Wittig,¹² Bottini,¹¹ Landor,¹⁰ it appears that 1-halocycloalkenes and strongly basic nucleophiles can give rise to either cyclo-

alkynes or cycloallenes, depending upon the particular halide, base, and reaction conditions employed. Factors such as the relative rates of cycloalkyne and cycloallene formation, the rate of cycloalkyne-cycloallene interconversion, and cycloalkyne-cycloallene relative stability are probably important in determining which reaction path is followed in a given system. Unfortunately, little is known concerning the above factors. In preliminary results²² from a study of the quantitative conformational analyses of C_8 , C_9 , and C_{10} cycloalkynes and cycloallenes (extended Wiberg²³ scheme), we have found that the energies of the conformations of minimum energy in these systems are complex composites of bond angle, torsional, and nonbonded energy terms. Accordingly, it is doubtful that the cycloalkyne-cycloallene equilibrium data of Moore and Ward⁹ provide reliable insight into the relative stabilities of cycloalkynes and cycloallenes in smaller ring systems. One interesting point that has been noted concerns the general difficulty of placing a triple bond in the lower members of the medium-sized rings. For simple geometrical reasons alone, the collinear, four-atom grouping of a strain-free triple bond cannot be placed in a carbocyclic ring containing less than nine carbon atoms without introducing substantial bond angle distortions at one or more positions. Conformational analysis of the C_8 - C_{10} cycloalkynes have made it evident that the restrictions that the linear four-atom acetylenic array impose on a cyclic system are not as severe as might be expected on the basis of geometrical considerations. This is true owing to the fact that $\text{C}-\text{C}\equiv\text{C}$ bond angles are relatively easy to distort; the bending force constants for $\text{C}-\text{C}\equiv\text{C}$ bond angles are about one-third those for $\text{C}-\text{C}-\text{C}$ bond angles.²⁴ It is not clear how important a role these force constant differences might play in determining conformational preferences and relative cycloalkyne stabilities in the smallest cycloalkynes, for it is known that highly strained systems cannot be satisfactorily treated using the usual quantitative conformational analysis schemes.

Experimental Section

Boiling points are uncorrected. Nmr and infrared spectra were routinely recorded and are assumed to be in satisfactory agreement with authentic or predicted spectra when they are not explicitly discussed. The nmr spectra were obtained from dilute chloroform- d_1 solutions using a Varian Associates A-60 spectrometer. Chemical shifts are reported as parts per million displacements from tetramethylsilane as an internal standard. Infrared spectra were generally recorded on both Perkin-Elmer Model 137 and Model 137-G (near-infrared) Infracord spectrometers. Quantitative glpc determinations were carried out on an F & M Scientific Model 609 flame-ionization gas chromatograph equipped with a Minneapolis-Honeywell recorder (Model Y153-999) fitted with a Disc Instruments integrator. All of the columns used with the F & M instrument were stainless steel and 8 ft in length (0.25 in. o.d.). The columns and their designations are: 20% silicone gum GE XE-60 on 60-80 mesh Chromosorb P (XEA); 20% Carbowax 20M on 60-80 mesh Chromosorb P (20CWA); 10% Carbowax 20M on 60-80 mesh Diatoport S (10CWA). Preparative glpc was conducted on a F & M Model 720 gas chromatograph fitted with 8-ft (0.375-in. o.d.) stainless steel columns. The columns were: 20% silicone gum GE XE-60 on 60-80 mesh Chromosorb P (XEP); 20% Carbowax 20M on 60-80 mesh Chromosorb P (CWP). Mass

(22) L. K. Montgomery, D. W. Garrett, and G. J. Eubanks, unpublished results.

(23) K. B. Wiberg, *J. Am. Chem. Soc.*, **87**, 1070 (1965).

(24) (a) J. H. Schachtschneider and R. G. Snyder, *Spectrochim. Acta*, **19**, 117 (1963); (b) J. L. Duncan, *ibid.*, **20**, 1197 (1964).

3) This was also true in the case of the coupling products from 1-chlorocyclopentene-2,5,5- d_2 and 1-chlorocyclohexene-2,6,6- d_2 .

4) L. K. Montgomery, A. O. Clouse, A. M. Crelier, and L. E. Legate, *J. Am. Chem. Soc.*, in press.

5) V. J. Shiner, Jr., and M. L. Smith, *J. Am. Chem. Soc.*, **83**, 593 (1961).

6) Reference 16, p 21.

spectra were recorded on a Consolidated Electrodynamics Corp Model 21-260 mass spectrometer.

Cyclohexanone-2,2,6,6- d_4 . A solution consisting of 45 g (0.46 mole) of cyclohexanone, 80 g (4.00 moles) of deuterium oxide (99.8%), 10 ml of triethylamine, and 400 ml of anhydrous dioxane was refluxed for 48 hr. Deuterium oxide, water, triethylamine, and dioxane were removed by distillation. The exchange was repeated four more times. Final distillation afforded 27.1 g (58%) of cyclohexanone-2,2,6,6- d_4 , bp 148–153°.

Cyclopentanone-2,2,5,5- d_4 . was prepared by Mr. D. Armstrong in the laboratories of V. J. Shiner, Jr., following a procedure similar to the one outlined above for cyclohexanone-2,2,6,6- d_4 . We wish to thank Professor Shiner for lending us this material.

Olefinic Chlorides. The preparation of 1-chloro-2-methylcyclopentene and 2-chloro-3-methylcyclopentene illustrates the general procedure which was employed for the preparation of olefinic chlorides from ketones. A solution of 39.2 g (0.40 mole) of 2-methylcyclopentanone in 45 ml of methylene chloride was added slowly to 103 g (0.50 mole) of phosphorus pentachloride in 530 ml of methylene chloride (4–5°). The solution was stirred for 1 hr at this temperature, allowed to warm to 18° over a 1-hr period, and poured onto crushed ice. The methylene chloride layer was separated and washed thoroughly with 40% sodium hydroxide solution and water. Removal of the solvent by distillation left a 26.4-g mixture of 1-chloro-2-methylcyclopentene, 2-chloro-3-methylcyclopentene, and 1,1-dichloro-2-methylcyclopentane. The latter compound was dehydrohalogenated following method 1.

Dehydrohalogenation Method 1. The crude chloride mixture was added dropwise over a 5-min period to a 0.34 *M* solution of methylsulfinyl carbanion (4.0 g of sodium hydride) in dimethyl sulfoxide (500 ml). The rate of addition was such that the temperature stayed within the range 18–32°. The solution was stirred an additional 5 min at 24° and poured into water. The reaction products were taken up in methylene chloride; the extract was washed thoroughly with water. Distillation afforded 8.36 g (18% based on ketone) of 1-chloro-2-methyl- and 2-chloro-3-methylcyclopentene (45:55), bp 120–123°. The two chlorides were separated employing preparative glpc (XEP, 125°, 200 cc/min).

In general the olefinic chlorides were purified by preparative glpc, stored in sealed ampoules under refrigeration, and redistilled immediately prior to use. Typical purity after distillation as assessed by glpc was 99% or greater.

1-Chloro-2-methylcyclohexene and 2-Chloro-3-methylcyclohexene. 2-Methylcyclohexanone (44.0 g, 0.397 mole), phosphorus pentachloride (103 g, 0.49 mole), and sodium methylsulfinyl carbanion (method 1; 7.2 g, 0.30 mole of sodium hydride in 300 ml of dimethyl sulfoxide) provided 7.3 g (14%; 99% purity by glpc; 20 CWA, 100°, 33 cc/min) of the two olefinic chlorides, bp 58–63° (23 mm) [lit.²⁵ bp 41–42° (8 mm)]. A 65:35 mixture of isomers was indicated by glpc. A 65:35 mixture was also inferred from nmr. The predominant isomer was 1-chloro-2-methylcyclohexene.

1-Chlorocyclopentene. Cyclopentanone (44.0 g, 0.52 mole), phosphorus pentachloride (135 g, 0.65 mole), and potassium *t*-butoxide (method 2; 12.4 g, 0.32 equiv of potassium in 400 ml of *t*-butyl alcohol) provided 16.3 g of crude 1-chlorocyclopentene, bp 99–108°, 93% purity by glpc (29%). Chromatographed material (CWP, 120°, 150 cc/min) was redistilled, bp 102–103° (lit.⁶ bp 102–103°).

1-Chlorocyclohexene. Cyclohexanone (19.6 g, 0.200 mole), phosphorus pentachloride (49.5 g, 0.238 mole), and potassium *t*-butoxide (method 2; 6.2 g, 0.159 equiv of potassium in 200 ml of *t*-butyl alcohol) provided 7.9 g of crude 1-chlorocyclohexene, bp 139–141°, 95% purity by glpc (33%). Chromatographed material (CWP, 145°, 150 cc/min) was redistilled, bp 140–141° (lit.²⁶ bp 142–143°).

1-Chlorocycloheptene. Cycloheptanone (44.8 g, 0.400 mole) and phosphorus pentachloride (104 g, 0.500 mole) gave 41.9 g of crude chlorides which was treated with base following method 3.

Dehydrohalogenation method 3 was very similar to method 1, the principal difference being that potassium *t*-butoxide (MSA Research Corp.) was employed as the base. The chlorides from cycloheptanone were added to a solution of 15 g of potassium *t*-butoxide in 190 ml of dimethyl sulfoxide. About 17 g (80% 1-chlorocycloheptene; 24%) of dehydrohalogenation products, bp 150–176°, were obtained. The chromatographed material (CWP, 140°,

150 cc/min) was redistilled, bp 55.0–55.5° (12 mm) [lit.¹⁰ bp 54–58° (14 mm)].

1-Chlorocyclopentene-2,5,5- d_3 . Cyclopentanone-2,2,5,5- d_4 (45.5 g, 0.517 mole), phosphorus pentachloride (135 g, 0.649 mole), and potassium *t*-butoxide (method 2; 45 g, 1.15 equiv of potassium in 875 ml of *t*-butyl alcohol) provided 17.9 g of olefinic chloride (93% purity; 31%), bp 103–105°. Chromatographed (CWP, 120°, 150 cc/min) and redistilled, bp 103–104°, 1-chlorocyclopentene-2,5,5- d_3 , n_D^{25} 1.4379, contained 3.00 ± 0.06 deuterons/molecule, as assessed by proton nmr (benzene, quantitative internal standard). There was no visually discernible absorption in the olefinic proton region.

1-Chlorocyclohexene-2,6,6- d_3 . Cyclohexanone-2,2,6,6- d_4 (26.6 g, 0.261 mole), phosphorus pentachloride (70.7 g, 0.340 mole), and potassium *t*-butoxide (method 2; 10 g, 0.26 equiv of potassium in 350 ml of *t*-butyl alcohol) provided 23.8 g of olefinic chloride (62% purity; 46%), bp 139–151°. Chromatographed (CWP, 145°, 150 cc/min) and redistilled, bp 139–141°, 1-chlorocyclohexene-2,6,6- d_3 , n_D^{25} 1.4797, contained 3.00 ± 0.06 deuterons/molecule, as assessed by proton nmr (biphenyl, quantitative internal standard). There was no visually discernible absorption in the olefinic proton region.

1-Chlorocycloheptene-2,7,7- d_3 was available from another study.¹⁰ Chromatographed (CWP, 140°, 150 cc/min) and redistilled, bp 52–53° (11 mm), 1-chlorocycloheptene-2,7,7- d_3 , n_D^{25} 1.4859, contained 2.89 ± 0.06 deuterons/molecule, as assessed by proton nmr (biphenyl, quantitative internal standard). There was no visually discernible absorption in the olefinic proton region.

***trans*-3-Chloro-2-pentene.** 3-Pentanone (137.6 g, 1.60 moles) and phosphorus pentachloride (416 g, 2.00 mole) gave about 100 g of a mixture of *trans*- and *cis*-3-chloro-2-pentene and 3,3-dichloropentane. The *trans* isomer, bp 92–93° (lit.²⁷ bp 92–93°), could be easily obtained in high purity by fractional distillation and was used in the attempted coupling experiment.

Phenyllithium Coupling Reactions. The reactions of 1-chloro-2-methylcyclohexene and 2-chloro-3-methylcyclohexene with phenyllithium illustrate the general procedure. A solution consisting of 3.692 g (0.0284 mole) of 1-chloro-2-methylcyclohexene, 2.308 g (0.0177 mole) of 2-chloro-3-methylcyclohexene, and 0.221 mole of phenyllithium²⁸ in 210 ml of ether was placed in a 300-ml stainless steel bomb, sealed, and heated at $150 \pm 10^\circ$ for 1.3 hr. The bomb was cooled in air (20 min), ice water (25 min), and Dry Ice-acetone (10 min), vented, and allowed to warm to room temperature. The reaction products were washed out of the bomb with water and ether. The ether layer was separated, washed with two 100-ml portions of water, and dried twice over 7-g quantities of anhydrous calcium chloride. Most of the ether was removed by distillation, and the reaction products were analyzed by glpc. Cyclohexanone was employed as an internal standard for low-boiling components (20 CWA, 100°, 33 cc/min) and *N,N*-dimethylaniline for high-boiling components (20 CWA, 225°, 30 cc/min). Detector response conversion factors were determined for most compounds. The responses of 1-chloro-2-methylcyclohexene and 2-chloro-3-methylcyclohexene were assumed to be equal. A mixture of 3-methyl-1-phenylcyclohexene and 4-methyl-2-phenylcyclohexene (*vide infra*) was used to estimate the conversion factor for 3-methyl-1-phenylcyclohexene. A summary of the analyses for key reaction products is provided in Table IV. Benzene, ethylbenzene, and biphenyl were also present. The substitution products were isolated employing glpc (XEP, 205°, 200 cc/min). 3-Methyl-2-phenylcyclohexene was identified by comparing its nmr and infrared spectra with those of an authentic sample. The second product, judged to be 3-methyl-1-phenylcyclohexene, possessed characteristic infrared absorption bands at 1639, 1597, and 1572 cm^{-1} (*vide infra*). The nmr spectrum consisted of complex absorption (5.0 protons, assigned) from 7.5 to 6.8, complex absorption (0.83 proton) from 6.00 to 5.92, and complex absorption (10.3 protons) from 2.6 to 0.8 which included a well-defined doublet (6.5 cps) at 1.04 (*vide infra*). The chloride analysis in Table IV was carried out following a procedure outlined by Kolthoff and Stenger.²⁹

1-Chloro-2-methylcyclopentene and Phenyllithium. 1-Chloro-2-methylcyclopentene (0.8382 g, 0.00723 mole) and 100 ml of 0.76 *M*

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thium (0.076 mole) in ether was heated at $150 \pm 10^\circ$ for 1.3 hr. A summary of the reaction products is provided in Table I. **trans-3-methylcyclopentene and Phenyllithium.** 2-Chloro-3-methylcyclopentene (1.8476 g, 0.01593 mole) and 140 ml of 1.19 M phenyllithium (0.167 mole) in ether were heated at $150 \pm 10^\circ$ for 1.3 hr. A summary of the reaction products is provided in Table II A, 70° , 200 cc/min). The substitution products were by glpc (XEP, 125° , 200 cc/min). The product identified as 1-phenylcyclopentene possessed characteristic infrared bands at 1618, 1597, and 1571 cm^{-1} (*vide infra*). The spectrum consisted of complex absorption (5.0 protons, assigned), complex absorption (0.85 proton) from 6.10 to 6.9, complex absorption (8.15 protons) from 6.10 to 5.93, and absorption (8.15 protons) from 2.9 to 1.5, which included a doublet (7 cps) at 1.07 (*vide infra*). The product identified as 3-phenylcyclopentene possessed characteristic infrared bands at 1623, 1597, and 1572 cm^{-1} (*vide infra*). The spectrum consisted of complex absorption (5.0 protons, assigned), complex absorption (0.85 proton) from 6.10 to 6.9, a crude doublet (~ 2 cps, 0.7 proton) at 6.07, complex absorption at 3.2–1.3 (8.2 protons), and a doublet (7 cps, 2.2 at 1.08 (*vide infra*)).

1-Chlorocyclopentene-2,5,5- d_2 and Phenyllithium. 1-Chlorocyclopentene-2,5,5- d_2 (9.0048 g, 0.0538 mole) and 210 ml of 0.98 M phenyllithium (0.203 mole) in ether were heated at $150 \pm 10^\circ$ for 1.3 hr. The reaction mixture containing 5.88 g (65.3%; 20 CWA, 70° , 35 cc/min) of 1-chlorocyclopentene-2,5,5- d_2 and 1.31 g (10.7%; 20 CWA, 25° , 35 cc/min) of deuterated 1-phenylcyclopentene. Both products were isolated utilizing preparative glpc. The nmr and infrared spectra of the recovered chloride were virtually identical to those of the starting material. Proton nmr analysis of the recovered 1-phenylcyclopentene indicated the presence of 0.14 ± 0.02 deuterons and 1.84 ± 0.20 deuterons in the olefinic and saturated positions, respectively. The phenyl protons were used as an internal standard for the analysis. The quoted error was calculated from six integrations using a Gaussian distribution analysis and employing a 99.5% confidence

1-Chlorocyclopentene and Phenyllithium. Deuterium Oxide. 1-Chlorocyclopentene (8.179 g, 0.0798 mole) and 0.85 M phenyllithium (0.204 mole) in ether were heated at $150 \pm 10^\circ$ for 1.3 hr. Exactly 50.0 ml of deuterium oxide was added during the reaction. The products were then processed in the manner described above. The reaction products included 3.04 g (37.5%; 20 CWA, 70° , 35 cc/min) of 1-chlorocyclopentene and 2.76 g (23.7%; 20 CWA, 25° , 35 cc/min) of 1-phenylcyclopentene. Analysis by glpc (glpc, mass spectrometry) indicated that 12.4% of the starting phenyllithium was present at the end of the reaction. Nmr analysis of glpc-collected coupled product indicated the presence of 0.20 ± 0.03 deuterons and no greater than 0.2 deuterons in the olefinic and saturated ring positions, respectively.

1-Chlorocycloheptene-2,7,7- d_2 and Phenyllithium. 1-Chlorocycloheptene-2,7,7- d_2 (5.1308 g, 0.0384 mole) and 110 ml of 1.03 M phenyllithium (0.113 mole) in ether were heated at $150 \pm 10^\circ$ for 1.3 hr. The reaction products included 1.83 g (35.8%; 20 CWA, 70° , 35 cc/min) of 1-chlorocycloheptene-2,7,7- d_2 and 0.97 g (19.4%; 20 CWA, 170° , 35 cc/min) of deuterated 1-phenylcycloheptene.

Both compounds were isolated utilizing preparative glpc. The nmr and infrared spectra of the recovered chloride were identical with those of the starting material. Proton nmr analysis of the deuterated 1-phenylcycloheptene indicated the presence of 0.17 ± 0.02 deuterons and 1.96 ± 0.12 deuterons in the olefinic and saturated ring positions, respectively.

trans-3-Chloro-2-pentene and Phenyllithium. *trans*-3-Chloro-2-pentene (5.0482 g, 0.04828 mole) and 125 ml of 1.24 M phenyllithium (0.124 mole) in ether were heated at $150 \pm 10^\circ$ for 1.3 hr. Approximately one-half (2.25 g, 44.8%) of the starting chloride was unreacted (10 CWA, 70° , 30 cc/min). Neither *trans*- nor *cis*-3-phenyl-2-pentene, *trans*- nor *cis*-2-phenyl-1-pentene, nor acetylenic elimination products (1- and 2-pentyne) were observed (10 CWA, 70° , 30 cc/min).

1-Chlorocyclopentene-2,5,5- d_2 and Phenyllithium. A solution consisting of 6.0738 g (0.05926 mole) of 1-chlorocyclopentene-2,5,5- d_2 and 220 ml of 0.94 M phenyllithium (0.206 mole) in ether was heated at $150 \pm 10^\circ$ for 1.3 hr. Analysis of the products by glpc (20 CWA, 70° , 225° , 35 cc/min) showed that 2.97 g (35.3%) of 1-chlorocyclopentene-2,5,5- d_2 and 2.47 g (21.2%) of substitution product were present. The chlorides were collected by glpc. Nmr analysis (biphenyl internal quantitative standard) indicated

that 0.01428 mole of each reactant survived reaction. From this result a kinetic isotope effect, k_H/k_D , of 3.36 ± 0.40 was calculated¹⁸ assuming simple competition. The nmr and infrared spectra of the substitution product were very similar to those for 1-phenylcyclopentene.

1-Chlorocyclohexene, 1-Chlorocyclohexene-2,6,6- d_2 , and Phenyllithium. A solution consisting of 6.0233 g (0.05162 mole) of 1-chlorocyclohexene, 2.0236 g (0.01691 mole) of 1-chlorocyclohexene-2,6,6- d_2 , and 180 ml of 1.00 M phenyllithium (0.180 mole) in ether was heated at $150 \pm 10^\circ$ for 1.3 hr. Analysis of the products by glpc (XEA, 90° , 160° , 35 cc/min) showed that 3.01 g (38.8%) of unreacted olefinic chlorides and 1.74 g (15.9%) of substitution product were present. The chlorides were collected by glpc. Nmr analysis (biphenyl internal quantitative standard) indicated that 0.01345 mole of 1-chlorocyclohexene and 0.01313 mole of 1-chlorocyclohexene-2,6,6- d_2 survived reaction. A k_H/k_D of 5.34 ± 0.40 was calculated¹⁸ from these data. The nmr and infrared spectra of the substitution product were very similar to those for 1-phenylcyclohexene.

1-Chlorocycloheptene, 1-Chlorocycloheptene-2,7,7- d_2 , and Phenyllithium. A solution consisting of 7.0284 g (0.05381 mole) of 1-chlorocycloheptene, 2.6302 g (0.01968 mole) of 1-chlorocycloheptene-2,7,7- d_2 , and 230 ml of 0.74 M phenyllithium (0.170 mole) in ether was heated at $150 \pm 10^\circ$ for 1.3 hr. Analysis of the products by glpc (20 CWA, 110° , 170° , 35 cc/min) showed that 3.26 g (29.5%) of unreacted olefinic chlorides and 2.73 g (21.4%) of substitution product were present. The chlorides were collected by glpc. Nmr analysis (biphenyl internal standard) indicated that 0.00701 mole of 1-chlorocycloheptene and 0.01468 mole of 1-chlorocycloheptene-2,7,7- d_2 survived reaction. A k_H/k_D of 7.16 ± 0.40 was calculated¹⁸ from these data. The nmr and infrared spectra of the substitution product were very similar to those for 1-phenylcycloheptene.

Possible Olefinic Products. A number of phenyl-substituted olefins were prepared from appropriate ketones by way of a two-step sequence. In the first, a tertiary phenylcarbinol was synthesized from the ketone (phenyllithium or phenylmagnesium bromide). The Grignard route was preferable owing to the fact that biphenyl, which was usually difficult to separate from the final product, invariably contaminated the phenyllithium preparations. When it was convenient, the phenylcarbinols were isolated and recrystallized. The second step consisted of formic acid dehydration.⁶

2-Methyl-1-phenylcyclopentene and 3-methyl-2-phenylcyclopentene¹⁰ were prepared from 2-methylcyclopentanone. The two olefins could not be conveniently separated by preparative glpc and were isolated as a mixture (XEP, 205° , 200 cc/min). The mixture possessed important infrared absorption bands at ~ 1650 , ~ 1621 , 1597, and 1571 cm^{-1} . The C=C stretching bands overlapped and were difficult to assign precisely. The nmr spectrum consisted of complex absorption from 7.6 to 7.0 (5.0 protons, assigned), complex absorption from 6.07 to 5.87 (0.29 proton), complex absorption from 2.9 to 1.5 (4.94 protons) which included a multiplet associated with the methyl groups of 2-methyl-1-phenylcyclopentene at 1.80, and a doublet (7 cps, 0.089 proton) at 1.07.

3-Methyl-1-phenylcyclopentene and 4-methyl-1-phenylcyclopentene were prepared from 3-methylcyclopentanone. The mixture of olefins (XEP, 205° , 200 cc/min) possessed important infrared absorption bands at 1623, 1597, and 1572 cm^{-1} . The nmr spectrum of the mixture consisted of complex absorption from 7.4 to 6.8 (5.0 protons, assigned), complex absorption from 5.95 to 5.78 (0.93 proton), complex absorption from 3.0 to 1.1 (4.9 protons), and a doublet (6.5 cps) at 1.05 (2.9 protons).

2-Methyl-1-phenylcyclohexene and 3-methyl-2-phenylcyclohexene¹¹ were prepared from 2-methylcyclohexanone and separated employing glpc (XEP, 205° , 200 ml/min).

3-Methyl-1-phenylcyclohexene and 4-methyl-2-phenylcyclohexene¹² were prepared from 3-methylcyclohexanone. The mixture of isomers possessed important infrared absorption bands at ~ 1645 , 1597, and 1645 cm^{-1} . The nmr spectrum of the isomers consisted of complex absorption at 7.6–6.9 (5.0 protons, assigned), complex absorption at 6.15–5.92 (1.00 proton), and complex absorption at 2.6–0.9 (10.2 protons), which included two overlapping doublets (5–7 cps) centered near 1.05.

1-Phenylcyclopentene, 1-phenylcyclohexene, 1-phenylcycloheptene, trans- and cis-3-phenyl-2-pentene, trans- and cis-2-phenyl-2-pentene, and 2-phenyl-1-pentene were also prepared in high purity from appropriate ketones.

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1-Chlorocyclohexene-2,6,6-*d*₂ and Phenyllithium. 1-Chlorocyclohexene-2,6,6-*d*₂ (4.5663 g, 0.03815 mole) and 100 ml of 1.00 *M* phenyllithium (0.100 mole) in ether were heated at $150 \pm 10^\circ$ for 1.3 hr. The reaction products included 2.13 g (46.6%; XEA, 90° , 35 cc/min) of 1-chlorocyclohexene-2,6,6-*d*₂ and 0.79 g (12.5%) of deuterated 1-phenylcyclohexene. Both compounds were isolated utilizing

preparative glpc. The nmr and infrared spectra of the recovered chloride were virtually identical with those of the starting material. Proton nmr analysis of the deuterated 1-phenylcyclohexene indicated the presence of 0.82 ± 0.09 deuterium and 1.93 ± 0.11 deuterons in the olefinic and saturated ring positions, respectively.

Proton Transfers in Dipolar Aprotic Solvents. III. Transfers from Triphenylmethane in Dimethyl Sulfoxide Solution^{1,2}

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Abstract: The reactions of triphenylmethane with *t*-butoxide, *n*-propoxide, and dimsyl ions in dimethyl sulfoxide solution have been studied. Triphenylmethane reacts with dimsyl ion and *n*-propoxide ion to form trityl anion with second-order rate constants of 8×10^3 and $6 \times 10^3 M^{-1} \text{sec}^{-1}$, respectively. The reaction of triphenylmethane with *t*-butoxide ion is too slow to measure under our reaction conditions, and an upper limit of $8 \times 10^2 M^{-1} \text{sec}^{-1}$ is set on the rate constant for this reaction. Equilibrium constants for the reactions of triphenylmethane with dimsyl ion, *t*-butoxide ion, and *n*-propoxide ion are 1.6×10^4 , 0.5, and 0.1, respectively.

As part of a continuing study of solvent effects on the rates of proton transfer reactions, we have measured the rates and equilibrium constants for the reactions of triphenylmethane with dimsylcesium, potassium *t*-butoxide, and potassium *n*-propoxide in dimethyl sulfoxide solution. Since the results obtained are pertinent to a number of recently reported studies of rates and equilibria of carbon acids,³ we wish to report these data now. Several corrections are made to a preliminary report of this work.⁴

Experimental Section

All materials were purified, stored, and handled under an atmosphere of purified argon.⁵

Materials. Dimethyl sulfoxide was purified by the method previously described,⁶ and was found to contain less than $5 \times 10^{-4} M$ acidic and basic impurities, and less than 20 ppm of water.

Dimsylcesium solutions of ca. 0.3 *M* were prepared from cesium amide as previously described.⁵ Less concentrated solutions were prepared by dilution. The ultraviolet spectrum of a $2.4 \times 10^{-3} M$ solution of cesium dimsyl in a 0.1-mm cell showed an absorption shoulder at 260 mμ ($\epsilon = 1.5 \times 10^3 M^{-1} \text{cm}^{-1}$), and no peaks or shoulders at longer wavelengths. The 60-Mc nmr spectrum of a 0.24 *M* solution showed a single sharp peak for the solvent and no other visible bands within 800 cps on either side of the solvent peak. Any band with an intensity of as much as 0.5% of that of the solvent would have been seen. The infrared spectrum of a 0.24 *M* solution of dimsylcesium *vs.* pure dimethyl sulfoxide showed a single band at $840\text{--}850 \text{ cm}^{-1}$ ($\epsilon \approx 1.2 \times 10^3 M^{-1} \text{cm}^{-1}$) which we believe to be due to the S—O stretch of the dimsyl ion.

Potassium *t*-butoxide (MSA Research Corp.) was twice sublimed under vacuum at ca. 100° prior to use.

Potassium *n*-propoxide was prepared by reaction of metallic potassium with dry deoxygenated *n*-propyl alcohol, followed by removal of excess *n*-propyl alcohol under vacuum. The resulting product was dried under vacuum at ca. 100° for 3 hr. Titration of a weighed sample of the alkoxide with aqueous standard acid indicated a purity of better than 99.5%.

Triphenylmethane was recrystallized from ethanol and dried under vacuum prior to use.

A sample of triphenylmethane-*d*₉ was kindly supplied by Professor P. T. Lansbury. Infrared analysis of the material showed greater than 90% isotopic purity.

Apparatus. Equilibrium measurements were carried out on a Cary Model 14 spectrophotometer fitted with the mixing cell apparatus diagrammed in Figure 1, and further described below.

Kinetic measurements were carried out on a small-scale stop-flow apparatus which we have previously described.⁶

Equilibrium Measurements. Solutions of triphenylmethane (the concentrations of triphenylmethane in the various measurements ranged from $5 \times 10^{-4} M$ to ca. $10^{-4} M$ in each determination) were added incrementally by means of a micrometer syringe, whose tip extended into the bulb of the apparatus shown in Figure 1, to 10.0 ml of the base solutions contained in the mixing cell. The solutions were mixed after each addition by simply tipping the cell back and forth several times. Care was taken that the solutions did not contact the rubber serum cap through which the syringe was inserted.

Plots of absorbance at 495 mμ, the wavelength of maximum absorption of the trityl anion, *vs.* concentration of triphenylmethane added gave straight lines whose slopes are the apparent extinction coefficients, ϵ' . Several experiments utilizing ca. $10^{-1} M$ solutions of dimsylcesium gave the true extinction coefficient of the trityl anion, ϵ , as $3.12 \times 10^4 M^{-1} \text{cm}^{-1}$. At lower concentrations of dimsyl anion, the observed apparent extinction coefficients can be used to calculate the ratio of trityl anion to triphenylmethane concentrations in the solution by eq 1.

$$(\text{Ar}_3\text{C}^-)/(\text{Ar}_3\text{CH}) = \epsilon'/(\epsilon - \epsilon') \quad (1)$$

This technique of measurement is necessary because of small amounts of impurities present which react with either the trityl anion or triphenylmethane. The fact that non-zero intercepts are obtained in the plots of absorbance *vs.* concentration show the presence of such impurities. One such plot is shown in Figure 2.

(6) C. D. Ritchie, G. A. Skinner, and V. G. Badding, *ibid.*, **89**, 2063 (1967).

(1) This work was supported by Grant No. GM 12832 from Public Health Service, National Institutes of Health.

(2) For previous papers in this series, see: C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 1730 (1967); **86**, 4488 (1964).

(3) See, for example: (a) G. A. Russell and A. G. Bemis, *ibid.*, **88**, 5491 (1966); (b) J. I. Brauman and D. F. McMillen, *ibid.*, in press; (c) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965.

(4) C. D. Ritchie and R. E. Uschold, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 1475.

(5) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 1721 (1967).

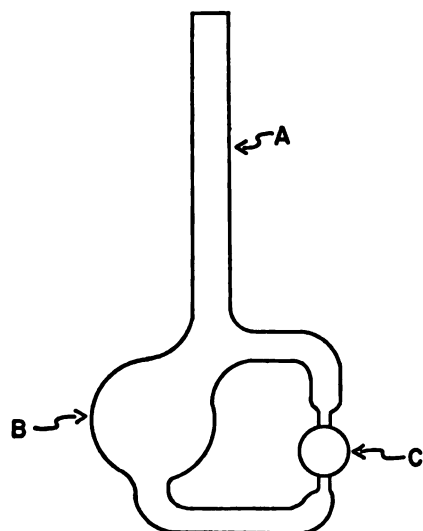


Fig. 1. Mixing cell used for triphenylmethane titrations: A, m.i.d. Pyrex tubing; B, bulb, ca. 12-ml capacity; C, cylindrical window cell, 1.0-cm path.

the equilibrium constant for the reaction of triphenylmethane with dimsyl ion has been obtained, then the equilibrium constant for the reactions of alcohols with dimsyl ion, and thus, with triphenylmethane, can be obtained. Analogous experiments to those described above in which triphenylmethane is added to solutions of the alkoxides are used to obtain the ratio of trityl ion to triphenylmethane concentrations at given alkoxide concentrations. These ratios and the equilibrium constant for the dimsyl-triphenylmethane reaction, the concentration of dimsyl ion at given concentrations of added alkoxide can be calculated, and from this, desired equilibrium constants are evaluated.

The values obtained for the various equilibrium constants are listed in Table I. The precision and accuracy of the data are listed below.

Table I. Equilibrium Constants at 25° for the Reactions
 $HA + CH_3SOCH_3^- \rightleftharpoons A^- + CH_3SOCH_3$

HA	Initial base concn $\times 10^3, M$	$K \times 10^{-4}$
Triphenylmethane	2.4	1.8
	1.2	1.3
	0.60	2.1
	6.0	1.4
	2.4	1.2
	1.2	1.5
	0.60	1.5
	6.5	2.7
	1.6	1.5
	Av	1.6 ± 0.4
<i>n</i> -Butyl alcohol	74.0	6.2
	1.8	5.6
	7.0	0.72
	4.2	1.2
	2.1	2.3
	1.1	1.0
	Av	3.0 ± 2.0
<i>n</i> -Propyl alcohol	5.1	7.7
	2.6	10.0
	1.2	29.0
	0.61	26.0
	5.2	5.9
	6.2	8.3
	4.3	8.3
	8.0	18.0
	Av	14.0 ± 7.0

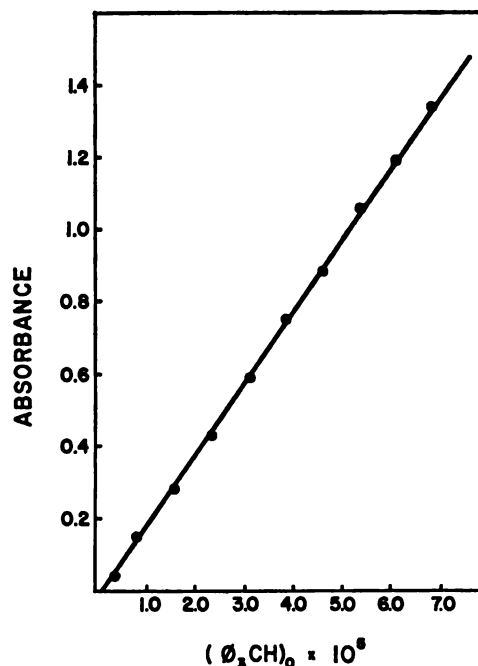


Figure 2. Absorbance at 495 m μ vs. concentration of triphenylmethane in $1.64 \times 10^{-3} M$ dimsylcesium in DMSO.

Kinetic Measurements. Solutions of known concentration of base and of triphenylmethane were prepared under an argon atmosphere and transferred to gas-tight syringes and then into the stop-flow apparatus. The reactions were followed by the appearance of the absorbance of the trityl anion at 495 m μ . Details of the general procedure used on the stop-flow apparatus have been given previously.⁶

In all runs, the concentration of base was much greater than the equilibrium concentration of trityl ion and the kinetics observed were those of pseudo-first-order reversible reactions. In the reactions with dimsyl ion, treatment of the data was straightforward using eq 2

$$\ln(C_a^\infty - C_a) = -k_p(C_0/C_a^\infty)t + \ln C_a^\infty \quad (2)$$

where C_a^∞ is the concentration of trityl ion at equilibrium, C_a is the concentration of trityl ion at time t , and C_0 is the initial concentration of triphenylmethane. The second-order rate constant for the reaction is equal to the pseudo-first-order constant, k_p , divided by the concentration of base. Some typical data for the reaction of dimsyl ion are shown in Table II.

Table II. Reaction of Triphenylmethane with Cesium Dimethyl at 25°

Concn of cesium dimethyl $\times 10^3, M$	Slope ^a	C_a^∞/C_0^b	$k_p \times 10^{-3}, M^{-1} \text{sec}^{-1}$
2.42	24.1	0.750	7.5
2.42	22.0	0.665	6.0
1.21	14.2	0.525	6.2
1.21	16.3	0.551	7.4
0.61	15.7	0.464	12.0
0.61	13.9	0.392	8.9
$k_R/k_D = 4.7 \pm 0.4$			8.0 ± 1.5

^a Slope of the plot of $\ln(C_a^\infty - C_a)$ vs. time (sec). ^b Ratio of trityl ion concentration at equilibrium to initial triphenylmethane concentration. In each run, the initial concentration of triphenylmethane was ca. $3 \times 10^{-3} M$.

The reaction of triphenylmethane with solutions of the alkoxides involves simultaneous reactions with dimsyl ion and alkoxide ion since appreciable amounts of dimsyl ion are formed by reaction of

the alkoxide with solvent. In each kinetic run, we have calculated the concentration of dimsyl ion present from the observed ratio of trityl ion to triphenylmethane concentrations at equilibrium in the reactions. Knowing the concentration of dimsyl ion and the rate constant for reaction of dimsyl ion, the observed first-order rate constants in alkoxide solutions can be corrected for the reaction of dimsyl ion and the second-order rate constants for reaction of the alkoxides calculated. This calculation involves the implicit assumption that the concentration of dimsyl ion does not change during the run. Since a dilution is involved in mixing the reactants in the stop flow, and since the ratio of concentration of dimsyl ion to that of alkoxide is concentration dependent, the assumption is that the alkoxide-solvent equilibrium is established much more rapidly than reaction with triphenylmethane. The constancy of the observed rate constants with varying initial concentration of base provides support for this assumption, as does the observed linearity of the kinetic plots. The data obtained for the reactions of the alkoxides are summarized in Table III.

Table III. Reactions of Triphenylmethane with Potassium Alkoxides at 25°

Initial base concn $\times 10^3$, M	R^a	Dimsyl concn ^b $\times 10^4$	C_a^∞/C_0	k_{exptl}^c , sec ⁻¹	k_{cor}^d , sec ⁻¹	$k_2^e \times 10^{-3}$ M ⁻¹ sec ⁻¹
Potassium <i>t</i> -butoxide						
4.2	1.86	17.4	0.650	13.1	-0.8	0.0
2.1	0.91	8.5	0.477	6.65	0.15	0.0
1.1	0.77	7.2	0.436	5.85	0.10	0.0
Potassium <i>n</i> -propoxide						
5.1	0.93	8.8	0.442	28.4	21.4	5.1
2.6	0.57	5.4	0.364	17.9	13.6	6.5
1.2	0.24	2.2	0.192	7.58	5.81	5.8
0.61	0.17	1.6	0.148	4.27	2.98	6.1
Av 5.9 ± 0.4						

^a Ratio of trityl ion to triphenylmethane concentration at equilibrium. The initial concentrations of triphenylmethane were from 2.5×10^{-3} M. ^b Concentration of dimsyl ion, calculated from R . ^c Pseudo-first-order rate constant defined by eq 2. ^d Pseudo-first-order rate constant for reaction with alkoxide ion. ^e Second-order rate constant for reaction with alkoxide ion.

The reaction of triphenylmethane-*d*₁ with dimsyl ion was also studied. This reaction involves formation of trityl ion simultaneous with hydrogen-deuterium exchange, and the rate expression cannot easily be put into the form of a plot. The integrated rate expression is given by eq 3

$$C_a^\infty - C_a = C_0 \{ (k_1 - k_1') / [k_1(C_0/C_a^\infty) - k_1'] \} e^{-k_1 t} + \{ k_1(C_0 - C_a^\infty) / [k_1(C_0/C_a^\infty) - k_1'] \} e^{-k_1'(C_0/C_a^\infty)t} \quad (3)$$

where k_1 is the pseudo-first-order rate constant for reaction with triphenylmethane, k_1' is the analogous constant for reaction of triphenylmethane-*d*₁, and the other symbols are defined as in eq 2.

Rate constants were calculated by means of the method of steepest descents using a program written in Fortran IV language for this particular problem. A single kinetic run gave values for both k_1 and k_1' independent of the value previously obtained for the rate constant for the undeuterated compound. An average value of $k_H/k_D = 4.7$ was obtained at 25°. Rate constants for the reaction of the hydrogen compound calculated from these data were in good agreement with the independently determined value.

Sources of Error and Accuracy of Data. The very basic carbanion solutions dealt with in the present work are extremely sensitive to small amounts of impurities. It is known that oxygen reacts with triphenylmethane anion to produce hydroperoxide anions^{2a} very rapidly. In addition, any compound which could act as even a weak acid ($pK < 30$) would react with dimsyl ion to make our solutions less basic than we expect on the basis of titrations for dimsyl ion.

The fact that the plots obtained from the titrations of the base solutions with triphenylmethane, as typically shown in Figure 2, have intercepts at $ca. 10^{-4}$ M indicates that we do not have appre-

ciable amounts of oxygen in the solutions used there. Since equilibrium constants calculated from the equilibrium concentrations in the kinetic runs agree with those determined by the titration technique fairly well, we may assume that appreciable amounts of oxygen were not present in these runs. Titrations of the solvent for acidic impurities⁶ would have shown the presence of any acid with a pK up to $ca. 25$. Standardization of the dimsyl solutions by titration of formanilide in dimethyl sulfoxide and by titration with standard acid in water ensures that no acidic species with pK less than $ca. 21$ is present.

Sulfides, sulfones, and water probably all have pK 's greater than 20 and less than that of dimethyl sulfoxide, and could reasonably go undetected and yet cause serious errors in the measurements reported here. Although water would have been detected at concentrations greater than $ca. 10^{-3}$ M (18 ppm), there could be enough present to cause some difficulty. We have observed, however, that the addition of a drop of water to a 5×10^{-4} M solution of dimsylcesium causes a marked cloudiness of the solution. It therefore appears that cesium hydroxide is probably too insoluble to cause difficulty in base solutions of greater than $ca. 10^{-3}$ M. We believe that the most likely source of error is the presence of traces of dimethyl sulfone. It would be interesting to know the pK of this compound.

Steiner⁷ has reported a value for the equilibrium constant of the reaction of triphenylmethane with dimsyl ion as 3×10^4 . In view of the difficulties mentioned above, we are satisfied with the agreement within a factor of 2 of our value with this one.

If Steiner's value for the equilibrium constant of the reaction of triphenylmethane with dimsyl ion is used in place of the value reported in this paper, the equilibrium constants for the reactions with the alcohols and dimsyl ion would be increased by a factor of 2, as would the rate constant for the reaction of dimsyl ion with triphenylmethane. These errors, however, would have little effect on the reported values for the rate and equilibrium constants for the reactions of the alkoxides with triphenylmethane.

In any case, the fair agreement of our values for the equilibrium constants with those reported by Steiner indicates that the values reported in the present paper are accurate to within a factor of ~ 2 . Considering the difficulties of the measurements, and for the present purposes, we are content with this accuracy.

Discussion

In a preliminary report of this work,⁴ we overlooked the possibility of the reactions of the alkoxides with solvent to form appreciable amounts of dimsyl ion in solution.⁸ The rate and equilibrium constants reported there are, therefore, completely in error. The two most serious errors are in the reported values for the reverse rate constants of the reactions of the alkoxides and in the value for the rate of reaction of *t*-butoxide.

The fact that *t*-butoxide contributes virtually nothing to the rate of formation of trityl ion in solutions of potassium *t*-butoxide is quite surprising and raises the question of the identity of the active base in other studies of proton abstraction in solutions of *t*-butoxide.¹ Since *n*-propoxide reacts with triphenylmethane quite rapidly, even though it is a weaker base than *t*-butoxide, it appears that the slowness of reaction of *t*-butoxide must be due to a steric effect. Examination of molecular models shows that this is a reasonable postulate, and, in fact, Streitwieser has suggested that a steric effect may be responsible for the slowness of reaction of methoxide ion with triphenylmethane in methanol solution.⁹ It seems possible, also, that the reactions of both *n*-propoxide and dimsyl ion with triphenylmethane are subject to a steric effect if Streitwieser's suggestion is correct.

(7) E. C. Steiner, preprint of paper to be presented in Petroleum Chemistry Section, 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967.

(8) This possibility was pointed out to us by Dr. E. C. Steiner. We would like to express our appreciation to him for this suggestion, and for many later discussions and suggestions.

(9) A. Streitwieser, Jr., *Progr. Phys. Org. Chem.*, **3**, 58 (1965).

Data have been reported^{9,10} which allow the calculation of a second-order rate constant of *ca.* $10^{-9} M^{-1} \text{sec}^{-1}$ for the reaction of triphenylmethane with methoxide ion in methanol at 45°. We can, therefore, estimate that *n*-propoxide in dimethyl sulfoxide reacts at least 10^{14} times faster than does methoxide in methanol with triphenylmethane. This tremendous rate enhancement must be attributed to a solvent effect if we reasonably assume that methoxide and *n*-propoxide would react at the same rate in a given solvent. (Unfortunately, the solubility of potassium methoxide in pure dimethyl sulfoxide is too low to allow easy measurement of its reactions.) With the analogous assumption that the basicity of methoxide and *n*-propoxide would be nearly the same in a given solvent,¹¹ we can estimate that the change of solvent from methanol to dimethyl sulfoxide increases the basicity of *n*-propoxide by a factor of not more than 10^{11} . If one uses Steiner's recently reported⁷ value of 26.9 for the *pK* of methanol in DMSO with the value of 18.3 for the *pK*

of methanol in methanol,⁸ the increase in basicity of methoxide is only 8.6. We therefore conclude that factors other than solvation of the alkoxide^{3c} contribute to the enhanced rates of proton abstraction on going from hydroxylic to nonhydroxylic solvents.

A reasonable explanation of the origin of this extra rate-enhancing factor is the postulate of the necessity of solvent reorganization which we have recently used to explain the enhanced rates of reactions of nucleophiles with carbonium ions in nonhydroxylic solvents.⁶ In a hydroxylic solvent, the base must be hydrogen bonded to solvent molecules. At the transition state, this solvation is lost and compensation by solvent-solvent hydrogen bonding has not fully occurred. Thus, the rate of reaction is slowed in both directions. In the reverse direction, solvent molecules which are in the initial state hydrogen bonded to other solvent molecules must break away and start to reorganize to solvate the products.

As we have pointed out previously,⁶ this idea is a simple extension of the concepts suggested by earlier workers.¹²

(12) E. A. Moelwyn-Hughes, *Proc. Roy. Soc. (London)*, **A164**, 295 (1938); **A212**, 260 (1952); E. F. Caldin, *J. Chem. Soc.*, 3345 (1959); K. T. Leffek, R. E. Robertson, and S. Sugamori, *J. Am. Chem. Soc.*, **87**, 2097 (1965); and other references cited in these works.

(10) A. Strietweiser, Jr., J. I. Brauman, J. H. Hammons, and A. H. Pudjaatmaka, *J. Am. Chem. Soc.*, **87**, 384 (1965).

(11) There is a great deal of evidence that the basicities of the simple alcohols are not far different from one another in any single solvent; see: R. P. Bell, "The Proton in Chemistry," Cornell University Press, Inc., Ithaca, N. Y., 1959, p 45.

Proton Exchange of Triethylammonium Ion in Aqueous Solution¹

E. K. Ralph, III, and Ernest Grunwald

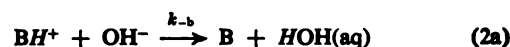
Contribution from the Lecks Chemical Laboratories, Brandeis University, Waltham, Massachusetts 02154. Received January 13, 1967

Abstract: Rates of exchange of NH protons of triethylammonium ion (BH^+) with H_2O and D_2O have been measured by nuclear magnetic resonance techniques in acid solutions over a range of pH. The following reactions and rate constants (corrected to infinite dilution) were found: $\text{BH}^+ + \text{OH}^-$, $k_{-b} = (1.7 \pm 0.5) \times 10^{10} \text{ sec}^{-1} M^{-1}$ at 30°; $\text{BH}^+ + \text{OH}_2 + \text{B}$ (symmetrical exchange), $k_1 = (1.82 \pm 0.08) \times 10^8 \text{ sec}^{-1} M^{-1}$ at 30°; $\text{B} + \text{H}_3\text{O}^+$, $k_{-a} = 2 \times 10^{10} \text{ sec}^{-1} M^{-1}$ at 25°; $\text{B} \cdot \text{HOD} + \text{D}_2\text{O} \rightarrow \text{B} \cdot \text{DOD} + \text{HOD}$, $k_H^* = (3.1 \pm 0.5) \times 10^8 \text{ sec}^{-1}$. Of these rate constants, only k_1 is considerably smaller than expected from data for methylamines, probably due to steric hindrance. Acid dissociation constants are reported for BH^+ as a function of BHCl concentration; $\text{p}K_A^\circ = 10.81$ at 25°. H_2O - D_2O solvent isotope effects on K_A are discussed.

We wish to report nuclear magnetic resonance (nmr) measurements of the rate of proton exchange between triethylammonium ion and water in light and heavy water. The substrates, triethylammonium ion and triethylamine (which are in equilibrium at the given pH), are of interest because the site at which N-H proton transfer takes place in these molecules is under steric compression.² Both chemical evidence and space-filling molecular models suggest that the volume that would normally be assigned to the hydrogen atom or the unshared electron pair on nitrogen is invaded by part of an ethyl group.²

We find that the following proton transfer reactions of triethylammonium ion (BH^+) are kinetically significant in the pH range 5–8: (i) symmetrical proton

exchange (eq 1), and (ii) reaction with hydroxide ion (2a) followed rapidly by 2b).



At pH < 1, acid dissociation produces an amine hydrate (eq 3), which subsequently exchanges its water molecule (eq 4).



(1) Work supported by the National Science Foundation under Grant GP 3921.

(2) H. C. Brown and S. Sujishi, *J. Am. Chem. Soc.*, **70**, 2878 (1948).

On comparing the new data with previously reported rate constants for similar reactions of ammonia and the

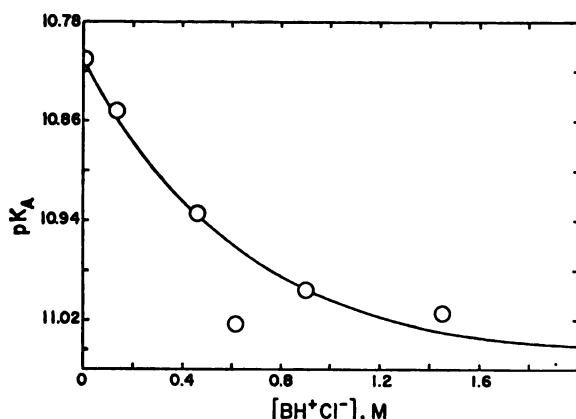


Figure 1. pK_A for triethylammonium ion as a function of triethylammonium chloride concentration, water, 25°.

methylamines,^{3a} we find that k_2 is only one-fifth the value that we would have predicted if there were no steric hindrance, while k_{-b} , k_a , and k_{-a} are "normal." k_H also appears to be "normal"; it is smaller than the values reported for the methylamines and smoothly continues the trend for k_H to decrease with increasing number and size of alkyl substituents on nitrogen.³

Results

In the pH range 5–8, the rate of proton exchange between triethylammonium ion and water was measured by nmr line-broadening techniques, using water of normal isotopic composition. In the pH range <1, the rate was too slow for those techniques and isotopic exchange between BH^+ and D_2O –DCl was measured instead. Since both measurements extended up to moderately high BH^+ concentrations, we also report K_A for BH^+ as a function of concentration.

K_A Measurements. Acid dissociation constants were measured by a differential potentiometric method,⁴ using triethylammonium chloride as the substrate. K_A is defined in eq 5, where the terms in brackets denote molar concentrations. Results are shown in Figure 1.

$$K_A = [B][H^+]/[BH^+] \quad (5)$$

Extrapolation to infinite dilution yields the thermodynamic constant, $pK_A^\circ = 10.81$ at 25°, which may be compared with previously reported pK_A° values of 10.75,⁵ 10.87,⁶ and 10.67⁷ at 25°. K_A values at 30° (needed in the kinetic analysis) were obtained from the data in Figure 1 and a previously reported⁶ value of 12.24 kcal for ΔH_A° .

Proton Exchange, pH 5–8. In the measurements reported in this section, the temperature was 30°, the solvent was H_2O , the solute was 0.05–0.2 M triethylammonium chloride, and the pH was adjusted by adding NaOH and measured with a pH meter. Under these conditions, the rate law for NH–OH proton exchange

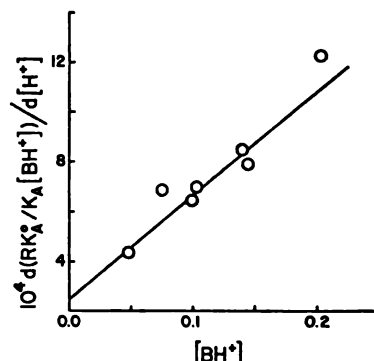


Figure 2. Plot of kinetic data for NH–OH proton exchange according to eq 8: triethylammonium ion in H_2O at 30°.

throughout the pH range 5–8 was found to be given by eq 6, where R denotes the rate of exchange (in moles/l.

$$R = k_{-b}[BH^+][OH^-] + k_2[BH^+][B] \quad (6)$$

sec). To allow for kinetic salt effects in the calculation of the rate constants, it is convenient to introduce eq 7 in which k° (or K°) denotes the respective rate (or equilibrium) constant at infinite dilution, and y denotes the molar activity coefficient with respect to the infinitely dilute reference state. In (7a) and (7b), the

$$k_{-b} = k_{-b}^\circ y_{BH^+} y_{OH^-} / y_{\pm}^2 \approx k_{-b}^\circ y_{BH^+} y_{OH^-} \quad (7a)$$

$$k_{-b}^\circ y_{BH^+} y_{OH^-} / y_{\pm}^2 \approx k_{-b}^\circ \quad (7b)$$

$$k_2 = k_2^\circ y_{BH^+} y_B a_{H_2O} / y_{\pm}^2 \approx k_2^\circ \quad (7c)$$

$$[OH^-] = K_w^\circ / [H^+] y_{H^+} y_{OH^-} \quad (7d)$$

$$K_A = K_A^\circ y_{BH^+} / y_B y_{H^+} \quad (7e)$$

equal sign introduces formal expressions based on Brønsted's rate equation⁸; the approximate expressions that follow try to evaluate y_{\pm}^2 for the transition-state complex in terms of measurable activity coefficients for stable model substances. In (7c), K_w° is the autoprotolysis constant of water. On substituting eq 5 and 7 in (6) and rearranging, we obtain (8).

$$\frac{R}{[BH^+]} \frac{K_A^\circ}{K_A} = \frac{k_{-b}^\circ K_w^\circ + k_2^\circ K_A^\circ [BH^+]}{[H^+]} \quad (8)$$

Equation 8 was applied as follows: (a) $[H^+]$ was computed from pH and y_{H^+} ; y_{H^+} was taken to be the same as y_{\pm} for 0.01 M HCl in a KCl solution⁹ of the same ionic strength as the reaction mixture. (b) Plots were made of $RK_A^\circ/K_A[BH^+]$ vs. $[H^+]^{-1}$ at constant $[BH^+]$. (c) The slopes obtained in (b) were plotted vs. $[BH^+]$.

The result is shown in Figure 2, where the straight line is based on a weighted least-squares analysis of the data. According to (8) we identify the intercept as $k_{-b}^\circ K_w^\circ$, and the slope as $k_2^\circ K_A^\circ$. On introducing known values for K_w° and K_A° , we finally obtain $k_{-b}^\circ = (1.7 \pm 0.5) \times 10^{10} \text{ sec}^{-1} M^{-1}$ at 30° and $k_2^\circ = (1.82 \pm 0.08) \times 10^8 \text{ sec}^{-1} M^{-1}$ at 30°.

Proton–Deuteron Exchange, pH <1. In the measurements reported in this section, the temperature was 25°, the solvent was D_2O –DCl, and the solute was 0.5–

(3) (a) For a recent review, see E. Grunwald and M. Cocivera, *Discussions Faraday Soc.*, 39, 105 (1965). (b) Further analysis of k_H will be presented in a forthcoming paper: E. Grunwald and E. K. Ralph, III, *J. Am. Chem. Soc.*, in press.

(4) A. L. Bacarella, E. Grunwald, H. P. Marshall, and E. L. Purlee, *J. Org. Chem.*, 20, 747 (1955).

(5) W. C. Somerville, *J. Phys. Chem.*, 35, 2412 (1931).

(6) J. E. Ablard, D. S. McKinney, and J. C. Warner, *J. Am. Chem. Soc.*, 62, 2181 (1940).

(7) W. S. Fyfe, *J. Chem. Soc.*, 1347 (1955).

(8) J. M. Brønsted, *Z. Physik. Chem.*, 102, 169 (1922).

(9) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943, p 575.

1.8 *M* triethylammonium chloride. Exchange was followed by measuring the height, *h*, of the HOD proton nmr line as a function of time under conditions where *h* is proportional to [HOD]. Experimental plots of $\log(h - h_i)$ vs. time were linear, within the experimental error, with slope k_e . Since the deuterium isotope was present in large excess, the conversion of BH^+ to BD^+ at equilibrium was virtually complete and the rate of the back-reaction, $\text{BD}^+ \rightarrow \text{BH}^+$, could be neglected. Thus k_e is the pseudo-first-order rate constant for the forward reaction, $\text{BH}^+ \rightarrow \text{BD}^+$, as in (9), where R^* is the rate of proton-deuteron exchange (in moles/l. sec).

$$k_e = R^*/[\text{BH}^+] \quad (9)$$

Experimental results are summarized in Table I. The high acidity of the reaction mixtures reduces the rate of reactions 1 and 2 to less than 5% of R^* , so that

Table I. Data for Protium-Deuterium Exchange of Triethylammonium Chloride in D_2O -DCl at 25°

[Et ₃ NHCl]	[DCl]	$10^3 \times k_e$	η^*/η^{*0}	K_A^*/K_A^{*0}
1.27	0.349	10.3 ± 1.2	1.21	0.476
1.48	0.463	5.98 ± 0.12	1.28	0.436
1.05	0.431	11.3 ± 1.1	1.16	0.464
0.917	0.437	11.5 ± 0.06	1.13	0.470
0.506	0.466	10.9 ± 1.1	1.07	0.520
1.64	0.546	5.76 ± 0.23	1.33	0.397
1.80	0.798	3.30 ± 0.06	1.42	0.328
1.56	0.807	4.54 ± 0.90	1.32	0.330
1.85	0.965	2.90 ± 0.20	1.45	0.290
1.45	1.35	1.33 ± 0.07	1.33	0.223
1.84	1.37	1.78 ± 0.23	1.43	0.215

* The viscosity of the Et₃NHCl-DCl solution in D_2O relative to that of pure D_2O . * Computed as described in text; see eq 13.

these reactions can be neglected. The dominant mechanism for exchange consists of reactions 3 and 4, and the rate law is given accordingly by (10), where starred symbols are used to denote that the N-H compound is in D_2O . As it turned out that $k_{\text{H}}^*/k_{-\text{a}}^*[\text{D}^+] < 0.5$ in all experiments, it was convenient to rewrite (10) in the form (11), where $K_A^* = k_{\text{a}}^*/k_{-\text{a}}^*$. According

$$k_e = k_{\text{a}}^*k_{\text{H}}^*/(k_{-\text{a}}^*[\text{D}^+] + k_{\text{H}}^*) \quad (10)$$

to (11), at high acidities k_e varies as $[\text{D}^+]^{-1}$, with slope equal to $K_A^*k_{\text{H}}^*$; at lower acidities there is negative curvature, which affords the value of $k_{\text{H}}^*/k_{-\text{a}}^*$. However, as is well known, there are substantial deviations from dilute-solution behavior at acid and substrate concentrations of the magnitude we are using (see Table I). We allowed for these deviations as follows:

(a) $k_{\text{H}}^*/k_{-\text{a}}^*$ is regarded as independent of concentration. This assumption is not crucial since $k_{\text{H}}^*/k_{-\text{a}}^*[\text{D}^+] < 0.5$, and it is consistent with previous measurements on trimethylammonium ion in aqueous HCl.¹⁰ (b) The

$$k_{\text{H}}^* = k_{\text{H}}^{*0}\eta^*/\eta^* \quad (12)$$

medium effect on k_{H}^* is given by (12), where η^* is the bulk viscosity of the solution and the superscript zero denotes the value of the property at zero solute concentration, as before. Equation 12 has been verified

(10) E. Grunwald, *J. Phys. Chem.*, **67**, 2211 (1963).

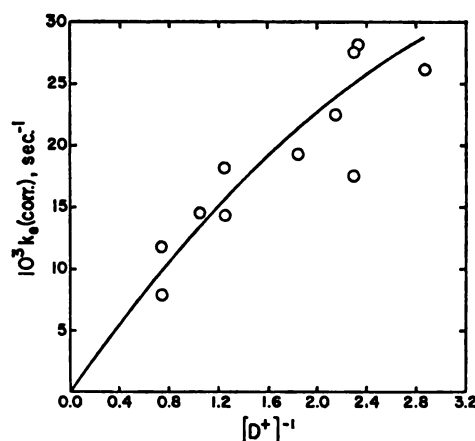


Figure 3. Plot of kinetic data for NH-OD proton exchange according to eq 14 and 15: $(\text{C}_2\text{H}_5)_3\text{NH}^+$ in D_2O -DCl at 25°.

for other amines in H_2O .¹¹ (c) The medium effect on K_A^* was obtained from (13). This equation assumes that medium effects due to BHCl and HCl are additive

$$\log(K_A^*/K_A^{*0}) = \log(K_A/K_A^0)_{[\text{BHCl}]} + \log(K_A/K_A^0)_{[\text{HCl}]} \quad (13)$$

and evaluates the additive terms in H_2O rather than D_2O . The first term is shown as a function of [BHCl] in Figure 1. The second term was evaluated as

$$\log(K_A/K_A^0)_{[\text{HCl}]} = -0.32[\text{HCl}]$$

on the basis of Arnett and Mach's H_0''' acidity function.¹² For anilines it has been shown that medium effects on K_A due to HCl in H_2O and DCl in D_2O are closely similar.¹³

Let us define a parameter $k_e(\text{cor})$ according to (14).

$$k_e(\text{cor}) = k_e K_A^{*0} \eta^*/K_A^* \eta^{*0} \quad (14)$$

It then follows from (a) to (c) above that (11) can be recast in the form

$$k_e(\text{cor}) = K_A^{*0} k_{\text{H}}^{*0} / [\text{D}^+] (1 + k_{\text{H}}^*/k_{-\text{a}}^*[\text{D}^+]) \quad (15)$$

The plot of $k_e(\text{cor})$ vs. $[\text{D}^+]^{-1}$ based on the experimental data is shown in Figure 3. $K_A^{*0} k_{\text{H}}^{*0}$ is evaluated from the limiting slope at high acidity as $(1.45 \pm 0.2) \times 10^{-2}$; $k_{\text{H}}^*/k_{-\text{a}}^*$ is evaluated from the curvature as 0.14 ± 0.07 . The precision measures include our estimate of determinate errors resulting from the treatment of medium effects. During the course of this work we tried various schemes for making the corrections, including making no correction at all. The initial slope, $K_A^{*0} k_{\text{H}}^{*0}$, was always between 0.012 and 0.018. The curvature, and therefore $k_{\text{H}}^*/k_{-\text{a}}^*$, was far less well defined and in one scheme even appeared to be zero.

Evaluation of K_A^{*0} and the Rate Constants According to the theory represented above K_A^{*0} is the "equilibrium constant" for reaction 16 in dilute solution.



We now wish to evaluate K_A^{*0} from K_A^0 (eq 17) and established theories of the H_2O - D_2O solvent isotope

(11) M. T. Emerson, E. Grunwald, M. L. Kaplan, and R. A. Kromhout, *J. Am. Chem. Soc.*, **82**, 6307 (1960).

(12) E. M. Arnett and G. W. Mach, *ibid.*, **86**, 2671 (1964).

(13) E. Högfeldt and J. Bigeleisen, *ibid.*, **82**, 15 (1960).

effect.¹⁴⁻¹⁷ To solve the relevant ratio (18), we intro-



duce the parameter L , defined in (19), which has been evaluated¹⁸ as 11.0 at 25°. The result is (20), with Φ

$$\frac{K_A^{*0}}{K_A^0} = \frac{[\text{B}\cdot\text{HOD}][\text{D}_2\text{O}^+][\text{H}_2\text{O}][\text{BH}^+\cdot\text{OH}_2]}{[\text{B}\cdot\text{HOH}][\text{H}_3\text{O}^+][\text{D}_2\text{O}][\text{BH}^+\cdot\text{OD}_2]} \quad (18)$$

$$L = [\text{H}_3\text{O}^+][\text{D}_2\text{O}]/[\text{D}_2\text{O}^+][\text{H}_2\text{O}]^2 \quad (19)$$

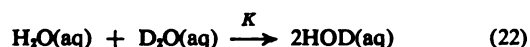
defined in (21). Note that Φ is a fractionation factor

$$K_A^{*0}/K_A^0 = L^{-1/2}\Phi \quad (20)$$

$$\Phi = \frac{[\text{B}\cdot\text{HOD}][\text{D}_2\text{O}]^{1/2}[\text{BH}^+\cdot\text{OH}_2]}{[\text{B}\cdot\text{HOH}][\text{H}_2\text{O}]^{1/2}[\text{BH}^+\cdot\text{OD}_2]} \quad (21)$$

for specific water isotopes in different microscopic environments: adjacent to B, adjacent to BH^+ , or in bulk solvent. We now wish to show that Φ is approximately unity.

Within the framework of the quoted theories,¹⁴⁻¹⁷ we may assume that hydrogen isotope fractionation factors are independent of the macroscopic solvent medium and, therefore, of the microscopic environment. Moreover, for water isotopes the distribution at isotopic equilibrium is essentially statistical.¹⁸ Thus, when each molecule exists in an aqueous environment, K for reaction 22 has the statistical value of 4.



On the same basis, when each molecule is adjacent to B, K' for the analogous reaction 23 has the statistical value of unity. Moreover, $[\text{B}\cdot\text{HOD}] = [\text{B}\cdot\text{DOH}]$



and, in view of $K' = 1$, both are equal to $[\text{B}\cdot\text{HOH}]^{1/2}[\text{B}\cdot\text{DOD}]^{1/2}$. Thus we may rewrite (21) in the form

$$\Phi = \frac{[\text{B}\cdot\text{DOD}]^{1/2}[\text{D}_2\text{O}]^{1/2}[\text{BH}^+\cdot\text{OH}_2]}{[\text{B}\cdot\text{HOH}]^{1/2}[\text{H}_2\text{O}]^{1/2}[\text{BH}^+\cdot\text{OD}_2]} \quad (24)$$

Each of the three factors in (24) is a fractionation factor involving H_2O and D_2O in a different microscopic environment. Thus, if fractionation factors are indeed independent of the environment (as suggested by the success of the theory¹⁴⁻¹⁷), $\Phi = 1$.

Applying eq 20, we then find that $K_A^{*0} = K_A^0 L^{-1/2} = 4.7 \times 10^{-12}$. Using this value and results given in the previous section, we obtain $k_{\text{H}}^{*0} = (3.1 \pm 0.5) \times 10^9 \text{ sec}^{-1}$ at 25° in D_2O and $k_{-a}^{*0} = 2 \times 10^{10} \text{ sec}^{-1} M^{-1}$ at 25° in D_2O . Both rate constants are of a magnitude appropriate to diffusion-controlled processes in an aqueous medium and should vary approximately inversely with the viscosity, as assumed above (eq 12). Thus, to obtain k_{H}^0 and k_{-a}^0 in H_2O , we multiply the above values by the relative viscosity $\eta_{\text{D}_2\text{O}}/\eta_{\text{H}_2\text{O}}$ or 1.23 at 25°.

(14) W. E. Nelson and J. A. V. Butler, *J. Chem. Soc.*, 1361 (1936).

(15) E. L. Purlee, *J. Am. Chem. Soc.*, 81, 263 (1959).

(16) C. G. Swain and R. F. W. Bader, *Tetrahedron*, 10, 182 (1960); C. G. Swain, R. F. W. Bader, and E. R. Thornton, *ibid.*, 10, 200 (1960). We are indebted to Dr. C. G. Swain for a helpful discussion of this problem.

(17) P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Phys. Chem.*, 68, 410 (1964).

Discussion

Kinetic and thermodynamic constants for proton transfer of ammonia, the methylamines, and triethylamine are compared in Table II. For ammonia and the methylamines, k_{-b}^0 and k_{-a}^0 are of the correct magnitude for diffusion-controlled reactions.^{18,19} The new values of k_{-b}^0 and k_{-a}^0 for triethylamine fit smoothly into this pattern. The fact that they are slightly smaller than those for the substrates of lower molecular weight is plausible in view of the lowering of molecular mobility and "steric factor" for reaction²⁰ that accompanies the increase in alkyl size. Clearly, whatever steric hindrance exists in triethylamine or its conjugate ion is insufficient to alter the diffusion-controlled mechanism of the respective reactions with hydrogen ion or hydroxide ion.

It is probable that the reaction measured by k_2 involves one water molecule, as stated in eq 1.^{2,21} For ammonia and the methylamines, the rate constant k_2 varies monotonically with base strength as measured by K_B , as shown in Table II.^{21b} From this monotonic

Table II. Data for Proton Transfer of Ammonia, Alkylamines, and Their Conjugate Acids in Water

Amine (B in eq 1-5)	$10^4 K_B^{*0}$ (25°)	$10^{-10} k_{-b}^{*0}$ (20 or 30°)	$10^{-10} k_{-a}^{*0}$ (25°)	$10^{-8} k_2^{*0}$ (25 or 30°)
NH_3	0.18	3.4 ^d	4.3 ^e	0.9 ^e
CH_3NH_2	4.1	3.7 ^d	...	5.3 ^e
$(\text{CH}_3)_2\text{NH}$	6.0	3.1 ^d	...	9.0 ^e
$(\text{CH}_3)_3\text{N}$	0.64	2.1 ^d	3.0 ^e	3.4 ^e
$(\text{Et})_3\text{N}$	6.5 ^f	1.7 ^e	2.7 ^{e,f}	1.8 ^e

^a $K_B = [\text{BH}^+][\text{OH}^-]/[\text{B}]$; data based on Table I, ref 3. ^b Units: $\text{sec}^{-1} M^{-1}$. ^c Assume that $k_{\text{H}}^{*0}/k_{\text{H}}^0 = k_{-a}^{*0}/k_{-a}^0 = \eta_{\text{H}_2\text{O}}^2/\eta_{\text{D}_2\text{O}}^2 = 1.23$. ^d Data at 20°; see ref 18. ^e Data at 25° based on Table I, ref 3. ^f Present work, 25°. ^g Present work, 30°.

relationship we would expect that a base of the strength of triethylamine reacts with $k_2 \approx 9 \times 10^8 \text{ sec}^{-1} M^{-1}$ at 25°. Since the actual value of k_2 for triethylamine is only $1.8 \times 10^8 \text{ sec}^{-1} M^{-1}$ at 25°, there seems to be a (possibly steric) retardation of k_2 by a factor of one-fifth. As a matter of fact, when models of the transition-state complex $\text{Et}_3\text{N}\cdot\text{H}_2\text{O}\cdot\text{HNET}_3^+$ are constructed from space-filling atomic models, it is apparent that there is significant steric hindrance, both in formation and solvation of the transition-state complex.

Experimental Section

Materials. Deuterium chloride was prepared by the addition of dichlorodimethylsilane (Aldrich) to 99.5 mole % D_2O^{22} (Matheson Coleman and Bell). H_2O was distilled from KOH in all-glass ap-

(18) M. Eigen, W. Kruse, G. Maass, and L. De Maeyer, "Progress in Reaction Kinetics," Vol. 2, G. Porter, Ed., Pergamon Press, Inc., New York, N. Y., 1964, p 308.

(19) M. T. Emerson, E. Grunwald, and R. A. Kromhout, *J. Chem. Phys.*, 33, 547 (1960); E. Grunwald, *J. Phys. Chem.*, 67, 2208 (1963).

(20) M. Eigen and K. Kustin, *J. Am. Chem. Soc.*, 82, 5952 (1960).

(21) (a) Z. Luz and S. Meiboom, *J. Chem. Phys.*, 39, 366 (1963). (b) If OH bond breaking is more important in the transition state than B-H bond breaking ($\text{BH}^+\cdot(\text{OH}^-)\cdot\text{HB}^+$ makes an important contribution) we expect k_2 to increase with basicity, as found. It should be noted also that the data in Table II have not been corrected for statistical factors (for example, $g = 4$ for the unsolvated ammonium ion). The relationship of k_2/g vs. $K_B g$ is not monotonic. However, there is some question whether the statistical factor for the solvated ion is the same as g for the unsolvated ion.

(22) W. H. Greive and K. F. Sporek, *J. Chem. Educ.*, 43, 381 (1966).

paratus. Triethylammonium chloride (Eastman) was recrystallized three times from absolute ethanol.

pH Measurements. A Beckman research pH meter was used. The pH of the reaction mixtures was measured in a small glass reservoir fused directly to the top of the nmr sample tube. A glass-Ag|AgCl combination electrode (Beckman Model 39030) was used in all measurements.

Proton Exchange in H_2O . The rate of NH-OH proton exchange between triethylammonium ion and water was determined from nmr measurements of exchange broadening of the dominant water line. The exchange broadening was taken as $T_2^{-1} - T_1^{-1}$. T_2 and T_1 were measured by spin-echo techniques and rates were calculated as described previously.²² The chemical shift between NH and OH protons was found to be 4.32 ppm in moderately dilute aqueous solution at 30°. The rate calculations also required knowledge of J_{NH} , the ^{14}N -H spin-spin coupling constant, and of T_1 , the relaxation time of the ^{14}N nucleus in triethylammonium ion. However, the result is not sensitive to these variables and semiquantitative esti-

mates are sufficient. We used the values, $J_{NH} = 55$ Hz and $T_1 = 2.5 \times 10^{-3}$ sec, that were obtained for trimethylammonium ion. (Actual measurements were made in methanol; the T_1 value obtained in methanol was then corrected for the change in solvent viscosity to yield the value listed above.)

Proton-Deuteron Exchange in D_2O -DCl. Production of HOD in D_2O -DCl after introduction of triethylammonium chloride was measured by repeated scanning of the HOD proton nmr line in quasi-slow passage. A known weight of BHCl salt was introduced quickly into an nmr sample tube containing a known amount of D_2O -DCl at room temperature (25°). The mixture was stirred at once to dissolve the BHCl, and placed in the sample probe of the nmr magnet. Scanning of the HOD line was begun immediately. Since the D_2O initially contained ca. 0.5 M HOD, the plot of HOD signal height vs. time consisted of two distinct regions: (1) an initial, rapid, increase (with time constant T_1) as the HOD protons in the sample attain equilibrium with the magnetic field; (2) a subsequent, slower, increase as the HOD concentration increases due to exchange with BH^+ . This second portion was used to evaluate k_e . T_1 for the HOD protons in representative reaction mixtures was found to be 5-7 sec.

(23) E. Grunwald and E. Price, *J. Am. Chem. Soc.*, **86**, 2965, 2970 (1964).

Nuclear Magnetic Resonance Spectroscopy. Benzene- $^{13}C^{1a}$

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Abstract: The high-resolution ^{13}C spectrum of benzene has been analyzed. The long-range carbon-proton coupling constants, $J_{CCH} = +1.0$ Hz, $J_{CCCH} = +7.4$ Hz, and $J_{CCCCH} = -1.1$ Hz, have been related to proton-proton coupling constants in selected model compounds.

The practical use of ^{13}C nuclear magnetic resonance has been hindered by low natural abundance of this nucleus (1.1%), low inherent sensitivity to nmr detection (1.6% relative to protons at constant field), and long relaxation times. Various methods have been used to overcome these difficulties including the use of enriched materials,² observation of the spectrum under rapid-passage conditions in either the dispersion or absorption mode³ (which sacrifices resolution for better signal-to-noise ratios), complete proton decoupling⁴ which enhances the signal-to-noise ratios at the expense of coupling information, internuclear double resonance,⁵ and flow techniques.⁶ The development of field-frequency stabilization techniques⁷ has made time-averaging⁸ techniques both possible and practical.

Previously reported ^{13}C spectra of benzene were obtained either under rapid-passage conditions³ and showed only a broad doublet due to the one-bond C-H coupling, or with proton decoupling⁴ and gave only a single line. Bernstein⁹ has recently studied the

proton spectrum of 2,3,4,5-tetradeuterio-1,2- $^{13}C_2$ -benzene and has determined the four coupling constants in this AA'XX' system. The especially interesting result is the two-bond coupling J_{CCH} which was found to be +1.0 Hz. The one-bond coupling J_{CH} has been determined by several workers and is ~ 159 Hz.^{3,10}

Experimental Section

The benzene sample used in this study contained 10% carbon disulfide and 10% tetramethylsilane (v/v). The sample was degassed and sealed under nitrogen in a 10-mm, precision-bore sample tube.¹¹

The deuteriobenzenes were obtained from Merck Sharpe and Dohme of Canada.

The spectrometer used in this work was a special instrument developed for us by F. Nelson and V. Burger of Varian Associates and features a digital frequency sweep for ^{13}C at 15 MHz provided by a Hewlett-Packard 5110-5100A frequency synthesizer controlled by a Varian Associates V-4355 digital programmer. The probe was double tuned to 15 and 60 MHz with the 60 MHz for field-frequency stabilization being derived from the stable driver frequency of the synthesizer. The field was locked by conventional techniques to the proton resonances in the sample, in the present case to tetramethylsilane. Spectra were accumulated on a Varian C-1024 computer of average transients. A block diagram of the spectrometer system is shown in Figure 1.

Comparison spectra for the seven-spin system of ^{13}C and six protons were calculated using the Swalen-Reilly NMRT¹² program

(1) (a) Supported in part by Public Health Service Research Grant 11072-04 from the Division of General Medical Sciences and the National Science Foundation. (b) National Science Foundation Pre-doctoral Fellow, 1965-1967.

(2) K. Frei and H. J. Bernstein, *J. Chem. Phys.*, **38**, 1216 (1963).

(3) P. C. Lauterbur, *J. Am. Chem. Soc.*, **83**, 1838 (1961).

(4) E. G. Paul and D. M. Grant, *ibid.*, **86**, 2977 (1964).

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(6) S. Forsen and A. Rupprecht, *J. Chem. Phys.*, **33**, 1888 (1960).

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(12) C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **32**, 1378 (1960).

Digital Frequency Sweep N.m.r. Spectrometer

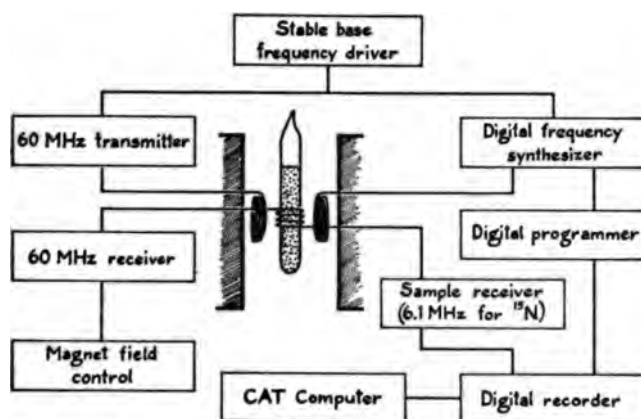


Figure 1. Digital frequency sweep nmr spectrometer.

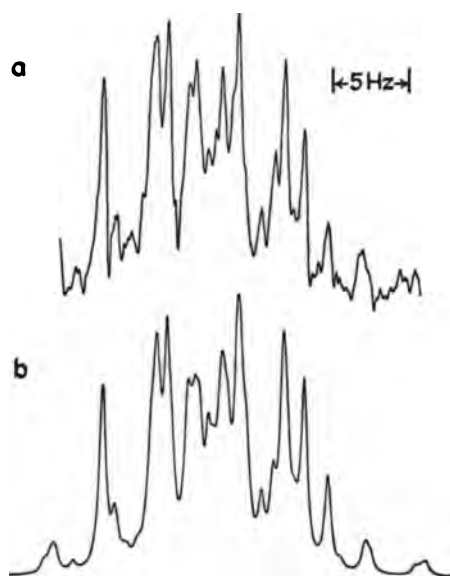


Figure 2. (a) Natural abundance ^{13}C spectrum of benzene showing the high-frequency half, taken with a sweep rate of 0.25 Hz/sec for 67 scans using TMS as internal reference at 60,006,000 Hz. The left edge of this spectrum is at 15,084,550 Hz and the right edge is at 15,084,525 Hz. (b) Calculated spectrum obtained with the parameters in Table I.

with an IBM 7094 computer and the resulting spectra were plotted on a CalComp plotter.

Results and Discussion

The chemical shift of benzene- ^{13}C relative to internal carbon disulfide in the sample used in this work was found to be 968.0 ± 0.3 Hz, or 64.1 ppm at 15.1 MHz. One-half of the experimental spectrum of benzene is shown in Figure 2a. Because of the complexity of this spectrum, it was found helpful to study some deuterated benzenes to aid in the interpretation. The ^{13}C spectrum of 1,2,3,5-tetradeuteriobenzene, which was particularly useful in this respect, is shown in Figure 3. The carbons attached to deuterium appear as a broad triplet, in contrast to the previous observation¹³ that such carbons cannot be observed at all because of extremely short relaxation times. The carbons directly attached to a proton show the effect of long-range cou-

(13) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).

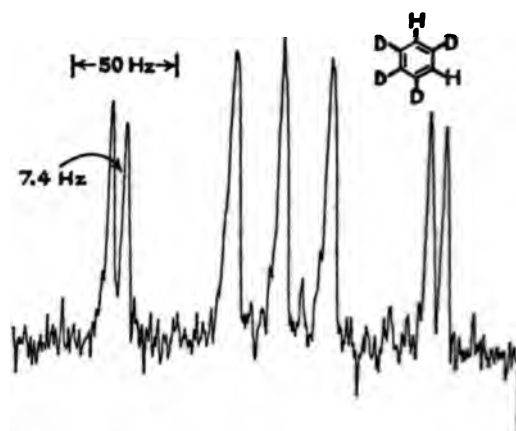


Figure 3. Natural abundance spectrum of 1,2,3,5-tetradeuteriobenzene after 217 scans. The outer four lines arise from ^{13}C -H while the middle three lines arise from ^{13}C -D.

pling to the other proton in the molecule. Since all proton-proton, proton-deuterium, and carbon-deuterium couplings in this particular case are small compared to the carbon-proton couplings, the three-bond coupling constant J_{CCCH} was determined to be ± 7.4 Hz from a first-order analysis of the spectrum. The magnitude of this coupling is confirmed by the observation of a doublet of triplets for the carbons attached to protons in 1,3,5-trideuteriobenzene, with the small coupling constant again being 7.4 Hz.

The ^{13}C spectrum of benzene was calculated using the proton-proton coupling constants determined from observation of the ^{13}C satellites in the proton spectrum¹⁴ or interpolation of the observed variation of proton-proton coupling constants of substituted benzenes with electronegativity,¹⁵ two long-range coupling constants determined from deuterated benzenes, and a value for the four-bond coupling constant calculated from the difference between J_{CCCH} and J_{CCH} and the known value of J_{CCH} . The parameters used are shown in Table I and the calculated spectrum in Figure 2b. The agreement is excellent.

Table I. Benzene Coupling Constants Calculated by the Extended Hückel Theory

J	Calcd, Hz	Obsd, Hz
CH	98.3	157.5
CCH	-5.9	+1.0
CCCH	1.4	+7.4
CCCCH	0.13	-1.1
HCCH	3.7	+7.7, ^a 7.7 ^b
HCCCH	0.25	+1.37, ^a 1.4 ^b
HCCCCH	0.63	+0.59, ^c 0.6 ^b

^a Reference 9. ^b Reference 15. ^c Reference 14.

Recently attempts have been made to calculate carbon-proton coupling constants¹⁶ using the extended Hückel theory of Hoffmann.¹⁷ Calculations of this

(14) J. M. Read, Jr., R. E. Mayo, and J. H. Goldstein, *J. Mol. Spectry*, **21**, 235 (1966).

(15) S. Castellano and C. Sun, *J. Am. Chem. Soc.*, **88**, 4741 (1966).

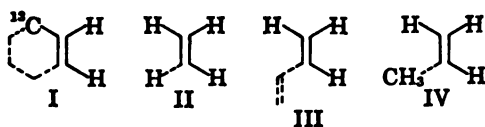
(16) R. C. Fahey, G. C. Graham, and R. L. Piccioni, *ibid.*, **88**, 193 (1966).

(17) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).

type have been performed on benzene and the results are shown in Table I.

The agreement between observed and calculated coupling constants is rather poor. The discrepancies seem general for π -electronic systems and have been accounted for¹⁸ through neglect of σ - π interaction, coupling through the π system which is not taken into account, and other factors.

Since the available data for proton-proton couplings are much more extensive than for carbon-proton coupling, it would be particularly desirable to be able to relate couplings involving ^{13}C and protons to those involving only protons. A theoretical basis for this has already been described,¹⁸ but the treatment has only been applied to aliphatic systems, and with limited success. Assuming that the carbon in question is in the same steric and electronic environment as a certain proton and that the Fermi contact term is the dominant coupling mechanism, the two coupling constants such as J_{CCCH} and J_{HCCCH} can be related by a single parameter which depends only on the hybridization of the carbon in question. Assuming a specific form for the carbon 2s orbital (a Slater orbital with exponent 3.25 was used), the constant relating the two couplings¹⁸ was determined as 0.40 for an sp^3 carbon giving the relationship $J_{\text{CCCH}} = 0.4J_{\text{HCCCH}}$. Previously this relationship has only been applied to intramolecular comparison of coupling constants,¹⁹ but with the correct choice of model compounds, there seems to be no reason why it should not be extended to intermolecular comparisons. Several compounds (II-IV) are proposed as models for benzene



(18) G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Am. Chem. Soc.*, **84**, 37 (1962).

(19) The poor agreement originally found by Karabatsos and co-workers¹⁸ may be due to the choice of model compounds and neglect of the possibility of opposite signs for some of the coupling constants.

(I). The predicted benzene coupling constants based on the relevant coupling constants for these compounds are given in Table II.

Table II. Relationship of CH and HH Coupling Constants

	J_{CCH}	J_{CCCH}
Benzene (obsd)	+1.0	+7.4
Calcd from J_{HH} in		
Ethylene ^a	+1.0	+7.6
Butadiene ^b	+0.7	+6.8
Propene ^c	+0.8	+6.8

^a R. M. Lynden-Bell and N. Sheppard, *Proc. Roy. Soc. (London)*, **A269**, 385 (1962). ^b R. T. Hobgood and J. H. Goldstein, *J. Mol. Spectry.*, **12**, 76 (1964). ^c P. C. Lauterbur and R. J. Kurland, *J. Am. Chem. Soc.*, **84**, 3405 (1962).

The choice of a correct model compound for the four-bond coupling is difficult. Although the analogy is imperfect, a negative sign has been predicted for the four-bond, proton-proton coupling constant in allene²⁰ which is 7.1 Hz.²¹ There are two equivalent paths possible for transmission of the spin information in allene, and they are expected to give an additive effect. On this basis a single path with three intervening sp^2 -hybridized carbon atoms should lead to a proton-proton coupling constant of -3.5 Hz which with Karabatsos' formulation leads to prediction of -1.4 Hz for the four-bond coupling constant J_{CCCH} in benzene.

The general agreement is excellent and it appears profitable to investigate further the relation between the magnitudes of the two- and three-bond, carbon-proton coupling constants with those in analogously constituted systems involving proton-proton coupling.

Acknowledgments. We thank Professor G. W. Robinson for loaning us samples of the deuterated benzenes used in this investigation and George Petersson for a copy of his program for extended Hückel molecular orbital calculations.

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The Proton Magnetic Resonance Spectra of Arylcarbonium Ions. Neighboring Group Anisotropies and Charge Distributions¹

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Abstract: The nmr spectra of a number of arylcarbonium ions in fluorosulfonic acid solution are analyzed with the aid of a computer. The chemical shift parameters obtained are compared with some previously reported. They are interpreted with the aid of a double toroid ring-current model for the anisotropy of neighboring phenyls. They are then discussed with reference to charge distributions as determined by some molecular orbital models.

The proton nmr spectra of arylcarbonium ions have been the subject of both qualitative³ and quantitative⁴ investigations for several years. Among the earliest attempts at quantitative analysis was that of O'Reilly and Leftin^{4c} on triphenylcarbonium ion. A considerable dispute over the assignment of chemical shifts and coupling constants in triphenylcarbonium ion^{3c,4c} seemed to subside with the publication by Dehl, *et al.*,^{4c} of deuterium-labeling studies and a computer-simulated spectrum. It seemed to us that the more sophisticated techniques now available in the rapidly developing field of nmr spectroscopy warranted a reinvestigation of some arylcarbonium ions. Impetus was also provided by the fact that early attempts to interpret the chemical significance of the chemical shifts were based on the wrong chemical shift assignments and an incomplete model for the ring-current effect.^{4c}

ions and suggested that the interpretation previously reported in the literature required some modification.^{4a} We here report a detailed analysis of the nmr spectra of several arylcarbonium ions at 60 MHz, including a reanalysis of triphenylcarbonium ion at 60 and 100 MHz. We make an attempt to discuss the observed chemical shifts in terms of realistic models for the geometry, ring-current effect, and charge distribution in these ions.

Experimental Section

Materials. Chlorosulfonic acid was distilled immediately before use; fluorosulfonic acid was distilled over anhydrous potassium fluoride, placed in oven-dried, glass-stoppered bottles, sealed with paraffin, and stored in a drybox. All transfers of fluorosulfonic acid were accomplished in the drybox by pipet. Carbonium ion precursors were the carbinols with the exception of compounds 1 (phenylpropionic acid), 2 (benzoic acid), 3 (benzophenone), 4 (acetophenone), and 7 (1,1-diphenylethylene) in Table I. Solid pre-

Table I. Proton Nmr Parameters for Several Arylcarbonium Ions

Compd	Carbonium ion	Chemical shifts, τ values			α H or CH ₃	Coupling constants, Hz					
		<i>ortho</i>	<i>meta</i>	<i>para</i>		$J(o,m)$	$J(o,p)$	$J(o,m')$	$J(o,o')$	$J(m,p)$	$J(m,m')$
1	C ₆ H ₅ CH ₂ CH ₂ C ⁺ (OH) ₂	2.80	2.80	2.80							
2	C ₆ H ₅ C ⁺ (OH) ₂ ^{a,c}	1.73	2.24	1.94		8.2	1.2	0.5	1.2	8.0	1.7
3	(C ₆ H ₅) ₃ C ⁺ OH ^{a,c}	1.88	2.17	1.85		8.2	1.2	0.5	1.2	8.0	1.7
4	C ₆ H ₅ C ⁺ (OH)CH ₃ ^{a,c}	1.57	2.22	1.84	6.69	8.2	1.2	0.5	1.2	8.0	1.7
5	(C ₆ H ₅) ₃ C ⁺ ^{a,b} (60 MHz)	2.31	2.13	1.76		7.95	1.40	0.33	1.21	7.55	0.89
6	(C ₆ H ₅) ₃ C ⁺ ^{a,b} (100 MHz)	2.32	2.14	1.76		8.13	1.20	0.43	1.26	7.54	1.14
7	(C ₆ H ₅) ₂ C ⁺ CH ₃ ^b	1.93	2.10	1.68	6.30	8.12	1.05	0.74	1.30	7.37	1.39
8	(C ₆ H ₅) ₂ C ⁺ H ^{b,c}	1.54	2.02	1.62	0.19	8.2	1.2	0.5	1.2	7.5	1.7
9	C ₆ H ₅ C ⁺ (CH ₃) ₂ ^{b-d}	1.12	1.99	1.37	6.43	8.1	1.0	0.7	1.3	7.4	1.4

^a In chlorosulfonic acid solution. ^b In fluorosulfonic acid solution. These were similar, but less well resolved, in chlorosulfonic acid.^{4a}

^c Coupling constants for these systems, particularly the small ones, can only be regarded as approximate, since resolution was too poor to warrant refinement of the calculations. ^d Spectrum determined at -40° .

In an earlier paper we presented a preliminary analysis of the proton nmr spectra of a number of arylcarbonium

(1) The author is grateful to the National Science Foundation (GP 5507) for support of this research.

(2) Fellow of the Alfred P. Sloan Foundation, 1962-1965. Address correspondence to the Department of Chemistry, Michigan State University, East Lansing, Michigan 48823.

(3) (a) G. A. Olah, M. B. Comisarow, C. A. Cupas, and C. U. Pittman, Jr., *J. Am. Chem. Soc.*, **87**, 2997 (1965); (b) G. A. Olah, *ibid.*, **86**, 932 (1964); (c) R. Dehl, W. R. Vaughan, and R. S. Berry, *J. Org. Chem.*, **24**, 1616 (1959); (d) R. B. Moodie, T. M. Connor, and R. Stewart, *Can. J. Chem.*, **37**, 1402 (1959); (e) C. MacLean, J. H. van der Waals, and E. L. Mackor, *Mol. Phys.*, **1**, 247 (1958).

(4) (a) D. G. Farnum, *J. Am. Chem. Soc.*, **86**, 934 (1964); (b) T. Schaeffer and W. G. Schneider, *Can. J. Chem.*, **41**, 966 (1963); (c) R. S. Berry, R. Dehl, and W. R. Vaughan, *J. Chem. Phys.*, **34**, 1460 (1961); (d) C. MacLean and E. L. Mackor, *Mol. Phys.*, **4**, 241 (1961); (e) D. E. O'Reilly and H. P. Leftin, *J. Phys. Chem.*, **64**, 1555 (1960).

cursors were commercial samples twice recrystallized and dried under vacuum before use. Liquid samples were distilled and a middle cut was taken. Gas chromatographic analysis in all cases resolved only one component in greater than 99% purity. Phenyl-dimethylcarbinol was obtained as a crystalline solid, mp 32.5-33.5°, by two sublimations. Nmr samples were made up to 1 to 10% concentration by the addition of a methylene chloride solution of the precursor to vigorously stirred acid at -40° . The acid layer was drawn off for use.

Determination of the Spectra. The proton nmr spectra were determined at 60 and 100 MHz on the Varian A-60 or HA-100 instruments. At low concentrations (1%) the Varian CAT was employed to bring out the spectrum. It was demonstrated that the chemical shifts (relative to tetramethylammonium fluoroborate internal standard taken as τ 6.87^{4c}) and general appearance of the spectra were relatively insensitive to concentration (from 1 to 10% for 4, 7, and 9 of Table I) and temperature (from -40 to $+40^\circ$).

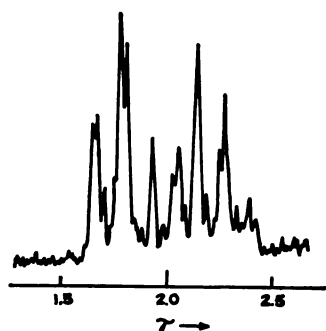


Figure 1. Nmr spectrum (60 MHz) of benzoic acid in chlorosulfonic acid.

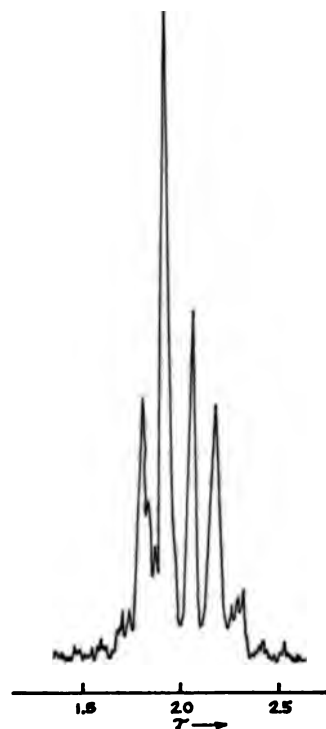


Figure 2. Nmr spectrum (60 MHz) of benzophenone in chlorosulfonic acid.

In those cases which could be determined in both acids, the shifts were nearly the same, but the spectra in fluorosulfonic acid were better resolved (presumably because of the greater fluidity). The structures of the carbonium ions were assured by the reproducibly characteristic nmr patterns, the near identity of the ultraviolet spectra of the diluted solutions of 4 and 9 (Table I) with those reported in the literature,⁶ and recovery of the parent alcohol in 60% yield or better by quenching in iced aqueous base in the cases of triphenylcarbinol (5), benzhydrol (8), benzophenone (3), and benzoic acid (2). The spectrum of methylphenylcarbonium ion (7) has appeared in the literature.^{4a} Our spectrum was similar in appearance, but better resolved. Spectra were determined on both 500 Hz and 250 Hz nominal scale widths, calibrated with known standards to determine the actual scale widths.

Analysis of the Spectra. Nmr spectra were analyzed with the aid of the nmr simulation computer program, LAOCOON II, devised by Bothner-By.⁶ Spectra were computed on a Control Data Corp. 1604 computer, traced on a curve-plotter, and compared with the determined spectra. A line-width factor of 0.8 (approximately equal to width at half-height in Hertz) gave computed spectra of comparable appearance to the experimental ones. Iterations to

(5) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Am. Chem. Soc.*, **77**, 3044 (1955).

(6) We thank Dr. Bothner-By for providing us with the program deck and instructions for LAOCOON II.

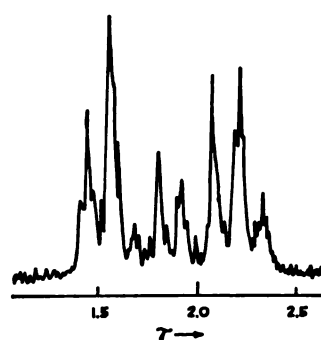


Figure 3. Nmr spectrum (60 MHz) of acetophenone in chlorosulfonic acid.

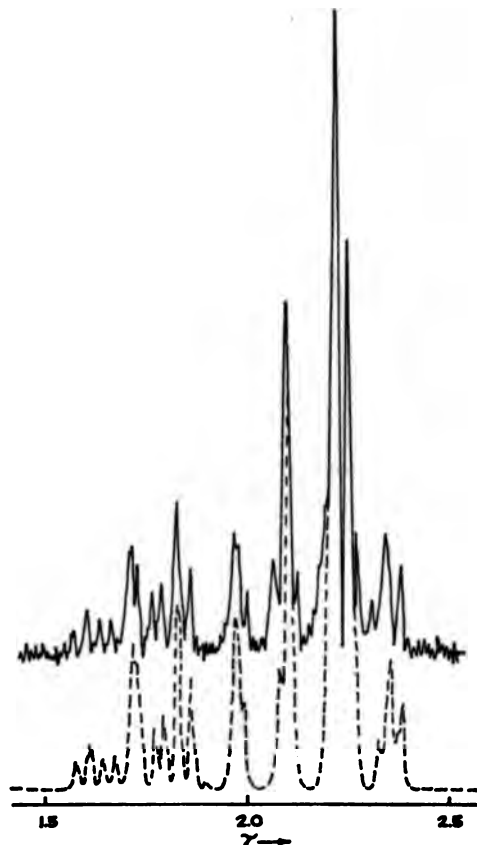


Figure 4. Nmr spectrum (60 MHz) of triphenylcarbinol in fluorosulfonic acid (upper curve) and computer-simulated spectrum (lower curve) using parameter values given in Table I.

determine the best fit were performed separately at 60 and 100 MHz for triphenylcarbonium ion. The results at the different frequencies were in close agreement (within 0.5 Hz). To assist in the preliminary choice of parameters 20 spectra with identical approximate coupling constants but differing chemical shifts were computed. An approximate fit to one of these provided the starting point for the iteration procedure. In the cases of acetophenone (phenylmethylhydroxycarbonium ion), benzoic acid (phenyldihydroxycarbonium ion), and phenyldimethylcarbonium ion, separation of the peaks was sufficient to assign chemical shifts by inspection after the initial comparison. For benzophenone (diphenylhydroxycarbonium ion) the poorer resolution did not warrant an attempt at a closer assignment than that obtained by estimation from the first comparison. The determined and simulated spectra for the several carbonium ions are compared in Figures 1-8. The chemical shifts and coupling constants are given in Table I. The assignment of the *ortho*, *meta*, and *para* protons rests firmly on the large (7-8 Hz) coupling of the *ortho* proton to one *meta* proton, the large (7-8 Hz) coupling of the *meta* proton to both *ortho* and *para* protons, and the low intensity of the peaks corresponding to the single *para* proton.

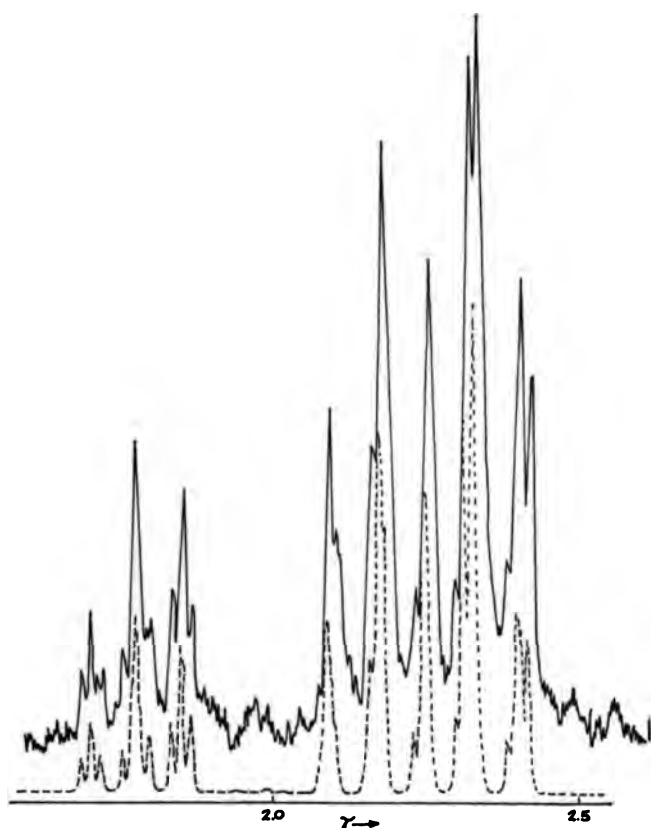


Figure 5. Nmr spectrum (100 MHz) of triphenylcarbinol in fluorosulfonic acid (upper curve) and computer-simulated spectrum (lower curve) using parameter values given in Table I.

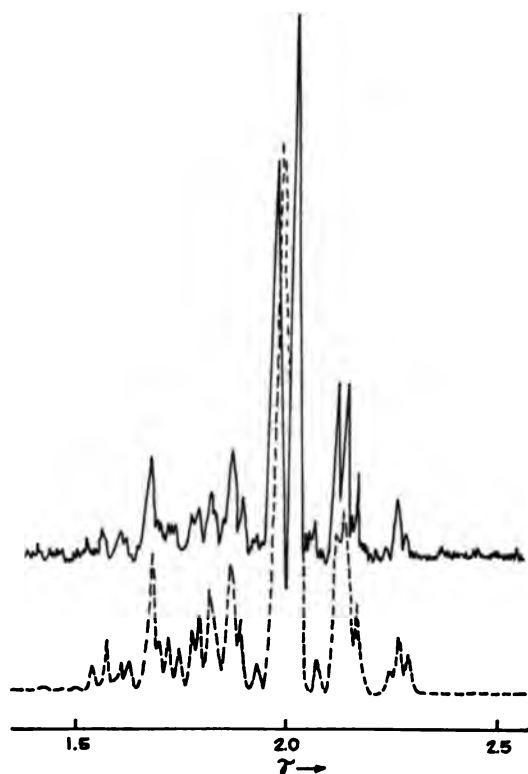


Figure 6. Nmr spectrum (60 MHz) of 1,1-diphenylethylene in fluorosulfonic acid (upper curve) and computer-simulated spectrum (lower curve) using parameter values given in Table I.

There is some variance in the values reported for triphenylcarbinol ion from several sources. These values are compared in Table II. The chemical shifts obtained in this work are in reason-

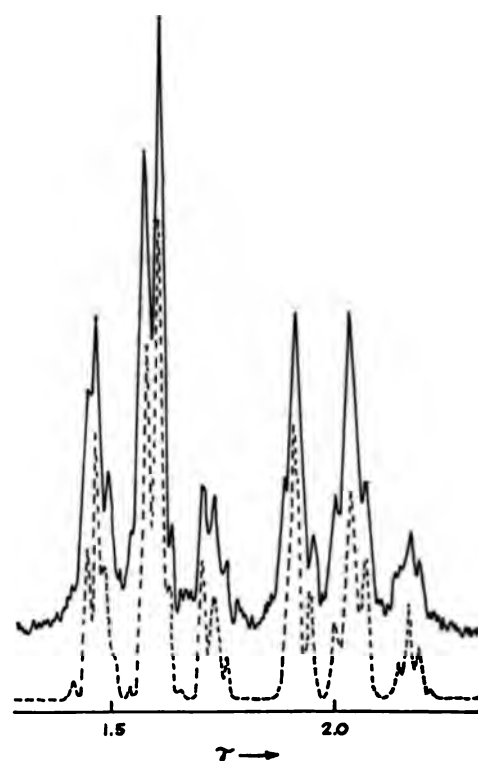


Figure 7. Nmr spectrum (60 MHz) of diphenylcarbinol in chlorosulfonic acid (upper curve) and computer-simulated spectrum (lower curve) using parameter values given in Table I.

able agreement with those of Schaeffer and Schneider^{4b} and Berry, *et al.*,^{4c} while coupling constants are quite comparable with those obtained by the latter authors. The variations probably are the result of different solvents and reference standards as well as the difficulty of analyzing the 60-MHz spectrum without the aid of a computer.

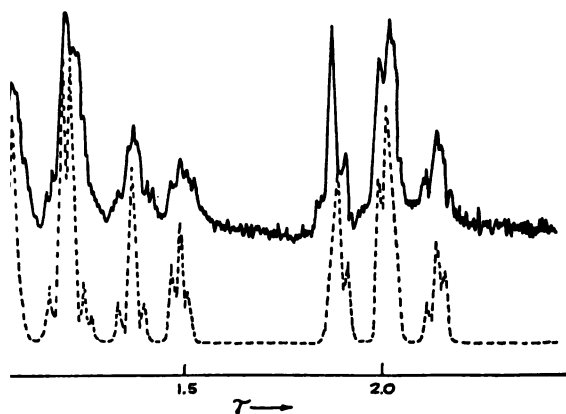
Table II. Comparison of Nmr Parameters from Several Sources for Triphenylcarbonium Ions

	Source ^a				
	1	2	3	4	5
$\tau(\text{ortho})$	2.38	2.30 (2.45 ^b)	2.29	2.99	2.32
$\tau(\text{meta})$	2.13	2.45 (2.30 ^b)	2.12	2.49	2.14
$\tau(\text{para})$	1.73	1.93	1.76	2.24	1.76
$J(o,m)^c$			8.2		8.13
$J(o,p)$			1.2		1.20
$J(o,m')$			0.5		0.43
$J(o,o')$			1.2		1.26
$J(m,p)$			8.0		7.54
$J(m,m')$			1.7		1.14

^a Source code numbers are 1, ref 4b; 2, ref 4c; 3, ref 4c; 4, ref 3b; 5, this work. ^b Alternate assignments. ^c J values given in Hertz.

Discussion

Several general features emerge from the data from nmr analysis of several arylcarbonium ions as given in Table I. The chemical shift value for the phenyl protons of phenylpropionic acid in sulfuric acid solution (τ 2.80) is given as a reference point. As expected, all the arylcarbonium ion chemical shifts fall below this value, and the p -proton resonance moves progressively downfield as the electron-releasing ability of the substituents on the α -carbon decreases. This qualitative correlation of the position of the p -proton resonance with the electron demands placed on the phenyl by the



3. Nmr spectrum (60 MHz) of phenyldimethylcarbinol in lonic acid at -40° (upper curve) and computer-simulated n (lower curve) using parameter values given in Table I.

ium ion is expected and has been noted in the re.^{4a} The *o*- and *m*-proton resonances are much gular and are apparently significantly perturbed sotropies of the α substituents.^{4a} Thus for the diphenyl (8), hydroxydiphenyl (3), methyldi- (7), and triphenylcarbonium ion (6), the *o*-resonances (τ 1.54, 1.88, 1.93, and 2.32) fall ssively upfield, apparently independently of the of the positive charge on the phenyl. This order, er, does correlate with the size of the α substit- and, therefore, with the angle of twist of the s from coplanarity. Increased twisting from arity (up to about 45°) will result in increased ig of the *o*-protons by neighboring phenyl opy as illustrated in Figure 9. For the *meta* al shifts (2.02, 2.17, 2.10, and 2.14) the influence positive charge and anisotropy might be better ed; thus the correlation is not expected to be as . As an incidental point, all the coupling con- fall within the ranges quoted in the literature for tic compounds,⁷ in spite of the major perturba- the positive charge.

order to examine the quantitative validity of some ideas suggested in the previous paragraph, it was ary to develop a quantitative picture of the oring phenyl anisotropy effect as a function of gle of twist of the phenyls. A model for this based upon a modification of the Johnson- -Waugh-Fessenden⁸ double-loop ring-current has been described in another publication⁹ and 1 to the di- and triphenylcyclopropenium ions.

10 depicts the neighboring ring-current effect nction of the angle of twist for triphenylcarbon- n as calculated using this model (a double dough- circulating charge of radius and cross-sectional ter equal to 1.4 Å). The calculation determines ect of both the near and remote neighbor phenyl s *o*-, *m*-, and *p*-proton, assuming that all phenyls isted the same angle from coplanarity.⁹ The for a diphenylcarbonium ion should be one-half lues in Figure 10, provided only that interchange

B. Leane and R. E. Richards, *Trans. Faraday Soc.*, **55**, 707

S. Waugh and R. W. Fessenden, *J. Am. Chem. Soc.*, **79**, 846 83, 6677 (1958); C. E. Johnson and F. A. Bovey, *J. Chem. S.*, 1012 (1958).

G. Farnum and C. F. Wilcox, *J. Am. Chem. Soc.*, submitted ication.

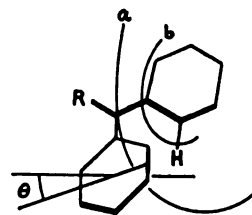


Figure 9. Neighboring ring-current effects in triphenylcarbonium ion: θ = twist angle, a = line of iso shielding, b = line of iso deshielding.

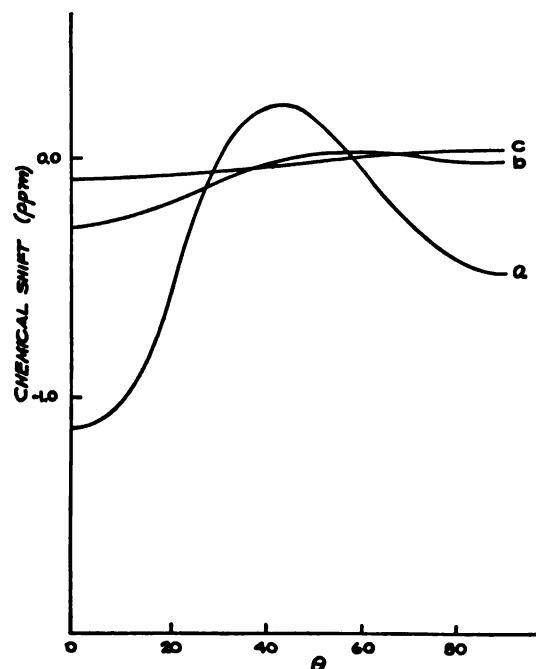


Figure 10. Plot of chemical shift due to neighboring ring-current effects vs. twist angle for triphenylcarbonium ion: a = *ortho*, b = *meta*, c = *para* protons.

of the two mirror-image propellor-like rotamers is rapid on an nmr time scale.⁹

Evaluation of the ring-current effect requires the actual angle of twist of the phenyls in triphenylcarbonium ion in solution, which is not known. Estimates range from 23° ^{4c} (near the van der Waals approach of the *o*-hydrogens) to 45° ,¹⁰ with X-ray analysis of the solid giving 35° .¹¹ In the absence of any convincing evidence to the contrary we have chosen

Table III. Chemical Shifts of Ring Protons of Several Arylcarbonium Ions Corrected for Neighboring Ring Anisotropies

Compd	Carbonium ion	Chemical shift, τ values		
		<i>ortho</i>	<i>meta</i>	<i>para</i>
2	$C_6H_5C^+(OH)_2$	1.73	2.24	1.94
3	$(C_6H_5)_2C^+OH$ (30° twist)	1.90	2.22	1.88
4	$C_6H_5C^+(OH)CH_3$	1.57	2.22	1.84
5	$(C_6H_5)_2C^+$ (45° twist)	2.08	2.14	1.80
7	$(C_6H_5)_2C^+CH_3$ (35° twist)	1.87	2.13	1.71
8	$(C_6H_5)_2C^+H$ (25° twist)	1.69	2.09	1.66
9	$C_6H_5C^+(CH_3)_2$	1.12	1.99	1.37

(10) N. C. Deno, P. T. Graves, and G. Saines, *ibid.*, **81**, 5790 (1959).

(11) A. H. Gomes de Mesquita, C. H. MacGillavry, and K. Erika, *Acta Cryst.*, **18**, 437 (1965).

Table IV. Comparison of the Observed Charge Contribution to the Chemical Shift of Phenylcarbonium Ions at Several Twist Angles with That Calculated from Molecular Orbital Models

Species (angle, deg)	Proton	Obsd ^b		Charge contribution to chemical shift ^a		HMO ^{c,f}		d,f		SCFMO ^{e,f}	
		Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel
Phenyldimethylcarbonium ion (0)	<i>ortho</i>	1.60	1.18	2.67	1.10	2.19	1.11	2.36	0.64		
	<i>meta</i>	0.77	0.57	1.16	0.48	1.45	0.74	1.95	0.53		
	<i>para</i>	1.35	1.0	2.43	1.00	1.97	1.00	3.67	1.00		
Diphenylcarbonium ion (25)	<i>ortho</i>	1.07	0.93	1.63	1.06						
	<i>meta</i>	0.70	0.61	0.84	0.54						
	<i>para</i>	1.15	1.00	1.54	1.00						
	(35) <i>ortho</i>	1.33	1.14	1.50	1.14						
	<i>meta</i>	0.75	0.65	0.78	0.59						
	<i>para</i>	1.17	1.00	1.32	1.00						
	(45) <i>ortho</i>	1.38	1.18	1.33	1.29						
	<i>meta</i>	0.78	0.67	0.71	0.68						
	<i>para</i>	1.17	1.00	1.03	1.00						
Triphenylcarbonium ion (25)	<i>ortho</i>	0.075	0.08	1.24	0.98						
	<i>meta</i>	0.50	0.52	0.71	0.56						
	<i>para</i>	0.97	1.00	1.27	1.00						
	(35) <i>ortho</i>	0.60	0.61	1.22	1.07						
	<i>meta</i>	0.60	0.61	0.69	0.61						
	<i>para</i>	0.98	1.00	1.13	1.00						
	(45) <i>ortho</i>	0.73	0.73	1.15	1.23						
	<i>meta</i>	0.65	0.65	0.65	0.69						
	<i>para</i>	1.00	1.00	0.94	1.00						

^a Column labeled abs gives values in parts per million downfield from the phenyl hydrogens of phenylpropionic acid. Column labeled rel gives values relative to *para* chemical shifts = 1.00. ^b Corrected for the neighboring ring-current effect at the angle in question. ^c Simple Hückel molecular orbitals. ^d Modified ω technique.¹⁵ ^e Self-consistent-field calculations.¹⁶ ^f Chemical shifts are calculated as the sum of the contributions from all carbon atoms using Musher's equations.¹²

to set the twist angles for diphenyl-, dihydroxydiphenyl-, methyldiphenyl-, and triphenylcarbonium ions at 25, 30, 35, and 45°, respectively, corrected the chemical shifts for the determined ring-current effects, and re-examined the thus-obtained order of chemical shifts. The results are shown in Table III. Although the *m*- and *p*-protons now correlate, and the *o*-protons are more nearly in line, the correction is not sufficient to bring complete order to the *o*-proton chemical shifts. We have been unable to find alternative reasonable choices of twist angles which improve the order. It is possible that a residual effect of the α -hydroxyl substituents is causing a downfield shift since the oxygenated cations (2, 3, and 4) appear at too low field, with the dioxygenated case 2 being particularly low.

With the chemical shifts corrected for neighboring ring-current effects in hand, it was possible to examine their correlation with predicted charge distributions in these ions. Two refinements of earlier work in this field^{3,4} were attempted in this investigation. First, earlier efforts had considered only the effect of the positive charge of the directly attached carbon atom. However, Musher has claimed¹² that all nearby positive charges have a significant effect. Therefore, using Musher's equations,¹² we set up a computer program which would calculate the chemical shifts at the *o*-, *m*- and *p*-protons resulting from point charges of specified values at all the carbon atoms in the mono-, di-, and triphenylcarbonium ions. Second, earlier attempts⁴ have determined the theoretical charge distribution in di- and triphenylcarbonium ions based upon *planar* molecules rather than realistically twisted ions. We therefore calculated the Hückel charge densities for these ions at twist angles of 25, 35, and 45°.¹³

(12) J. I. Musher, *J. Chem. Phys.*, **37**, 34 (1962).

(13) We thank Professor C. F. Wilcox for making a program available to us for these calculations.

The results of these combined calculations are summarized in Table IV.

Again a qualitative picture can be drawn. Thus, the larger relative¹⁴ downfield chemical shift observed for the *o*-protons of phenyldimethylcarbonium ion is correctly reproduced by both the Hückel and the ω -technique¹⁵ calculations, but not by the SCF¹⁶ method. The moderate chemical shift of the *m*-proton is in accord with all the calculations, in spite of the absence of charge at that position in the Hückel approximation. The relative chemical shifts for a 35° twisted diphenylcarbonium ion are extraordinarily well reproduced by the Hückel model, while much more difficulty is encountered with triphenylcarbonium ion, which shows more dispersal of charge to the *para* position than expected. Unfortunately, calculations by the ω -technique and SCF method for these twisted cations are not yet available for comparison. Since several approximate models have been interposed between the raw data and the numbers being compared in Table IV, it seems wise to be cautious in attempting any more quantitative analysis of the results.

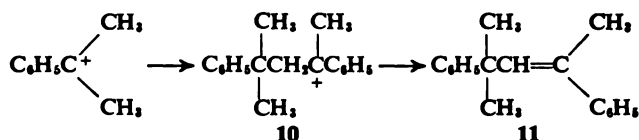
An incidental observation of some interest was made on solutions of the phenyldimethylcarbonium ion in fluorosulfonic acid. These solutions were stable only below -20°, as evidenced by the smooth, reproducible, rapid conversion of their characteristic nmr spectrum above that temperature to a new, well-resolved, and entirely different spectrum illustrated in Figure 11. The irreversible conversion was accompanied by a barely perceptible lightening of the lemon yellow color

(14) The discrepancy between the absolute values and the observed values is not surprising, since the Musher equations contain no correction for the solvent dielectric effect on the charge.

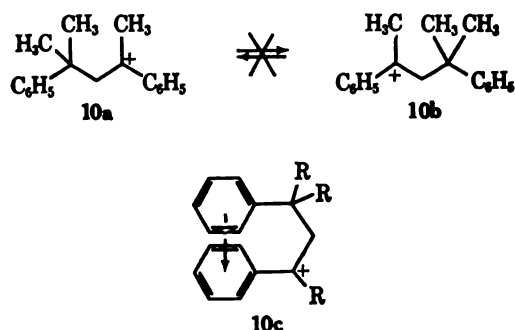
(15) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961.

(16) A. Brickstock and J. A. Pople, *Trans. Faraday Soc.*, **50**, 902 (1954).

of the solution. The new species was identified as the dimeric phenylmethyl-(2-phenylisobutyl)carbonium ion (10) by isolation of the corresponding olefin (11) in good yield by quenching the solution in iced aqueous sodium hydroxide. The olefin was purified by gas chromatography and characterized by its mass spectrum (parent peak, m/e 236) and nmr spectrum (τ 2.0–2.9, multiplet, area = 10.0; 4.13, quartet, $J = 2$ Hz, area = 0.6; 8.02, doublet, $J = 2$ Hz, area = 2.6; 8.80, singlet, area = 6.0) which left no doubt of its structure. The methyl and methylene resonances of the carbonium ion appeared at τ 6.18 (broad, area ca. 2), 6.61 (broad, area ca. 3), and 8.47 (sharp, area ca. 6).



The nmr spectrum of carbonium ion 10 deserves notice. It is entirely different from any which we have encountered in this work in that no phenyl resonance appears at the low-field position usually observed for *o*-protons, nor is there a clear separation between the phenyl conjugated with the carbonium ion center and that attached to the quarternary carbon. A rapid equivalencing of the phenyls by methyl migration (10a \rightleftharpoons 10b) cannot account for the results because the



methyl resonance signals are sharp and discrete, nor can they be the result of dimeric association, since the spectrum is the same at concentrations from 1 to 10%. We suggest that the unusual nmr spectrum of 10 is accommodated by a folded geometry, as in 10c ($\text{R} = \text{CH}_3$), in which the noncationic phenyl is associated with the cationic phenyl analogously to a charge-transfer complex or a solvation association. A similar explanation, named a "space-polarization effect,"

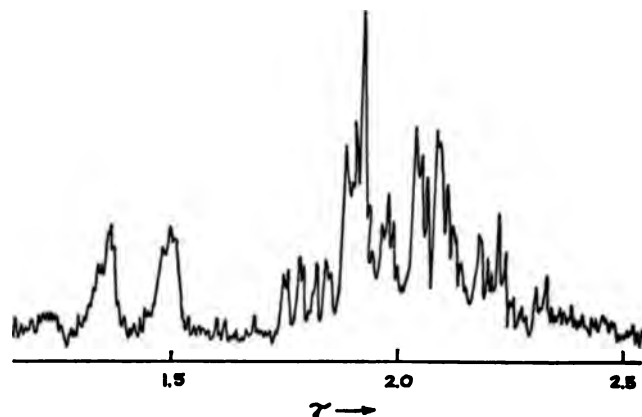


Figure 11. Nmr spectrum (60 MHz) of phenyldimethylcarbonium ion dimer.

has been offered by Williams for the anomalous ultra-violet spectrum of phenyl- β -phenylethylcarbonium ion (10c, $\text{R} = \text{H}$).¹⁷ The required folded geometry is readily achieved in molecular models.

In summary, the following conclusions seem justified on the basis of the treatment reported in this paper. (1) The *p*-proton resonance provides a reasonable qualitative measure of the extent of dispersion of positive charge onto the phenyl group of a phenylcarbonium ion. (2) When suitable corrections are made for neighboring ring-current effects and nonplanar geometries, the positive charges calculated by the simple Hückel approximation account for the ring chemical shifts of phenyldimethyl- and diphenylcarbonium ion in an entirely satisfactory way. However, triphenylcarbonium ion exhibits somewhat more dispersal of charge to the *para* position than expected. (3) Taken together, the results suggest that the twist angles of the polyphenylcarbonium ions examined are greater than 25°, and perhaps as high as 45° from coplanarity.

Acknowledgments. The author is grateful for the technical assistance of Mrs. Sharon Alderman, Dr. Alan Dow, Miss Marianne Nucci, and Mr. Alfred Hagadorn¹⁸ in preparation of some of the samples and determination of some of the spectra. He is also indebted to Professor C. F. Wilcox for contributing so much time and patience in valuable discussions.

(17) J. F. A. Williams, *Tetrahedron*, **18**, 1487 (1962).

(18) Summer participant in the National Science Foundation Undergraduate Research Participation Program.

Hyperfine Structure in the Electron Spin Resonance Spectra of Reduced Porphins

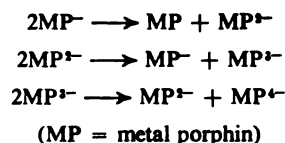
N. S. Hush^{1a} and J. R. Rowlands^{1b}

Contribution from the Department of Inorganic Chemistry, Bristol University, Bristol, England, and Southwest Research Institute, San Antonio, Texas 78206. Received January 19, 1967

Abstract: Electron spin resonance spectra with well-resolved hyperfine structure have been obtained by reduction of zinc tetrabenzporphin and zinc etioporphyrin I with sodium in tetrahydrofuran solution. Hyperfine structure has also been observed in the spectrum obtained from etioporphyrin I under the same conditions. The paramagnetic species in each case is considered to be either a trinegative ion of the porphyrin or a phlorin dianion PH^{2-} in which a hydrogen atom is attached to a methine carbon atom of the porphyrin skeleton.

Electron addition to porphin (P) or metal porphin (MP) molecules leads to the formation of a series of negative ions of increasing charge. Closs and Closs² studied the reduction of zinc $\alpha,\beta,\gamma,\delta$ -tetraphenylporphin in tetrahydrofuran and prepared salts of the mononegative and dinegative ions, corresponding to uptake of one and two electrons, respectively. Dodd and Hush³ have reported the formation of mono- and dinegative ions of complexes of a variety of substituted porphins, including metal derivatives of etioporphyrin, tetraphenylporphin, tetraazaporphin, tetrabenzporphin, and phthalocyanine. Evidence of two further one-electron steps, corresponding to the formation of trinegative and tetranegative ions, has been obtained by Clack and Hush.⁴ Felton and Linschitz⁵ have also reported polarographic results on tetraphenylporphin and etioporphyrin complexes which are in agreement with those of ref 3. Recent work on the reduction of metal phthalocyanines⁶ shows that salts of negative ions containing from one to four additional electrons can be isolated from solution.

The typical molecular symmetry of divalent metal complexes of porphins is D_{4h} . In some complexes the symmetry is lower, usually because the central metal atom lies slightly out of the plane of the ring. However, perturbations of this type are small and in either case the lowest empty ligand orbital has e symmetry. This means that up to four electrons can be accommodated in this orbital, in agreement with the experiment. An interesting feature of these ions is that the energies of



the disproportionation reactions are positive and remarkably constant over a range of porphin structures whose M^{II} is a closed-shell ion. An interpretation of this in terms of electron interaction energies has been given by Hush.⁷ It should also be mentioned that for some divalent transition metal porphins^{5,6} and phthalocyanines^{8,9} the first reduction step corresponds to

reduction of the metal to the +1 oxidation state; in subsequent steps, this is followed by electron addition to the ring, forming M^IP^{2-} ions, which are the analogs of the M^{II}P^- ions of porphin complex of closed-shell metal ions. These will not be further considered here, as they present special problems of interpretation.

The purpose of this communication is to present some results of measurements of the electron spin resonance spectra of solutions containing reduced porphins.

Closs and Closs² established that salts of tetraphenylporphin⁻ and tetraphenylporphin²⁻ were respectively paramagnetic and diamagnetic in tetrahydrofuran. Similar results have been found in the phthalocyanine series, both for phthalocyanine itself and for closed-shell metal complexes.

The electron spin resonance spectra of a number of mononegative ions of tetraphenylporphin and etioporphyrin derivatives, mostly obtained by electrolytic reduction in dimethyl sulfoxide solution, have been reported by Felton and Linschitz.⁵ These exhibit no hyperfine structure and have g values which, although close to the free-spin value, deviate by small but significant amounts in a number of complexes. Similar results have been obtained for metal phthalocyanine negative ions in dimethylformamide solution,⁶ also obtained by electrolytic reduction. The lack of hyperfine structure in these spectra has been explained on the basis that the electron is in a doubly degenerate orbital and that the separation of the hyperfine lines in the monoanion in which the spin density is averaged by "fast switching" perturbations (internal or external) to reflect the molecular symmetry is predicted to be smaller than individual line widths.

We have observed similar single-line electron spin resonance spectra of porphin mononegative ions obtained by reduction with sodium metal in tetrahydrofuran solution. The solutions (10^{-3} – 10^{-4} M) were prepared by a technique described elsewhere.⁹ The electron spin resonance measurements were made at room temperature using a Varian V-4500 X-band spectrometer. Three molecules have so far been studied: zinc tetrabenzporphin, zinc etioporphin I, and etioporphin I (Figure 1). For the latter molecule, the initial reaction with sodium is replacement of the two central ring hy-

(1) (a) Bristol University, Bristol, England. (b) Southwest Research Institute, San Antonio, Texas.

(2) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **85**, 818 (1963).

(3) J. W. Dodd and N. S. Hush, *J. Chem. Soc.*, 4607 (1964).

(4) D. W. Clack and N. S. Hush, *J. Am. Chem. Soc.*, **87**, 4238 (1965).

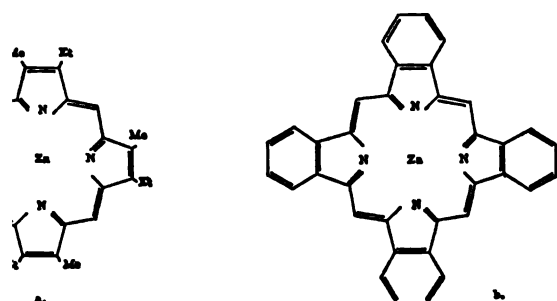
(5) R. W. Felton and H. Linschitz, *ibid.*, **88**, 1113 (1966).

(6) D. W. Clack and N. S. Hush, unpublished data.

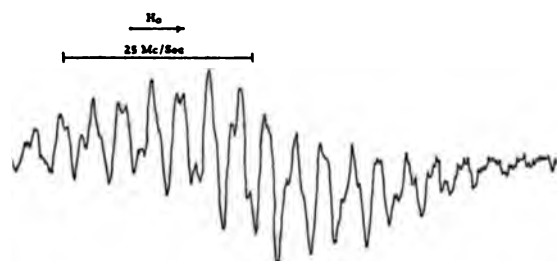
(7) N. S. Hush, *Theoret. Chim. Acta*, **4**, 108 (1966).

(8) D. H. Whiffen, *Mol. Phys.*, **6**, 223 (1963).

(9) N. S. Hush and J. R. Rowlands, *ibid.*, **6**, 317 (1963).



(a) Zinc etioporphyrin I; (b) zinc tetrabenzporphyrin.



Hyperfine structure of reduced zinc tetrabenzporphyrin.

atoms;³ reduction of the disodium complex proceeds in successive one-electron steps.

the reduction was allowed to proceed past the gative ion stage in dilute solution, different were obtained. In this case, the electron spin ce spectra of the solution began to exhibit hyper- icture, which was better resolved as the reduc- ceeded.

course of the reaction was qualitatively followed rving the characteristic color changes.³ Thus, : etioporphyrin, hyperfine structure appeared e green mononegative ion was almost entirely d to the crimson dinegative ion. The spectra l for zinc tetrabenzporphyrin and zinc etiopor- olutions are shown in Figures 2 and 3, respec- These exhibit similar hyperfine patterns. xtrum obtained from etioporphyrin solutions 4) is not so well resolved as the previous two.

irst possibility to consider is that these spectra e of ions produced by the addition of three s to the lowest e_g antibonding orbital. It is ediatly obvious, however, why the trinegative $^{3-}$ should yield an electron spin resonance n with hyperfine structure whereas both we and orkers⁵ have shown that the mononegative ion ingle-line electron spin resonance spectrum with rvable structure. Furthermore, the observed e is not compatible with that predicted for a on. As in the MP^- ion (as mentioned above) e electrons in the trinegative ion MP^{3-} are in a degenerate orbital,³ and the spin density distri- will depend on the type of external or internal ation coupling the two components. The aver- ration of the lines predicted⁵ for a system frozen : e_{gx} (or e_{gy}) configuration for an average com- $(1/\sqrt{2})(e_{gx} + e_{gy})$, or for "rapid switching"

the two components, is less than line widths observed for ions with 3E ground states. Never- our observed spectra for zinc tetrabenzporphyrin : etioporphyrin (Figures 5 and 6, respectively)

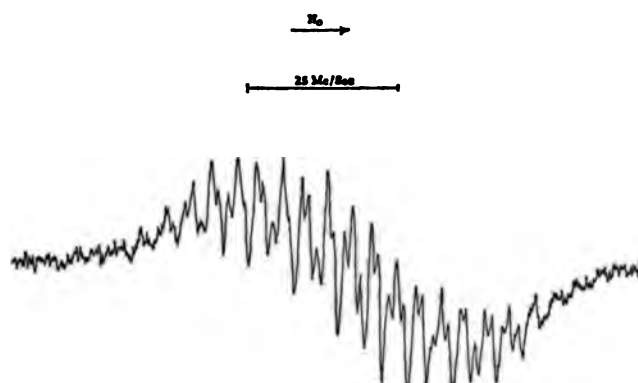


Figure 3. Hyperfine structure of reduced zinc etioporphyrin.

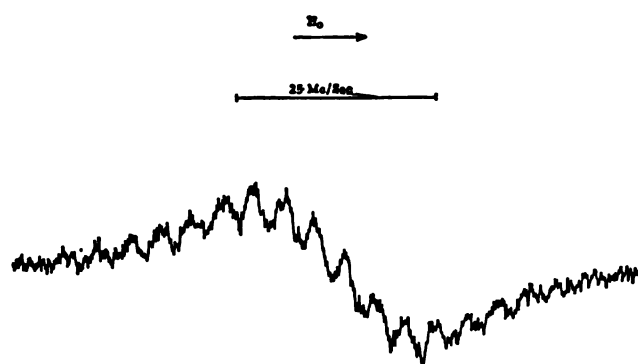


Figure 4. Hyperfine structure of reduced etioporphyrin I.

are at least compatible with the interaction of an un- paired electron with four equivalent nitrogen atoms and four equivalent protons with coupling constants as in Table I, if some allowance is made for some minor inconsistencies in the relative intensity distributions. These discrepancies could well arise from incomplete averaging to zero of both the anisotropic hyperfine interactions and quadrupole interactions. The poor agreement between the computed spin density distribu- tion and the observed could well arise from the fact that no attempt has been made to allow for configuration interaction.

Table I. Observed and Calculated Hyperfine Splittings*

	Obsd, gauss	Calcd, gauss	
		$\delta = 0$	$\delta = 1.0$
Zinc tetrabenzporphyrin	A_N 2.59		
	A_H 1.55		
Zinc etioporphyrin I	A_N 2.62	1.36	0.725
	A_H 1.63	2.25	2.58

* Calculated values were taken from ref 4.

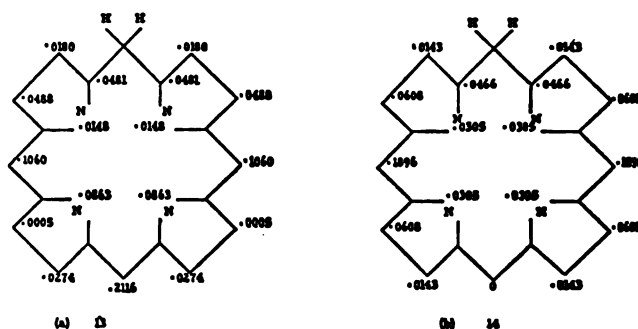
A second possibility to be considered is that the ion giving rise to the observed structure is the phlorin di- negative ion. It is known from previous work^{2,3} that the dinegative ions are relatively easily protonated, and that even in apparently aprotic solvents it is difficult to obtain dilute solutions of the dinegative ions of porphyrins free from protonated species. Protonation of the dinegative ion of zinc $\alpha,\beta,\gamma,\delta$ -tetraphenylporphyrin in tetrahydrofuran leads to the formation of a salt of the phlorin anion $ZnPH^-$, where the hydrogen has added

$$2\text{ZnP}^- + \text{H}^+ \longrightarrow \text{ZnP} + \text{ZnPH}^-$$

It is not accidental that the porphin ϵ_g energy level also occurs in the energy spectrum of the protonated species within the framework of Hückel theory. It is easily shown that doubly degenerate energy levels E_i of an n -center system A will each occur once in the $(n - 1)$ -center system A' derived from A by removal of one of the centers. Furthermore, where the wave functions $|e_i\rangle$ of A, with real components $|e_{1i}\rangle$ and $|e_{2i}\rangle$, are written as linear combination of one-center functions $|\phi_i\rangle$, *i.e.*

$$|e_{1i}\rangle = \sum_{j=1}^A C_{1ij} |\phi_j\rangle$$

$$|e_{2i}\rangle = \sum_{j=1}^A C_{2ij} |\phi_j\rangle$$



14

13

A

B

$$|i(A')\rangle = \frac{1}{\sqrt{1+\lambda^2}}\{|e_{1i}\rangle + \lambda|e_{2i}\rangle\}$$

The distribution in this orbital will give rise to a complex hyperfine pattern, which does not appear to be compatible with any observed. One reason for this may be that configuration interaction has not been taken into account. It is known that the formation of porphyrin dinegative ions P^{2-} or MP^{2-} from porphyrin is not satisfactorily described as addition of two electrons to the lowest porphyrin e_g level. If this were so, the ground state would be a triplet, and the fact that it is, in all cases so far examined, a singlet state shows that configuration interaction with excited states is important in determining the ground-state properties. It is equally likely that the ground state of PH^{2-} is strongly influenced by configuration interaction. It is even possible that the ground state may be the Hückel excited state b in Figure 8 in which an electron has been promoted from the penultimate doubly filled level. The Hückel energy difference between these levels is 0.3131β for the phlorin dianion derived from porphyrin. However, even this possibility would lead to a calculated hyperfine spectrum which is not compatible with the observed spectra. Taking the values $Q_H = 25$ gauss, $Q_N = 30$ gauss, $Q_{CH_3} = 35$ gauss, the hyperfine constants

for the three methine hydrogen atoms (Q_H), the nitrogen atom (Q_N), and the methylene group (Q_{CH_2}) are $A_H = 2[65(2)]$, $5[29(1)]$, $A_N = 2[61(2)]$, and $A_{CH_2} = 6[79(2)]$ gauss, respectively. In computing the methylene coupling we have taken the spin density to be proportional to the square of the sum of the coefficients of the H orbital at each carbon atom, *i.e.*, of the form $Q(C_1 + C_2)^2$ rather than $Q(C_1^2 + C_2^2)$.⁸ These couplings would lead to a spectrum with a width of 40 gauss which is far in excess of the experimental spectrum. Furthermore, in order to fit the total number of lines observed, further hyperfine interactions with peripheral methylene groups would have to be invoked, which would make the situation worse.

It is clear on the basis of this discussion that much further experimental work on a range of substituted porphyrin structures must be carried out before definitive

analysis can be attempted. It is also clear that simple Hückel spin density calculations are not sufficiently accurate for meaningful theoretical predictions to be made of the nature of these porphyrin reduction products.

We note in conclusion that Mauzerall and Feher¹⁰ have obtained a transient paramagnetic radical by irradiation of porphyrin-phlorin mixtures in glycerine solution. This is probably the neutral phlorin radical PH. The identification of intermediates of this type is essential for an understanding of porphyrin oxidation-reduction reactions, and for an understanding of the electron spin resonance signals observed in photosynthetic materials.¹¹

(10) D. Mauzerall and G. Feher, *Biochim. Biophys. Acta*, **79**, 430 (1964).

(11) B. Commoner, J. Townsend, and G. E. Pake, *Nature*, **174**, 4432 (1954).

Photochemical Conversion of 7-Methoxycycloheptatriene to 1-Methoxybicyclo[3.2.0]hepta-3,6-diene¹

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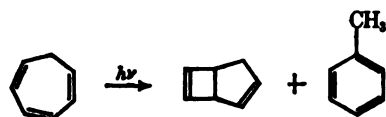
Contribution from the Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50010. Received February 7, 1967

Abstract: The photochemical conversion of 7-methoxycycloheptatriene to 1-methoxybicyclo[3.2.0]hepta-3,6-diene is shown to involve initial photoisomerization to 1-methoxycycloheptatriene followed by photochemical valence isomerization to the bicyclic product. Irradiation of 1-methoxycycloheptatriene gives 7-methoxycycloheptatriene and the bicyclic valence tautomer. The sigmatropic reactions of order [1,7] involved in the interconversion of 7-methoxycycloheptatriene and 1-methoxycycloheptatriene are shown to arise from singlet states. The 1,7-hydrogen shift by which 1-methoxycycloheptatriene is converted to 7-methoxycycloheptatriene is remarkably specific. No 2-methoxycycloheptatriene could be detected. The photochemical valence tautomerization of 1-methoxycycloheptatriene to 1-methoxybicyclo[3.2.0]hepta-3,6-diene is shown to arise from a singlet state of the triene.

Photoisomerization of cycloheptadienes, cycloheptatrienes, and tropolones to unsaturated derivatives of bicyclo[3.2.0]heptane is one of the most generally applicable photochemical reactions.³ Irradiation of cycloheptatriene gives both toluene and bicyclo[3.2.0]hepta-2,6-diene.^{3,4} Toluene is the major product in the vapor phase⁴ and the bicyclic valence tautomer in solution.⁵ Irradiation of certain substituted cyclo-

heptatrienes gives rise to 1,5-hydrogen shifts which lead to isomeric cycloheptatrienes when substituents are present.⁹ More complex thermal isomerizations are observed with 7,7-disubstituted cycloheptatrienes.¹⁰

We now wish to report a photoisomerization reaction which is anomalous both in solution and in the vapor phase with respect to the behavior of cycloheptatriene. Irradiation of 7-methoxycycloheptatriene or 7-ethoxycycloheptatriene in ether solution gives in each case the 1-alkoxybicyclo[3.2.0]hepta-3,6-diene. Yields in excess of 90% have been obtained, and vpc and nmr analysis of the crude reaction mixture shows that the reactions are essentially quantitative.



heptatrienes gives isomeric cycloheptatrienes by 1,7-hydrogen shifts.⁶⁻⁸ Thermal isomerization of cyclo-

(1) A preliminary report of portions of this research has been published: O. L. Chapman and G. W. Borden, *Proc. Chem. Soc.*, 221 (1963). Portions of this work were abstracted from the thesis of G. W. Borden, Iowa State University, 1963. Photochemical Transformations. XIX.

(2) (a) Predoctoral Fellow, National Institutes of Health, 1961-1963; (b) Postdoctoral Fellow, National Institutes of Health, 1965-1966.

(3) For a review see O. L. Chapman, *Advan. Photochem.*, **1**, 323 (1963).

(4) R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 3432 (1962).

(5) W. G. Dauben and R. L. Cargill, *Tetrahedron*, **12**, 186 (1961).

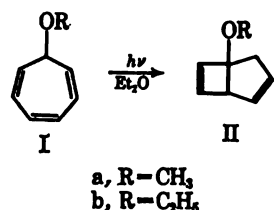
(6) W. von E. Doering and P. P. Gaspar, *J. Am. Chem. Soc.*, **85**, 3043 (1963).

(7) W. R. Roth, *Angew. Chem.*, **75**, 921 (1963).

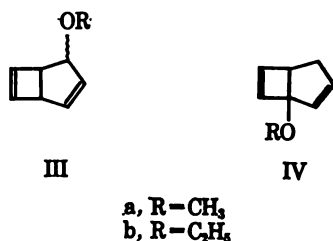
(8) A. P. ter Boorg and H. Kloosterziel, *Rec. Trav. Chim.*, **84**, 241 (1965).

(9) (a) G. Büchi and E. M. Burgess, *J. Am. Chem. Soc.*, **84**, 3104 (1962); (b) A. P. ter Boorg, H. Kloosterziel, and N. van Meurs, *Proc. Chem. Soc.*, 359 (1962); (c) A. P. ter Boorg, H. Kloosterziel, and N. van Meurs, *Rec. Trav. Chim.*, **82**, 717, 741, 1189, (1963); (d) E. Weth and A. S. Dreiding, *Proc. Chem. Soc.*, 59 (1964); (e) A. P. ter Boorg and H. Kloosterziel, *Rec. Trav. Chim.*, **84**, 245 (1965); (f) H. J. Dauben, private communication.

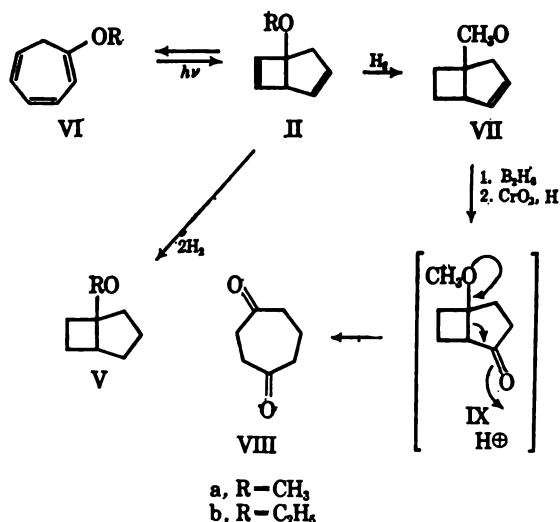
(10) J. A. Berson and M. R. Willcott, III, *J. Am. Chem. Soc.*, **87**, 2751, 2752 (1965); **88**, 2494 (1966).



The ultraviolet spectra of the photoproducts show no maxima above 220 mμ, which suggests bridging of the ring. The nmr spectra of the photoproducts IIa and b show in each case four olefinic protons, three protons on saturated carbon, and methoxyl (IIa) or ethoxyl (IIb) protons. The presence of the cyclobutene double bond could be detected by the characteristic coupling constant (IIa, 2.9 cps)¹¹ and field position (IIa, τ 3.80; IIb, τ 3.77). The first indication that the photoproducts were not the simple valence tautomers IIIa and b was the absence of a resonance characteristic of the >CHOR group in the nmr spectra of the tetrahydro derivatives

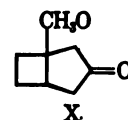


of the photoproducts. This must mean that the alkoxy functions are at the bridgehead in the tetrahydro derivatives Va and b and consequently that the photoproducts are either IIa and b or IVa and b. A decision in favor of the 1-alkoxybicyclo[3.2.0]hepta-3,6-diene structures (IIa and b) was possible on the basis of the thermal transformations of the photoproducts. When IIa and b were dropped through a pyrolysis column preheated to 340–350° the sole products were 1-methoxycycloheptatriene (VIa) and 1-ethoxycycloheptatriene (VIb) respectively. A control experiment showed that the 7-alkoxycycloheptatrienes (Ia and b) were converted only partially to the 1-alkoxycycloheptatrienes (VIa



(11) O. L. Chapman, *J. Am. Chem. Soc.*, **85**, 2014 (1963); P. Laszlo and P. von R. Schleyer, *ibid.*, **85**, 2016 (1963); G. V. Smith and H. Kriloff, *ibid.*, **85**, 2017 (1963).

and b) under identical conditions.¹² Irradiation of the 1-alkoxycycloheptatrienes gave the valence tautomers IIa and b. Confirmation of the assigned structures was obtained by the sequence of reactions described below. In the reduction of the photoproducts it had been noted that the two double bonds were reduced at different rates. Addition of 1 equiv of hydrogen gave the dihydro derivative VII in which the cyclobutene double bond had been selectively reduced. The nmr spectrum of VII showed a multiplet at τ 4.30 due to the cyclopentene protons. The characteristic absorption of the cyclobutene protons (τ 3.80) was no longer present. Hydroboration followed by chromic acid oxidation¹³ gave 1,4-cycloheptanedione (VIII). Hydroboration and oxidation of VII could give rise to two possible ketones IX and X. No evidence for the pres-



ence of X was obtained. Tetrahydropseudo- γ -tropolone methyl ether (IX) is known to be transformed rapidly to 1,4-cycloheptanedione in acid solution.¹⁴ The alternate structure IVa for the photoproduct cannot account for the formation of VIII since the oxygen functions after partial reduction, hydroboration, and oxidation of IV must be either 1,2 or 1,3 with respect to each other rather than 1,4 as required by the formation of VIII.

Irradiation of 7-methoxycycloheptatriene at low pressure in the vapor phase gave a mixture which consisted of 7-methoxycycloheptatriene (14%), 1-methoxycycloheptatriene (38%), and 1-methoxybicyclo[3.2.0]hepta-3,6-diene (48%). This was the first indication that 1-methoxycycloheptatriene might be an isolable intermediate in the formation of IIa and suggested that the reaction in solution should be monitored carefully.

The photochemical transformation of 7-methoxycycloheptatriene was monitored by ultraviolet and nmr spectroscopy and by vapor phase chromatography.¹⁵ The ultraviolet spectra of the solution during irradiation show disappearance of the 255-mμ maximum of 7-methoxycycloheptatriene and appearance and decay of a maximum at about 280 mμ. Both vapor phase chromatography and nmr spectra show the formation and destruction of an intermediate (Figures 1 and 2). Isolation of the intermediate and comparison of spectra identified it as 1-methoxycycloheptatriene (VIa). Careful monitoring of the photochemical rearrangement of 7-methoxycycloheptatriene (Ia) in the early phase of the reaction showed that 1-methoxycycloheptatriene (VIa) was the sole primary product since the concentration *vs.* time plot for this substance extrapolated to zero at zero time (Figure 3).

(12) The thermal isomerization of 7-methoxycycloheptatriene has been studied in detail.^{14d,f} The first product from 7-methoxycycloheptatriene is 3-methoxycycloheptatriene and the second is 1-methoxycycloheptatriene. More extensive rearrangement would have been observed at the temperatures used except for the very short residence time in the pyrolysis column.

(13) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961).

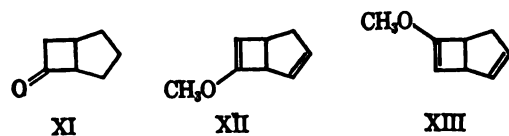
(14) O. L. Chapman and D. J. Pasto, *ibid.*, **82**, 3642 (1960).

(15) Under the conditions of the analysis, 7-methoxycycloheptatriene isomerized to 3-methoxycycloheptatriene. Both 1-methoxycycloheptatriene and 1-methoxybicyclo[3.2.0]hepta-3,6-diene were stable to the conditions.

lar extrapolation for 1-methoxybicyclo[3.2.0]-1,3,6-diene (IIa) did not pass through the origin (see 3). The bicyclic product (IIa) thus is a secondary product formed only after 1-methoxycycloheptatriene is formed. It should be noted that the bicyclic photoproduct is formed very early in the reaction when a relatively small fraction of the light is being absorbed by VIa. The photoisomerization of VIa to I has must be a reasonably efficient process (see Figures 4 and 5 for nmr spectra of VIa and IIa, respectively).

No evidence for any intermediate beside 1-methoxycycloheptatriene was obtained. A sequence of two hydrogen transfer processes (known to occur naturally)^{14,15} could convert 7-methoxycycloheptatriene to methoxycycloheptatriene. If this were the case, methoxycycloheptatriene would be an intermediate between 7-methoxycycloheptatriene and 1-methoxycycloheptatriene. With this in mind, 3-methoxycycloheptatriene was irradiated. The reaction mixture was complex in contrast to the clean reactions of 7-methoxycycloheptatriene and 1-methoxycycloheptatriene. The crude product was separated into two fractions. The first fraction was shown to contain at least three bicyclic compounds. One was separated and identified as 1-methoxybicyclo[3.2.0]hepta-3,6-diene (IIa).

The other two bicyclic compounds were not separated. Hydrolysis of the mixture gave rise to infrared carbonyl absorptions characteristic of five-membered and four-membered ring ketones suggesting presence of enol ethers. Reduction of the mixture after work-up, bicyclo[3.2.0]heptan-6-one (XI) was identified by comparison of its infrared spectrum with that of an authentic sample.¹⁶ The formation of XI suggests that XII and/or XIII is present in the mixture. The second fraction consisted of a mixture of methoxy-



heptatrienes.¹⁷ The nature of the photoproducts of 3-methoxycycloheptatriene makes it very clear it is not an intermediate in the photochemical rearrangements of 7-methoxycycloheptatriene.

Irradiation of 1-methoxycycloheptatriene for short periods of time gave 1-methoxybicyclo[3.2.0]hepta-3,6-diene (IIa) and 7-methoxycycloheptatriene (Ia). Longer irradiation gave only the bicyclic valence tautomer IIa. A photostationary state is thus established between 7-methoxycycloheptatriene and 1-methoxycycloheptatriene which is displaced by conversion of methoxycycloheptatriene to 1-methoxybicyclo[3.2.0]-1,3,6-diene. Two points of substantial interest arise when one considers the reactions involved. First, is it that the 1,7-hydrogen shift in VI is so specific,

The mode of formation of XI is not completely clear. It might be a reductive cleavage of the ether or more likely hydrolysis of a derivative of XII or XIII in work-up. The authentic sample of XI was prepared by D. L. Garin, Ph.D. Thesis, Iowa State University,

It can be argued that the mixture of methoxycycloheptatrienes is an artifact resulting from the work-up procedure. The mixture of bicyclic compounds, however, must have been formed in a photochemical process and clearly shows that the photochemical transformations of methoxycycloheptatriene are less specific than those of 7-methoxycycloheptatriene and 1-methoxycycloheptatriene.

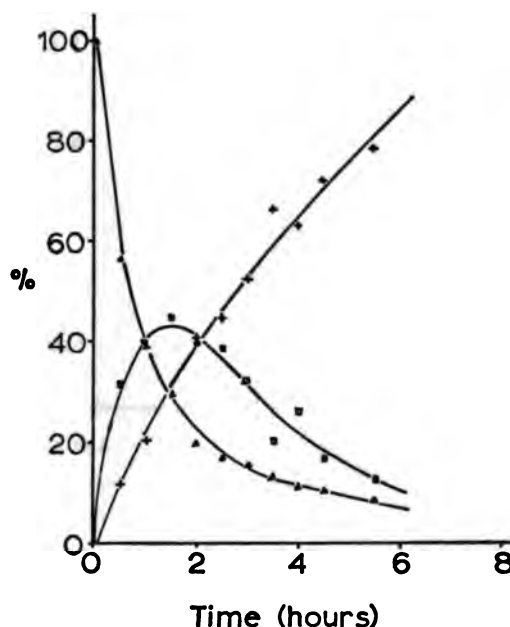
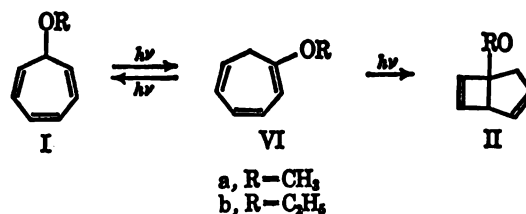


Figure 1. Plot of per cent 7-methoxycycloheptatriene (Ia, Δ), 1-methoxycycloheptatriene (VIa, □), and 1-methoxybicyclo[3.2.0]hepta-3,6-diene (IIa, +) vs. time of irradiation.

i.e., why is no 2-methoxycycloheptatriene formed? Second, why is isomerization to the bicyclic valence tautomer so much more efficient when a methoxyl



group is present in the 1 position?¹⁸ The specificity of the 1,7-hydrogen shift in VIa is even more dramatic when considered in the light of the lack of specificity in the reactions of 3-methoxycycloheptatriene and other substituted cycloheptatrienes.⁶⁻⁸

The multiplicities of the states responsible for the reversible 1,7-hydrogen shifts and the photoisomerization to the bicyclic system are of some interest. The photoisomerization of 7-methoxycycloheptatriene to 1-methoxycycloheptatriene was not sensitized by acetophenone ($E_t \sim 74$ kcal/mole)¹⁹ and was not quenched by oxygen. The photosensitization experiments with 7-methoxycycloheptatriene were very clean because the absorption of 7-methoxycycloheptatriene above 3400 Å is negligible. The filter system used had zero transmission below 3400 Å and 65% transmission at 3600 Å. All of the light was absorbed by the sensitizer, and no reaction could be detected by vpc analysis. Acetophenone ($E_t \sim 74$ kcal/mole) should have a sufficiently high triplet energy to transfer energy to the triene. The triplet energy of cycloheptatrienes is not known but should lie between that of simple olefins (ethylene, 82 kcal/mole)²⁰ and planar trienes (*trans*-1,3,5-hexa-

(18) Photoisomerization of cycloheptatriene⁴ in solution requires several days' irradiation while photoisomerization of 1-methoxycycloheptatriene under comparable conditions requires only a few hours' irradiation.

(19) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 4537 (1964).

(20) D. F. Evans, *J. Chem. Soc.*, 1735 (1960).

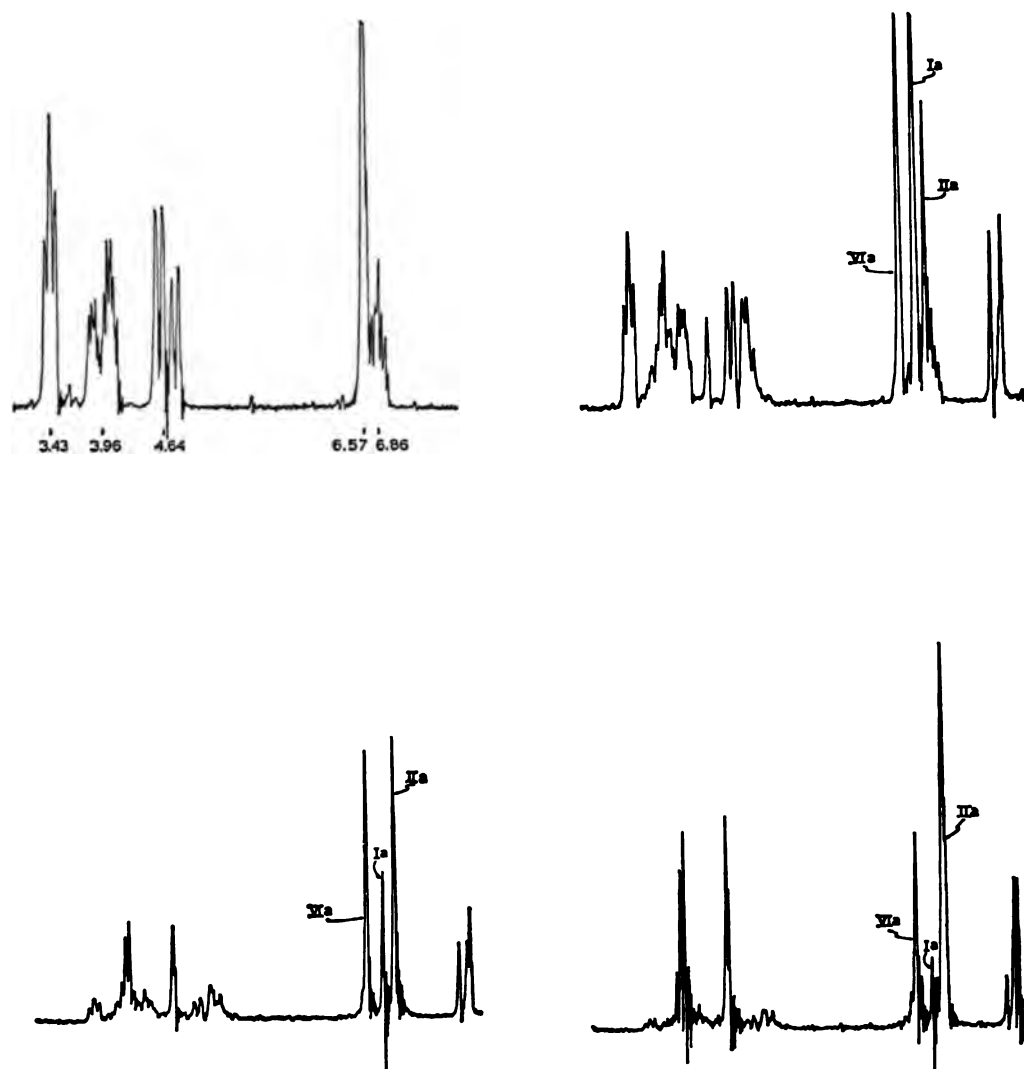


Figure 2. Upper left, 7-methoxycycloheptatriene (Ia) before irradiation. Resonance positions are given on the τ scale relative to internal tetramethylsilane. Upper right, sample after irradiation for 30 min. Lower left, sample after irradiation for 120 min. Lower right, sample after irradiation for 270 min.

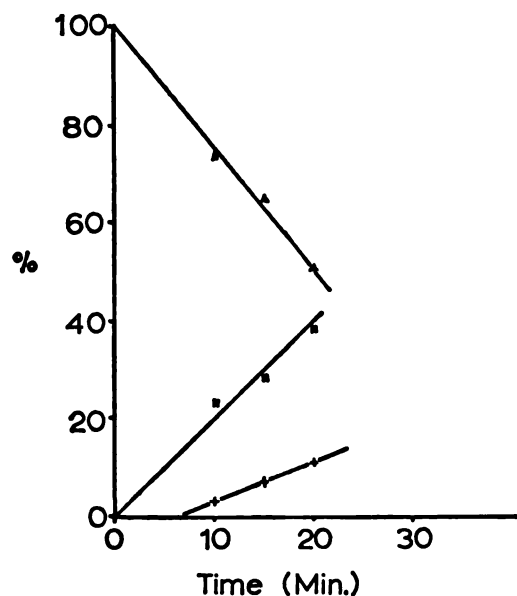
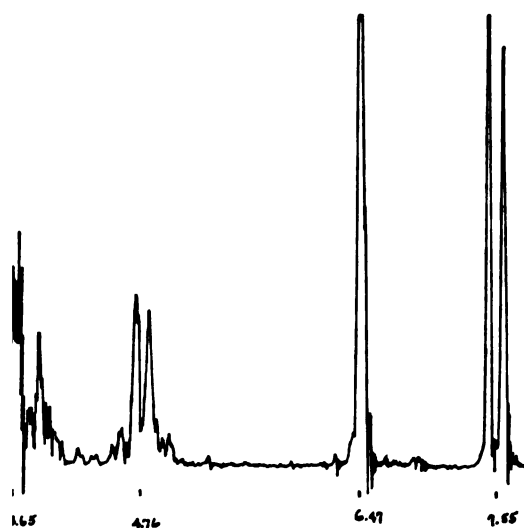


Figure 3. Plot of per cent 7-methoxycycloheptatriene (Ia, Δ), 1-methoxycycloheptatriene (VIa, \square), and 1-methoxybicyclo[3.2.0]hepta-3,6-diene (IIa, $+$) vs. time for the first 20 min of irradiation (vpc analysis).

triene, 47 kcal/mole)²⁰ and is probably somewhat closer to the latter.²¹ Neither the conversion of 1-methoxycycloheptatriene to 7-methoxycycloheptatriene nor the conversion to 1-methoxybicyclo[3.2.0]hepta-3,6-diene was affected significantly by oxygen. No evidence for photosensitization of either process by acetophenone was obtained. The photosensitization experiments were somewhat more complicated in this case because 1-methoxycycloheptatriene (λ_{\max} 290 m μ) has significant absorption above 3400 Å (ϵ_{3400} 4.1) and because it gives two products. The results, however, make it clear that reaction is much slower when most of the light is absorbed by sensitizer. When enough sensitizer is present to absorb >88% of the incident light, reaction is too slow to be detected in the usual irradiation period (1 hr).

(21) The nonplanar ground state of cycloheptatrienes makes it difficult to extrapolate the available results. Furthermore, it is clear that ring size affects triplet energy (1,3-cyclopentadiene, E_t = 58.4; 1,3-cyclohexadiene, E_t = 53.5 kcal/mole).²⁰ If 7-methoxycycloheptatriene is assumed to have a singlet (S_1)-triplet (T_1) gap of the same energy as *trans*-1,3,5-hexatriene (59.8 kcal/mole)²⁰ and the maximum (2550 Å) of the $S_0 \rightarrow S_1$ absorption band is used as a measure of the $S_0 \rightarrow S_1$ transition energy, the result is an estimated triplet energy of about 52 kcal/mole, which is in a reasonable range.



Nuclear magnetic resonance spectrum of 1-methoxycycloheptatriene (VIa). Calibration is on the τ scale relative to tetramethylsilane.

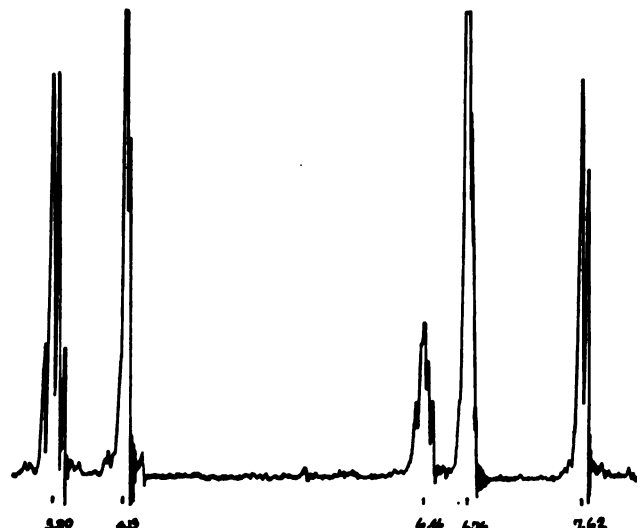
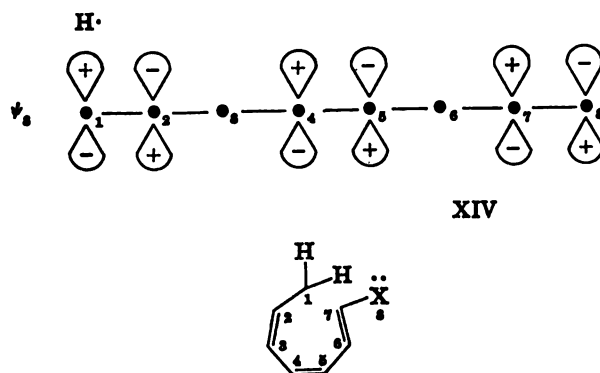


Figure 5. Nuclear magnetic resonance spectrum of 1-methoxybicyclo[3.2.0]hepta-3,6-diene (IIa). Calibration is on the τ scale relative to internal tetramethylsilane.

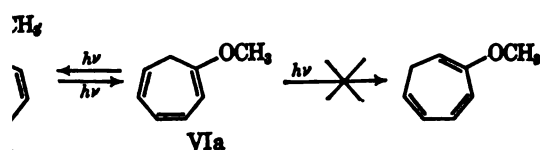
It is reasonable to conclude that the reversible chemical 1,7-hydrogen shift between 7-methoxycycloheptatriene and 1-methoxycycloheptatriene in a singlet state regardless of which compound absorbs the light. This conclusion is in accord with the recognized inefficiency of intersystem crossing in conjugated olefins.²⁰ There remains a question whether the reaction occurs *via* an electronic excited state or a vibrationally excited ground state. The thermal isomerization gives products derived from 5-hydrogen atom shifts does not preclude reaction *via* a vibrationally excited ground state. No essential distinction between the two possibilities is possible, although it seems reasonable that vibrational activation would be extremely rapid in solution. Orbital symmetry arguments also suggest that the conversion of I and VI occurs *via* electronic states.²² We conclude that the photochemical conversion of 7-methoxycycloheptatriene and 1-methoxycycloheptatriene probably proceeds *via* the singlet excited state of the triene in each case. The specificity of the photochemical interconversion of methoxycycloheptatriene and 1-methoxycycloheptatriene is of special interest. Orbital symmetry arguments suggest that photochemical, suprafacial, electrocyclic reactions of order [1,7] are allowed in cycloheptatrienes.²² This suggestion is consistent with experimental observation.⁶⁻⁸ A single sigmatropic shift of order [1,7] is possible for 7-methoxycycloheptatriene and leads to 1-methoxycycloheptatriene. Alternating sigmatropic shifts are possible for 1-methoxycycloheptatriene which should lead to 7-methoxy-

methoxycycloheptatriene is observed. Orbital symmetry arguments apply only to processes in which the transition state has some element of symmetry. Previously developed orbital symmetry arguments for hydrogen transfer reactions have been applied only to transfers between the terminals of systems of the type $>\text{CH}(\text{C}=\text{C})_m$.²³ In these cases the symmetry of the highest occupied molecular orbital is the controlling factor. The transition state for the conversion of VIa to Ia is asymmetric, and simple orbital symmetry arguments cannot be applied. It is interesting to note,



however, that the highest occupied molecular orbital (ψ_6 , XIV) for the electronically excited nine-electron, eight-atom π system²³ is such that suprafacial hydrogen transfer from position 1 to position 7 with continuous overlap is feasible,²⁴ while suprafacial transfer from position 1 to position 2 with continuous overlap is not feasible.

Photochemical valence isomerization of conjugated dienes to cyclobutenes involves singlet excited states in certain cases and triplet excited states in others. Srinivasan has shown that a singlet excited state is the reactive species in the valence isomerization of cycloheptatriene and has provided other examples of valence



cycloheptatriene and 2-methoxycycloheptatriene. Experimentally, only the sigmatropic shift leading to 7-

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(23) The ether oxygen atom with two electrons is included in the basic π system.

(24) In general, for systems in which two or more sigmatropic reactions of order [1, j] are possible, the reaction with the highest value of j is favored. This may be a consequence of the greater degree of conjugation in the transition state for the process with the highest value of j .²²

tautomerization *via* singlet excited states.^{4,25} Schenck and co-workers²⁶ have noted photosensitization of the valence tautomerization of *cis,cis*-1,3-cyclooctadiene, and Dauben and co-workers²⁷ have demonstrated photosensitization of the valence tautomerization of 1,1-bicyclohexenyl and have provided additional examples which proceed *via* singlet excited states. Liu²⁸ has shown that the photosensitized isomerization of *cis,cis*-1,3-cyclooctadiene first gives *cis,trans*-1,3-cyclooctadiene which undergoes thermal cyclization to bicyclo[4.2.0]oct-7-ene in the manner described by Fonken and co-workers.²⁹ Liu²⁸ has suggested that a similar sequence of reactions may occur in 1,1'-bicyclohexenyl.

In the photoisomerization of 1-methoxycycloheptatriene to 1-methoxybicyclo[3.2.0]hepta-3,6-diene it is clear that the reaction is not quenched by oxygen. Addition of acetophenone to the solution slows the reaction because of light absorption by the sensitizer. No photosensitization is observed. It thus seems likely that the triplet excited state is not involved in formation of the valence tautomer IIa. This again poses the problem of electronic *vs.* vibrational excitation. Formation of 1-methoxybicyclo[3.2.0]hepta-3,6-diene is favored in solution but not in the vapor phase. This observation strongly suggests that the reaction proceeds through an electronic excited state rather than a vibrationally excited ground state. Molecular orbital arguments also suggest that an electronic excited state is the species responsible for valence isomerization.³⁰

Experimental Section

Analytical Techniques. Nuclear magnetic resonance spectra were recorded at 60 Mc on either a Varian Associates A-60 analytical nmr spectrometer or upon a Varian Associates HR-60 nmr spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 21 double-beam infrared spectrophotometer. Ultraviolet spectra were recorded on a Beckman DK-2A ratio recording spectrophotometer. Gas chromatographic analyses were performed on an F & M Model 500 programmed temperature gas chromatograph or a Perkin-Elmer vapor fractometer using helium as a carrier gas at flow rates from 40 to 100 cc/min. Individual columns and conditions of chromatography are described as they appear in the Experimental Section.

Solvents. Benzene (Matheson Coleman and Bell) was purified just prior to use by the method of Fieser.³¹ Ethyl ether (Mallinckrodt) was distilled from phosphorus pentoxide and stored over sodium wire. Oxygen was removed by bubbling nitrogen gas through these solvents for 1 hr just prior to use.

Filter Solution. The filter solution used in this work was prepared by dissolving 0.600 g of 2,7-dimethyl-3,6-diazacyclohepta-1,6-diene perchlorate³² and 25 g of potassium hydrogen phthalate in 1 l. of water. This solution (1 ml), diluted to 10 ml with water, gave 65% transmission of light at 3660 Å and no transmission below 3400 Å (1-cm path).

(25) R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 4141 (1962); **85**, 4045 (1963).

(26) G. O. Schenck and R. Steinmetz, *Bull. Soc. Chim. Belges*, **71**, 781 (1962).

(27) W. G. Dauben, R. L. Cargill, R. M. Coates, and J. Saltiel, *J. Am. Chem. Soc.*, **88**, 2742 (1966); W. G. Dauben, *Pure Appl. Chem.*, **9**, 539 (1964).

(28) R. S. H. Liu, *J. Am. Chem. Soc.*, **89**, 112 (1967).

(29) K. M. Shumate, P. N. Neuman, and G. J. Fonken, *ibid.*, **87**, 3996 (1965).

(30) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965); H. C. Longuet-Higgins and E. W. Abrahamson, *ibid.*, **87**, 2045 (1965); H. E. Zimmerman, *ibid.*, **88**, 1564, 1566 (1966).

(31) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p 282.

(32) G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1139 (1940).

Preparation of 7-Methoxycycloheptatriene (I). Tropilidine chloride prepared by the method of Kursanov³³ was used to prepare 7-methoxycycloheptatriene according to the procedure of Doering and Knox.³⁴

Preparation of 3-Methoxycycloheptatriene. This material was prepared in 76% yield by the method of Weth and Dreiding,³⁴ bp 74–75° (25 mm).

Preparation of 1-Methoxycycloheptatriene (VIa). This material was prepared in 63% yield from 7-methoxycycloheptatriene according to the method of Weth and Dreiding,³⁴ bp 77–80° (30 mm).

Irradiation of 7-Methoxycycloheptatriene. A solution of 8.0 g (0.065 mole) of 7-methoxycycloheptatriene in 2.0 l. of anhydrous, oxygen-free ether was irradiated with a quartz-jacketed Hanovia immersion lamp (Type A) for 8 hr. After evaporation of the solvent, the residue was distilled through a short column to give 9.4 g (92%) of 1-methoxybicyclo[3.2.0]hepta-3,6-diene [bp 39° (20 mm)]. This was the highest yield obtained. Yields varied substantially (25–92%) and seemed to depend on the amount of polymerization during distillation. Vapor phase chromatography (using internal standards) and nmr analysis of the crude product showed an essentially quantitative yield of 1-methoxybicyclo[3.2.0]hepta-3,6-diene.

Anal. Calcd for C₈H₁₀O: C, 78.65; H, 8.25. Found: C, 78.83; H, 8.36.

1-Ethoxybicyclo[3.2.0]hepta-3,6-diene. A solution of 7-ethoxycycloheptatriene (10 g) in absolute ether (2 ml) was irradiated 8 hr with a Hanovia immersion lamp (Type A) encased in a quartz immersion well. Distillation of the ethereal solution through a short Vigreux column gave 1-ethoxybicyclo[3.2.0]hepta-3,6-diene (9.1 g, 91%), bp 47° (21 mm).

Anal. Calcd for C₉H₁₂O: C, 79.37; H, 8.88. Found: C, 79.53; H, 8.83.

Pyrolysis of 1-Ethoxybicyclo[3.2.0]hepta-3,6-diene. 1-Ethoxybicyclo[3.2.0]hepta-3,6-diene (2.0 g) was dropped into a preheated (340°) vertically mounted pyrolysis column packed with Pyrex helices and swept through with a stream of dry nitrogen. The exit from the pyrolysis column was connected to a trap immersed in a Dry Ice-acetone bath. The infrared, ultraviolet, and nmr spectra of the material collected in the trap were identical with those of an authentic sample of 1-ethoxycycloheptatriene.

A control experiment in which 7-ethoxycycloheptatriene was put through the same pyrolysis column at 340° gave only 30% 1-ethoxycycloheptatriene. At 410° complete conversion to 1-ethoxycycloheptatriene was achieved. The product in this case was isolated in 71% yield.

Pyrolysis of 1-Methoxybicyclo[3.2.0]hepta-3,6-diene. 1-Methoxybicyclo[3.2.0]hepta-3,6-diene was pyrolyzed in the manner described above with the column preheated at 352°. The product was identified by comparison of spectra with an authentic sample of 1-methoxycycloheptatriene.

In a control experiment pyrolysis of 7-methoxycycloheptatriene at 350° in the same column gave less than 40% conversion to 1-methoxycycloheptatriene. At 420° conversion was complete and 1-methoxycycloheptatriene was isolated in 74% yield.

1-Ethoxybicyclo[3.2.0]heptane. Platinum oxide (20 mg) in carbon tetrachloride (3 ml) was prerduced, and 1-ethoxybicyclo[3.2.0]hepta-3,6-diene (73 mg) was added. The solution absorbed 2.08 equiv of hydrogen. After filtration, the product was isolated by preparative-scale vapor phase chromatography on a $\frac{3}{8}$ in. \times 6 ft Ucon LB 550X on Chromosorb P (1:5) column. The nmr spectrum of the product showed only protons on saturated carbon.

Anal. Calcd for C₈H₁₀O: C, 77.14; H, 11.43. Found: C, 76.86; H, 11.14.

1-Methoxybicyclo[3.2.0]heptane. Platinum oxide (20 mg) in carbon tetrachloride (3 ml) was prerduced. 1-Methoxybicyclo[3.2.0]hepta-3,6-diene (97 mg) was added. The solution absorbed 2.05 equiv of hydrogen. The product was separated by preparative-scale vpc as described above. The nmr spectrum of the prod-

(33) This preparation was first reported by D. N. Kursanov and M. E. Volpin, *Dokl. Akad. Nauk SSSR*, **113**, 339 (1957). Since that time, other workers³⁴ have suggested that, while this preparation yielded a compound whose chemical properties were essentially the same as tropilidine chloride, in actual fact a chlorophosphorus complex was formed with cycloheptatriene.

(34) D. Bryce-Smith and N. A. Perkins, *J. Chem. Soc.*, 1339 (1962).

(35) W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **76**, 3203 (1954).

ed only protons on saturated carbon and the methoxyl

Calcd for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 76.16; H, 11.16.

Phase Irradiation of 7-Methoxycycloheptatriene. The system used consisted of a vacuum line containing two cold traps connected by a coil made from a 12-ft length of 10 mm (o.d.) bing. The coil was 4 in. high and 3 in. in diameter. A lamp (Type A) was mounted in the center of the coil. 7-Methoxycycloheptatriene (1.2 g) was introduced into one trap and the system was then evacuated. The system was then moved to the other trap and the 7-methoxycycloheptatriene slowly distilled to the coil to the other trap. This distillation was repeated and the condensed liquid was recovered. Vpc analysis showed 7-methoxycycloheptatriene (14%), 1-methoxycycloheptatriene (14%), and 1-methoxybicyclo[3.2.0]hepta-3,6-diene (48%).

1-Methoxybicyclo[3.2.0]hepta-3-ene. A solution of 1-methoxybicyclo[3.2.0]hepta-3,6-diene (2.74 g) in carbon tetrachloride containing 0.5% platinum on charcoal (50 mg) was permitted to absorb of hydrogen. Vpc analysis of the product showed one component (95%). The nmr spectrum of the product showed only traces of residual absorption due to the cyclobutene but showed a strong resonance at τ 4.30 for the cyclopentene.

The product proved to be rather sensitive and was used at step without further purification.

Reaction of 1-Methoxybicyclo[3.2.0]hepta-3-ene to 1,4-Cycloheptanedione. A mixture of sodium borohydride (0.55 g) and zinc chloride (0.1 g) in anhydrous ether (20 ml) was stirred for 1.4 hr under a nitrogen atmosphere. A solution of 1-methoxybicyclo[3.2.0]hepta-3-ene (6.2 g) in anhydrous ether (15 ml) was added. Boron trifluoride etherate (2.2 g) in anhydrous ether was added dropwise during 1 hr. After stirring for 2 hr, the hydride was destroyed with water (2 ml). A solution of dichromate (12.5 g) in sulfuric acid (4 ml of concentrated, 25 ml with water) was added over a 15-min period. After under reflux for 2 hr, the upper layer was separated, and the aqueous layer was extracted twice with ether (10 ml). The combined ether solutions were dried over magnesium sulfate and concentrated to 20 ml. Treatment of a 5-ml portion of the solution with 2,4-dinitrophenylhydrazine in ethanolic acid gave a recrystallization from nitrobenzene-ethanol, orange crystals, mp 242–243°. These crystals were identified as 1,4-cycloheptanedione bis(2,4-dinitrophenylhydrazone) by mixture melting point with an authentic sample and comparison of infrared. Analysis of the remainder of the ether solution by vpc gave only ether and 1,4-cycloheptanedione. Vpc analysis using an internal standard (*n*-butyl ether) gave an estimated yield of 1,4-cycloheptanedione of 21% (based 1-methoxybicyclo[3.2.0]hepta-3-ene).

Reaction of 3-Methoxycycloheptatriene. A solution of 3-methoxycycloheptatriene (8.5 g) in ether (2 l.) was irradiated for 1 hr with a Hanovia mercury lamp (Type A) in a quartz immersion vaporator of the ether and distillation gave an oil (4.74 g) (44%). The oil was separated into two fractions by preparative vpc (F silicone column), A (1.23 g) and B (680 mg).

Vpc analysis of fraction A showed the presence of three components. Careful separation of fraction A (1 g) by preparative vpc (diisodecyl phthalate column) gave 1-methoxybicyclo[3.2.0]hepta-3,6-diene (50 mg) and a mixture of two other bicyclic compounds (530 mg). Reduction of the mixture of bicyclic compounds (530 mg) in ethyl acetate (2.5 ml) containing 5% Pd-C, and removal of the solvent gave a colorless oil (500 mg).

Analysis of the oil showed the presence of at least three components. Separation of the oil by preparative-scale vpc (Ucon X column) gave fractions A-1 (50 mg), A-2 (18 mg), and A-3 (mg). Fraction A-1 showed only saturated protons (in CH_2OCH_3 absorption). A-2 also showed OCH_3 absorption. A-3 was identified as bicyclo[3.2.0]heptan-6-one by comparison of its infrared spectrum with that of an authentic sample.

The ultraviolet absorption of fraction B suggested that it was a mixture of isomeric methoxycycloheptatrienes. This was confirmed by the nmr spectrum of the mixture. Comparison of the nmr spectrum of the mixture with the spectra of authentic 1-, 2-, and 3-methoxycycloheptatrienes suggested the presence of 1-, 2-, and 3-methoxycycloheptatrienes.

A portion of A (230 mg) in ethanol (0.5 ml) and 1 *N* sulfuric acid (0.5 ml) was heated on a steam bath for 30 min. Extraction, drying, and removal of the solvent gave an oil which showed infrared absorption at 5.62, 5.78 (sh), 5.87, and 6.04 μ .

Monitored Irradiations of 7-Methoxycycloheptatriene. A. A solution of 7-methoxycycloheptatriene (8.0 g) in oxygen-free ether (1.75 l.) was irradiated with a Hanovia mercury lamp (Type A) in a quartz immersion well. Samples (50 ml) were withdrawn every 30 min and analyzed by ultraviolet, vpc, and nmr methods. The ultraviolet analysis showed steady decrease of the 255-m μ maximum of 7-methoxycycloheptatriene, buildup of a broad maximum at 280 m μ , and decay of the 280-m μ maximum. Vpc analysis (F silicone, 80°) gave the plots shown in Figure 1 which show the formation and destruction of an intermediate. The nmr analysis showed steady decrease in the OCH_3 signal (τ 6.63) of 7-methoxycycloheptatriene, rapid formation of a new OCH_3 signal (τ 6.47) at lower field and a CH_2 signal (τ 7.55, doublet, $J_{app} = 7.4$ cps)³⁷ due to 1-methoxycycloheptatriene, and slower formation of a OCH_3 signal (τ 6.76) and CH_2 signal (τ 7.62) due to 1-methoxybicyclo[3.2.0]hepta-3,6-diene. As the reaction progressed, the signals characteristic of 7-methoxycycloheptatriene disappeared first, then the signals characteristic of the intermediate (1-methoxycycloheptatriene) disappeared, leaving only signals due to 1-methoxybicyclo[3.2.0]hepta-3,6-diene.

B. A solution of 7-methoxycycloheptatriene (8.0 g) in ether (1.75 l.) was irradiated as described above. Samples were withdrawn every 5 min and analyzed by vpc. The results obtained are plotted in Figure 2. It is clear that 1-methoxybicyclo[3.2.0]hepta-3,6-diene is not formed until a significant amount of the intermediate (1-methoxycycloheptatriene) is formed. The bicyclic product thus is not a primary photoproduct of 7-methoxycycloheptatriene.

C. A solution of 7-methoxycycloheptatriene (8.0 g) in ether (1.75 l.) was irradiated as described above for 2 hr. Evaporation of the ether gave the crude mixture of photoproducts. The crude product showed three components (vpc). Separation of 1 g of the mixture by preparative-scale vpc gave 1-methoxybicyclo[3.2.0]hepta-3,6-diene (190 mg), 1-methoxycycloheptatriene (100 mg), and 3-methoxycycloheptatriene (thermal rearrangement product of 7-methoxycycloheptatriene, 120 mg). The products were identified by comparison of spectra with those of authentic samples.

Irradiation of 1-Methoxycycloheptatriene. A solution of 1.4 g (0.012 mole) of 1-methoxycycloheptatriene in 2 l. of anhydrous ether was irradiated for 9 hr with a quartz-jacketed Hanovia immersion lamp (Type A). The solution was concentrated on a rotary evaporator and distilled, giving 1-methoxybicyclo[3.2.0]hepta-3,6-diene (0.6 g 43%) identified by comparison of nuclear magnetic resonance and infrared spectra with that of a sample prepared by the irradiation of 7-methoxycycloheptatriene. No attempt to maximize the yield was made.

Short-Term Irradiation of 1-Methoxycycloheptatriene. A solution of 1-methoxycycloheptatriene (500 mg) in oxygen-free benzene (250 ml) was irradiated for 1 hr using a Pyrex-jacketed Hanovia immersion lamp (Type A). The solvent was distilled off, and the nmr spectrum of the crude reaction mixture was taken. Three peaks in the methoxy region were observed and identified as being due to 7-methoxycycloheptatriene, 1-methoxycycloheptatriene, and 1-methoxybicyclo[3.2.0]hepta-3,6-diene. Integration of these three peaks showed that the 7-methoxy compound composed approximately 20% of the total product mixture. Formation of 7-methoxycycloheptatriene could also be followed by the appearance of its characteristic ultraviolet absorption at 255 m μ .

Irradiation of 7-Methoxycycloheptatriene in the Presence and Absence of Oxygen. A solution of 1.0 g (0.0082 mole) of 7-methoxycycloheptatriene in 240 ml of oxygen-free benzene was irradiated with a Pyrex-jacketed Hanovia immersion lamp (Type A) for 3 hr. The solvent was evaporated from a 50-ml aliquot, and the nmr spectrum of the residue was taken. The amount of reaction was estimated by comparing the integral ratios of the peaks due to the methoxy groups of I, II, and III. This integration gave the values Ia (38%), VIa (17%), and IIa (45%).

The experiment was repeated using oxygen-saturated benzene and bubbling oxygen through the mixture during the reaction. The nmr spectrum of the crude product showed Ia (22%), VIa (14%), and IIa (64%). Errors in the integration are relatively large ($\pm 10\%$), but it is clear that continuous saturation of the solution with oxygen does not quench the reaction.

(37) The apparent splitting probably is not a true coupling constant.

The procedure used was adapted from that of Brown and

Irradiation of 1-Methoxycycloheptatriene in the Presence and Absence of Oxygen. A solution of 1-methoxycycloheptatriene (500 mg) in oxygen-free benzene (250 ml) was irradiated with a Pyrex-jacketed Hanovia immersion lamp (Type A) for 1 hr. A 50-ml aliquot of this solution was taken, and the solvent was removed. Examination of the residual oil by nmr showed Ia (21%), VIa (55%), and IIa (24%).

The same scale experiment was repeated using oxygen-saturated benzene (oxygen was bubbled through the solution throughout the period of irradiation). After 1-hr irradiation, nmr analysis showed Ia (19%), VIa (59%), and IIa (22%).

Irradiation of 7-Methoxycycloheptatriene in the Presence and Absence of Acetophenone. A solution of 100 mg (0.0082 mole) of 7-methoxycycloheptatriene in 5 ml of oxygen-free benzene was prepared. This solution (1 ml) was placed in each of two Pyrex nmr tubes. To one of the tubes 30 mg of acetophenone was added, then both were sealed. The tubes were irradiated with a Pyrex-jacketed Hanovia immersion lamp (Type A) through a 2-mm-thick layer of filter solution (described above). At appropriate intervals the tubes were removed, and the nmr spectra were run. After 12-hr irradiation no significant reaction had occurred in either tube.

Irradiation of 1-Methoxycycloheptatriene in the Presence and Absence of Sensitizers. These irradiations were carried out using nmr tubes as described above. However, in this case, after 1-hr irradiation ca. 50% of the 1-methoxycycloheptatriene had rearranged to a mixture of 7-methoxycycloheptatriene and 1-methoxybicyclo[3.2.0]hepta-3,6-diene. Addition of 1 molar equiv of acetophenone definitely slowed down the rearrangement while a 10 molar equiv excess of acetophenone effectively halted the rearrangement as did 1 equiv of benzophenone. At the concentrations used (0.16 M in substrate and sensitizer) 1-methoxycycloheptatriene (ϵ_{3600} 4.1) had a slightly higher absorbance (0.65 at 3600 Å) than acetophenone [ϵ_{3600} 3.1; $A(0.16 M) = 0.49$]. Using 0.16 M 1-methoxycycloheptatriene and 1.6 M acetophenone, the respective absorbances were 0.65 and 4.90. In this case >88% of the incident light is absorbed by the acetophenone. No reaction could be detected after 1-hr irradiation. Benzene absorption is not a problem (ϵ_{3400} 4.44×10^{-4} ; $\epsilon_{3600} \approx 0$).

Acknowledgment. This research was supported by a grant (AM 07520) from the National Institute of Arthritis and Metabolic Diseases and by a grant (G-15832) from the National Science Foundation.

The Mechanism of Isotopic Exchange between Arylmercuric Compounds and Elemental Mercury^{1a}

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Abstract: The mechanism of the facile isotope exchange between arylmercuric compounds in solution and metallic mercury was examined. All reasonable mechanisms except a true isotopic exchange at the surface of the liquid are eliminated. The reaction rate is not significantly limited by mass transport in either phase. The reaction shows a real but small solvent dependence which is not correlated with the solubility of the substrate or any common solvent parameter. This and the value of ΔS^\ddagger favor a rate-determining chemisorption step. The efficiency of substrate collisions with the metal is much higher than that of collisions with the Hg⁰ atoms in solution for bringing about exchange, suggesting a rate-determining electron transfer. Reactivity seems to be in the order $RHgI > RHgBr > RHgCl > RHgOAc \gg RHgR$. An over-all mechanism is proposed.

Several years ago Reutov and Ostapchuk² reported that the isotope exchange shown in eq 1, rather surprisingly, proceeded under mild conditions in a variety of solvents. Halogen atoms, aryl groups, and



certain special alkyl groups can be used as R_1 and R_2 .³⁻⁵ The original report has been confirmed and extended in a series of papers by Reutov and his co-workers,³ and by Pollard and Westwood.^{4,5} The most important findings of these workers have been that the reaction could be carried out under conditions where its rate was not transport controlled, and that it was totally unaccompanied by chemical changes. In the case that R_1

or R_2 is optically active there is not even a loss of optical activity accompanying the exchange.³ From these observations, and others, a mechanism involving a four-center transition state was deduced.

The present paper describes the exchange between *p*-methoxyphenylmercurials, $RHgX$, and elemental mercury. In contrast with previous work the rate of encounter of the substrate with the surface can be estimated. The surface area and conditions were more closely controllable than those of previous investigators. A much wider range of substrate concentrations was conveniently studied by labeling the organomercurial rather than the elemental mercury. The effect of solvent on reactivity and the solubility of the substrate in the same solvents were extensively studied. The effect of varying X, through the halogens and acetate, was studied. An upper limit was placed on the rate of the analogous reaction in homogeneous solution. The findings that the exchange is interfacial, largely unlimited by mass transport, and unaccompanied by chemical reactions were confirmed. Surface encounters are at least several orders of magnitude more effective than encounters with mercury atoms in solution for producing exchange. This finding, com-

(1) (a) Supported, in part, by the Petroleum Research Foundation through Grant PRF 1912-A3,4; (b) Sloan Foundation Fellow, 1960-1964; (c) Du Pont Teaching Assistant Awardee, 1963-1964; American Oil Foundation Fellow, 1964-1965; Shell Oil Co. Summer Fellow, 1963; National Science Foundation Summer Fellow, 1964; Du Pont Summer Fellow, 1966.

(2) O. A. Reutov and G. M. Ostapchuk, *Dokl. Akad. Nauk SSSR*, 117, 826 (1957).

(3) O. A. Reutov, *Angew. Chem.*, 72, 198 (1960); other papers by Reutov and his co-workers are referred to here.

(4) D. R. Pollard and J. V. Westwood, *J. Am. Chem. Soc.*, 87, 2809 (1965).

(5) D. R. Pollard and J. V. Westwood, *ibid.*, 88, 1404 (1966).

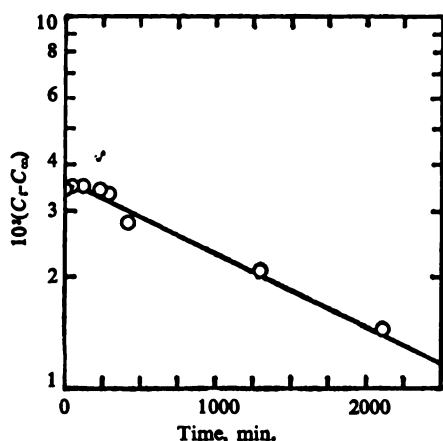


Figure 1. A typical plot of $\log(C_t - C_\infty)$ as a function of t for a homogeneous reaction; (RHgBr) was $1.38 \times 10^{-5} M$, and (Hg^0) was $0.99 \times 10^{-5} M$.

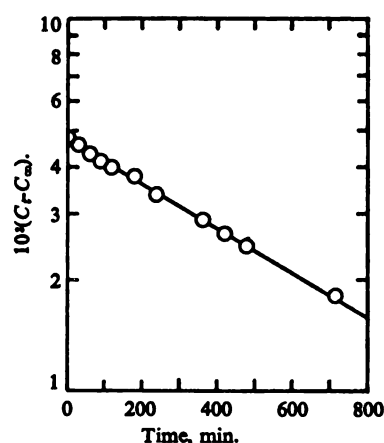


Figure 2. A typical plot of $\log(C_t - C_\infty)$ as a function of t for a heterogeneous reaction; (RHgBr) was $4.35 \times 10^{-5} M$, and 25.0 g of Hg^0 was used, giving a surface area of 2.0 cm^2 . The temperature was 25°.

bined with the other findings, suggests that electron transfer from the substrate to the metal is rate determining for the exchange.

Results

It can be shown⁶ that an isotopic exchange reaction in which a given element is exchanged between two different chemical environments follows the rate law shown in eq 2 within any given experiment regardless of the mechanism of the exchange. In eq 2 k is the

$$k = \frac{ab}{a + b} \frac{2.303}{t - t_0} \log \left(\frac{C_0 - C_\infty}{C_t - C_\infty} \right) \quad (2)$$

constant rate of exchange of labeled atoms between the two environments, with units of $M \text{ sec}^{-1}$; a and b are the concentrations of labeled substances in the two environments; t_0 is the time at which exchange was begun; t , the time at which it was interrupted; C_t is the counting rate at time t . Equation 2 is applicable to heterogeneous as well as homogeneous exchange reactions as long as the labeled atom does not accumulate significantly in the interfacial region. The disappearance of radioactivity from the labeled starting material was accurately described by eq 2, within the precision of the measurements, except where otherwise noted. Rate constants, k , were obtained by inspection from linear plots of $\log(C_t - C_\infty)$ as a function of time. Typical examples of such plots, for homogeneous and heterogeneous reactions, are shown in Figures 1 and 2.

Equation 2 is limited to exchange reactions which are unaccompanied by any net chemical change. The absence of such change was verified, in the present system, for a $5.4 \times 10^{-5} M$ solution of RHgBr in methanol, exchanging with a 25-g sample of liquid mercury (2.0- cm^2 surface area). The ultraviolet spectrum of the RHgBr solution was not detectably diminished during ten half-lives of exchange. About 2% diminution would have been clearly detectable.

Homogeneous Solution. Four rates were measured at 25° in homogeneous benzene solution, with initially labeled RHgBr, using analytical reagent grade benzene. (The solubility of mercury in benzene is $1.2 \times 10^{-5} M$ at 25°.) The half-lives were about 2 days.

The resultant k values are shown in Table I. The data are too scanty and imprecise to permit the establishment of a kinetic order with respect to either reagent, but if the reaction is *assumed* to be first order in each reagent the second-order rate constants, k_2 , shown in Table I are obtained. Their average is $0.25 \pm 0.05 M^{-1} \text{ sec}^{-1}$.

Table I. Rate of Exchange in Homogeneous Benzene Solution

(RHgBr), $10^5 M$	(Hg^0), $10^5 M$	$10^4 k$, $M^{-1} \text{ sec}^{-1}$	k_2 , $M^{-1} \text{ sec}^{-1}$
0.69	0.69	1.3	0.27
0.69	0.82	0.8	0.15
1.03	0.82	2.2	0.27
1.38	0.99	4.4	0.33

Some of the scatter may be due to catalysis by impurities. When the same reaction was carried out in a poorer grade of solvent k was larger by a factor of about 5 at comparable concentrations. If the kinetic order is incorrect, then the true, bimolecular, rate constant would be smaller yet. For these reasons, the value of k_2 given is more likely too large than too small.

Work on homogeneous solutions was not carried further because of the long half-lives and experimental difficulties involved.

Heterogeneous Exchange. Heterogeneous exchange experiments were carried out in a round-bottomed flask with a mechanical stirrer and openings for the addition and withdrawal of materials. It is identical with that previously described,⁸ except that it had an indentation in the bottom of the flask to help stabilize the mercury sample and a piece of speedometer cable between the stirring motor and the stirrer to reduce vibration of the flask. This apparatus does not break up the mercury sample at the stirrer speeds used.

In the heterogeneous experiments the concentration of mercury in liquid mercury (68 g-atoms l^{-1}) is higher by a factor of 10^5 than the highest solution concentration used, and the quantity of mercury in the liquid is

(6) O. Meyers and R. J. Prestwood in "Radioactivity Applied to Chemistry," A. C. Wahl and N. A. Bonner, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, pp 9 and 34.

(7) E. H. Klehr, Ph.D. Thesis, Iowa State University, 1959.

(8) P. Warrick, Jr., E. M. Wewerka, and M. M. Kreevoy, *J. Am. Chem. Soc.*, **85**, 1909 (1963).

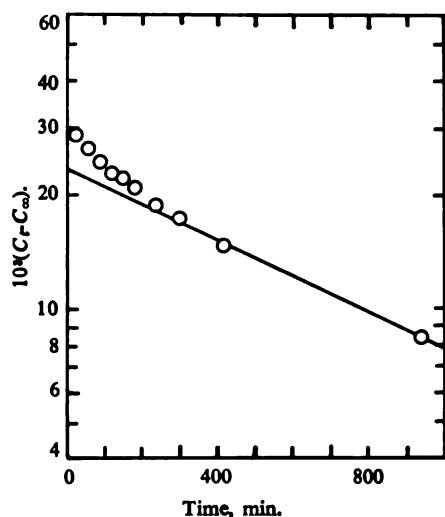


Figure 3. Typical curved plot of $\log(C_t - C_\infty)$ as a function of t at low (RHgBr). The (RHgBr) was $6.93 \times 10^{-4} M$ in benzene; 25 g of Hg^0 was used (2.0-cm² surface area) at 600 rpm and 25°. The solid line corresponds to a k_1 of $1.8 \times 10^{-5} \text{ sec}^{-1}$.

higher by a factor of 10^3 than that in solution, so eq 2 reduces to eq 3, in which a is the concentration of

$$k/a = 2.303/(t - t_0) \log(C_0/C_t) \quad (3)$$

RHgX.

Order With Respect to RHgBr. A series of experiments was carried out with varying concentrations of RHgBr in benzene, 25.0-g samples of Hg^0 (giving a 2.0-cm² surface area) at 25° and a stirring rate of 600 rpm. These were designed to test the reproducibility of the results and determine the order with respect to RHgBr. The results are shown in Table II. On repetition of an experiment without altering the apparatus reproducibility of better than 10% could usually be obtained. However, if the apparatus was disassembled and reassembled on another day, a discrepancy of almost a factor of 2 could sometimes be observed. This is exemplified by the results at $3.31 \times 10^{-4} M$ RHgBr and $3.82 \times 10^{-4} M$ RHgBr. Vibration of the apparatus is probably the cause of this variability. Reaction was notably faster when the apparatus was visibly vibrating. Within these limits the results in Table II are consistent with first-order behavior, and with no other simple order. The first-order rate constants, k_1 , given by k/a , may show a slight, systematic, trend toward higher values at lower (RHgBr). Disregarding any drift, the average value of k_1 was $1.6 \times 10^{-5} \text{ sec}^{-1}$ with an average deviation from the mean of $0.4 \times 10^{-5} \text{ sec}^{-1}$.

At (RHgBr) $< 2 \times 10^{-5} M$ curvature was increasingly apparent in plots of $\log(C_t - C_\infty)$ as a function of t . Such a plot is shown in Figure 3. The origin of the curvature is not known, but it is probably associated with the loss of a small quantity of RHgBr from solution, significant by comparison with the very small quantities initially involved. The terminal slope of such plots gave k_1 values consistent with those obtained at higher (RHgBr). The beginning of such curvature, unnoticeable at slightly higher (RHgBr), is probably responsible for the slight drift to higher values of k_1 at lower (RHgBr) in Table II.

Table II. Exchange of RHgBr in Benzene Solution with 25 g of Hg^0 at 25°

(RHgBr), 10 ⁴ M	10 ¹⁰ k, M ⁻¹ sec ⁻¹	10 ⁵ k/a, sec ⁻¹	k/a ² , M ⁻¹ sec ⁻¹
1.7	3.4	2.0	1.2
2.0	3.8	1.9	0.95
2.7 ^a	4.3 ^a	1.6 ^a	0.59 ^a
4.2 ^b	9.7 ^b	2.3 ^b	0.55
4.4	10.1	2.3	0.52
5.1	7.6	1.5	0.29
9.3	13.0	1.4	0.15
10.9	14.2	1.3	0.12
15.6	15.6	1.0	0.06
18.6	20	1.1	0.06
26.2	26	1.0	0.04
33.1	46	1.4	0.04
38.2	31	0.8	0.02
66.1	93	1.4	0.02

^a Four experiments, with average deviation from the mean, 2%.

^b Three experiments, with average deviation from the mean, 10%.

State of Aggregation of RHgBr. The method of differential vapor pressures⁹ was used¹⁰ to determine a van't Hoff i of 1.0 for RHgBr.

Mercury Surface Area. The rate was studied as a function of surface area, A , with RHgBr in benzene solution at 25°, at a stirring rate of 600 rpm. Except where noted, (RHgBr) was $4 \times 10^{-5} M$. The surface area was varied by varying the size of the mercury sample, and determined by measurement with calipers. In this way the surface area could be increased by a factor of more than 6. As shown in Table III, k_1/A is constant within the precision of the measurements. Variation of the sample size also changed the vertical distance between the stirrer and the mercury surface. It was independently shown that k_1 was invariant under comparable changes in the distance between the surface and the stirrer at constant mercury sample size and surface area. The 25-g sample, with 2.0-cm² surface area, was adopted as standard and used throughout the rest of this work. Rate constants per unit area can be obtained by dividing those reported by 2.0.

Table III. Variation of k_1 with Surface Area

A , cm ²	10 ⁵ k ₁ /A, sec ⁻¹ cm ⁻²
2.0	8.0 ^a
6.2	5.6
8.6	8.4
10.7	8.8
13.2	6.4

^a Average of 20 determinations, taken from Table II.

Stirring Rate. The variation of k_1 with stirring rate was studied for RHgBr in several solvents at 25° with 25-g mercury samples and substrate concentrations around $4 \times 10^{-5} M$. The results are shown in Table IV for benzene. They were similar for isooctane (2,2,4-trimethylpentane) and nitrobenzene. There is no significant variation of reaction rate with stirring rate at or above 400 rpm.

(9) S. Bruckenstein and A. Saito, *J. Am. Chem. Soc.*, **87**, 698 (1965).

(10) These measurements were kindly made for us by Mr. D. F. Untereker in consultation with Professor Bruckenstein.

IV. Variation of k_1 for RHgBr with
ing Rate in Benzene at 25°

Stirring rate, rpm	$10^4 k_1$, sec ⁻¹
100	0.6
200	0.8
400	1.6
600	1.6 ^a
800	1.7

average of 20 determinations, taken from Table II.

Medium and Ligand Effects. The variation in k_1 solvent and with X, in RHgX, was studied at 25°, 25-g mercury samples. In most systems several substrate concentrations were used, and first-order behavior verified. The results are shown in Table V.

V. Variation in Rate with Solvent and Ligand at 25°

Solvent	Substrate, $10^4 k_1$, sec ⁻¹			
	RHgOAc	RHgCl	RHgBr	RHgI
(H ₃) ₂ NH ₂ PO	0.21	0.24	0.21	0.24
H ₂ NO ₂			0.8	
H ₂ OCH ₃			1.0	
H ₂	0.16	0.41	1.6 ^a	6.0
H ₂ CH ₃			1.7	
H ₂ CO			1.9	
I ₂ OH		1.5	2.9	
O	3.7		4.4	
Cl ₂			7.7	
octane		6.4	9.8	10.5

average of 20 determinations, taken from Table II.

Effect of Temperature. In order to determine the thermodynamic parameters of activation, k_1 was measured for RHgBr in toluene, using a 25-g mercury sample at a 600 rpm stirring rate, at four temperatures between 1 and 40°. A total of seven determinations were made. The logarithm of k_1/T was a linear function of $1/T$ within the precision of the measurements. Standard equations¹¹ were used to get the enthalpy of activation, ΔH^\ddagger , by the method of least squares.¹² It gave the value, 8.1 kcal mole⁻¹, with 50% confidence limits of 0.2 kcal mole⁻¹ and 90% confidence limits of 0.3 kcal mole⁻¹.

The value of the entropy of activation, ΔS^\ddagger , depends on the standard state chosen for the starting state and the transition state. For ease of interpretation a 1 mole solution in toluene has been chosen for the starting state and 1 mole cm⁻² for the transition state. The smoothed value of k_1 at 25°, 1.75×10^{-5} sec⁻¹, then be multiplied by the solution volume, 0.15 ml and divided by the reactive surface area, 2 cm², before ΔF^\ddagger , the free energy of activation, can be obtained from eq 4.¹¹ In eq 4 k_r is the rate constant described

$$\Delta F^\ddagger = -RT \ln (k_r h / kT) \quad (4)$$

where, with a value of 1.3×10^{-6} l. sec⁻¹ cm⁻² at 25° in toluene, and the other quantities are the usual physical constants. This leads to a value of 25.5 kcal

M. M. Kreevoy in "Investigation of Rates and Mechanisms of Organic Reactions," S. L. Friess, E. S. Lewis, and A. Weissberger, Eds., Interscience Publishers, Inc., New York, N. Y., 1963, p 1392.

C. A. Bennett and N. L. Franklin, "Statistical Analysis in Chemistry and the Chemical Industry," John Wiley and Sons, Inc., New York, N. Y., 1954, pp 36-40.

mole⁻¹ for ΔF^\ddagger , and, via the usual thermodynamic equalities,¹¹ to a value of -58.4 cal mole⁻¹ deg⁻¹ for ΔS^\ddagger , with 50% confidence limits of 0.7 cal mole⁻¹ deg⁻¹.

Inhibition and Catalysis. A number of substances were tested for catalytic or inhibitory effects. For the most part these were substances known to or expected to adsorb on a mercury surface, or to complex the substrate. These experiments were carried out with RHgBr as the substrate, a 600-rpm stirring rate, and a 25-g mercury sample. In methanol as a solvent, 4×10^{-1} M sodium bromide and 1.4×10^{-1} M hydroquinone were without measureable effect. In benzene as a solvent, silicone grease and 6×10^{-4} M *p*-bromoanisole were without effect. However, 4×10^{-4} M stearic acid retarded the rate in benzene by a factor of about 2; 1.4×10^{-6} M HgBr₂, and also 2.6×10^{-6} M HgBr₂, accelerated it by about the same factor, both by comparison with a standard k_1 of 1.6×10^{-5} sec⁻¹. These changes appear to be outside of the scatter shown in Table II, although not far outside.

Reaction of HgBr₂ with Mercury. Mercuric bromide in solution reacts with liquid mercury, giving solid Hg₂Br₂. In isooctane, the ultraviolet spectrum of residual HgBr₂ can be detected, but no evidence of Hg₂Br₂ can be found in solution, so the equilibrium can be formulated as shown in eq 5. Using ²⁰³Hg as a



tracer, and assuming that all the mercury in solution was in the form of HgBr₂, the equilibrium constant K_5 was measured for benzene solutions. Five determinations were made: two starting with solutions of HgBr₂, liquid mercury, and no Hg₂Br₂, and three starting with liquid mercury, freshly precipitated Hg₂Br₂, solvent, and no HgBr₂. The average value of K_5 was 2.5×10^6 M⁻¹, with an average deviation from the mean of 0.5×10^6 M⁻¹, and no systematic difference between those run forward and those run backward.

The experiments to test the catalytic effectiveness of HgBr₂ were carried out at concentrations well below the equilibrium concentration of HgBr₂, 4×10^{-6} M, so that no Hg₂Br₂ should have been present at equilibrium. Nevertheless, a few minutes after the reaction was begun, a precipitate of Hg₂Br₂ appeared at the metallic surface. After about 1 hr, the precipitate redissolved, so that, at equilibrium, the conditions of equilibrium were satisfied. The exchange reaction (eq 1) was proceeding all during the precipitation and resolution, but its rate was not detectably affected by these phenomena. This whole group of observations undoubtedly deserves, and will receive, further attention.

Disproportionation. An attempt was made to determine the equilibrium constant K_6 for the reaction shown in eq 6. It was determined (by spectrophotom-



etry in the presence of 0.1 M NaI) that water in equilibrium with 8.2×10^{-4} M RHgBr contained less than 10^{-6} M of HgBr₂. Since the distribution constant of HgBr₂ between water and benzene is 0.90 (favoring benzene)¹³ an upper limit of 1.8×10^{-6} can be set for K_6 .

(13) M. S. Sherrill, Z. Physik. Chem., 43, 705 (1903).

Solubility. The solubility, S , of RHgBr in all the solvents used for rate measurements was determined at 25° . Each measurement was made at least once from each direction, *i.e.*, by saturating an initially unsaturated solution with excess solid, and by allowing an initially supersaturated solution to equilibrate with the solid. The concentration of the equilibrated solutions was determined spectrophotometrically in methanol, by means of their radioactivity, using labeled RHgBr in the other solvents. Both methods were used for isooctane, and were in good agreement. The results are shown in Table VI.

Table VI. Solubility of RHgBr at 25°

Solvent	S, M
Water	1.4×10^{-4}
Isooctane	5.1×10^{-4a}
Isooctane	5.2×10^{-4b}
Methanol	2.3×10^{-3}
Toluene	3.5×10^{-3}
Benzene	5.6×10^{-3}
Hexamethylphosphoramide	6.2×10^{-3}
Anisole	8.9×10^{-3}
Nitrobenzene	1.8×10^{-3}
Acetone	1.9×10^{-3}

^a Measured spectrophotometrically. ^b Measured by means of radioactivity.

In addition, 12 determinations of S in toluene were made at a series of temperatures between 0 and 55° . A plot of $\log S$ as a function of $1/T$ was linear, within the scatter of the measurements. From these data, using the van't Hoff equation¹⁴ and the method of least squares,¹² the standard enthalpy of solution, ΔH° , is $4.9 \text{ kcal mole}^{-1}$, with 50% confidence limits of $\pm 0.15 \text{ kcal mole}^{-1}$. Properly, this pertains to the midpoint of the temperature range studied, 27.5° . Using the standard equations, the entropy of solution, ΔS° , is $5.1 \pm 0.5 \text{ cal mole}^{-1} \text{ deg}^{-1}$ if an ideal, $1 M$, solution is chosen as standard state for RHgBr(soln) and the solid itself is the standard state for RHgBr(s) .

Discussion

The present work supports the earlier conclusion²⁻⁵ that the rate of the exchange reaction, eq 1, is not, generally, mass transport controlled. For the fastest exchanging compounds, in the most activating solvents, however, mass transport in the solution phase may play a role. For example, RHgI in isooctane exchanges with a rate constant almost half that for mercury reprecipitation under similar conditions⁸ after correction for the difference in surface area. The latter reaction is thought to be mass transport controlled,⁸ and it has been shown that the diffusion coefficient of atomic mercury in isooctane is not strikingly different from those of other species.¹⁵ Most of the other exchange reactions were substantially slower than that of RHgI in isooctane, however, so the mass transport process must be relatively unimportant in determining their rates. This conclusion is supported by the substantial variation in exchange rate with substrate structure and by the invariance of the exchange rate with the stirring

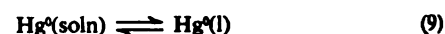
rate. In addition, ΔH^\ddagger for exchange in toluene is $\sim 5 \text{ kcal mole}^{-1}$ larger than would be expected for a transport-controlled reaction.¹⁶

The diffusion of radioactive mercury away from the interface seems totally unimportant in determining the exchange rate. This is shown by the linear plots of $\log C_i$ as a function of t ,⁶ by the variation of rate as a function of X and solvent, and by a calculation of the concentration of labeled mercury at the interface during an exchange. In this calculation it was assumed that a concentration of labeled mercury atoms, C_{Hg^*} , was continuously maintained by the exchange at the surface of a cylindrical well of mercury. (This is the condition that would prevail if the exchange rate were controlled by diffusion in the mercury.) Standard equations¹⁷ and the known self-diffusion coefficient of mercury¹⁸ were then used to calculate the concentration of labeled mercury, C_{Hg^*} , as a function of C_{Hg} and the distance from the surface, at a time comparable to a half-life for exchange. The area under this curve was equated to the quantity of labeled mercury deposited from the most concentrated reaction mixture in a half-life. This gave a value for the only variable, C_{Hg^*} . It was $3 \times 10^{-3} M$, which can be compared with a total mercury concentration of $68 M$ in $\text{Hg}^0(\text{l})$.

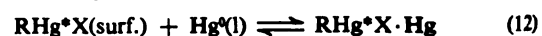
An exchange mechanism involving HgX_2 , shown in eq 7 and 8, has been discounted by Reutov.³ The pres-



ent results on disproportionation rigorously disallow it as the major exchange path. These set an upper limit of $10^{-6} M$ on the concentration of HgBr_2 in equilibrium with $8.2 \times 10^{-4} M$ RHgBr in benzene at 25° . Assuming the mercury reprecipitation and the reaction shown in eq 8 are mass transport limited they would both have first-order rate constants of $3.2 \times 10^{-4} \text{ sec}^{-1}$.⁸ This leads to an exchange rate of $3.2 \times 10^{-10} \text{ g-atom sec}^{-1}$, and an apparent first-order rate constant for RHgBr exchange of $4 \times 10^{-7} \text{ sec}^{-1}$. This is only 2.5% of the observed rate constant under these conditions, $1.6 \times 10^{-5} \text{ sec}^{-1}$. Even when the HgBr_2 concentration is increased by deliberate addition, the reactions shown in eq 7 and 8 cannot account for as much as 10% of the observed k_1 , so they cannot even account for the apparent catalysis by added HgBr_2 . Entirely similar reasoning excludes significant contributions to the overall exchange from the reactions shown in eq 9 and 10.



The foregoing excludes all of the reasonable mechanisms for exchange except those involving the direct interaction of RHgX with the surface. A generalized scheme for a surface mechanism is shown in eq 11-13.



In those equations, $\text{RHg}^*\text{X}(\text{surf.})$ represents unreacted

(16) L. L. Bircumshaw and A. C. Riddiford, *Quart. Rev.* (London), 6, 157 (1952).

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(14) G. N. Lewis and M. Randall, "Thermodynamics", 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1961, p 173.

(15) M. M. Kreevoy and H. B. Scher, *J. Phys. Chem.*, 69, 3814 (1965).

ate in contact with the surface and $\text{RHg}^*\text{X} \cdot \text{Hg}$ enters chemisorbed but unexchanged substrate. (13 represents the rate-determining step, k_1 is given $\propto K_{12} \times K_{11}$, where k is a rate constant, K is an equilibrium constant, and the subscript gives the equation to which the constant pertains. There should be no solvent specificity for K_{11} and not very much for K_{12} since it pertains to a reaction of a chemisorbed species, rather than one in solution. On the other hand, it would approximate inverse proportionality with S if it pertains to a process that removes RHgBr from solution. This suggests that k_1 should show an approximate inverse proportionality with S . Comparison of Tables V and VI reveals little correlation between k_1 and S . Reutov and Ostapchuk² have indicated that the rate is independent of solvent. While variation in k_1 with solvent is unquestionably real, considerably smaller than the variation in S . These observations make it unlikely that the reaction in eq 13 is rate determining. It has already been shown that mass transport, eq 11, is not rate determining. This leaves only the chemisorption step, eq 12, as the attractive rate-determining step. The present previous²⁻⁵ results are entirely compatible with the hypothesis provided that the transition state resembles the starting state.

Substituent effects on reactivity reported by Pollard and Westwood⁶ indicate that the aromatic fragment becomes somewhat electron deficient in the transition state, but the effects are small. Pollard and Westwood report a Hammett ρ of -1 for substitution by aryl groups. Values between 2 and 3 are commonly observed for generation of unit charge on an atom directly attached to the ring,¹⁹ and since there are substituted benzene rings in the present case, a larger effect might be expected if unit charge were developed. The present results could be taken to indicate development of an electron deficiency on mercury in the transition state, as the rate increases steadily with decreasing electronegativity. However, such a variation would imply that di-*p*-anisylmercury (R) should react faster than RHgI . In fact it has a rate constant which extrapolates to $3.6 \times 10^{-10} \text{ l. sec}^{-1}$ at 25° in benzene.⁵ This is slower by some powers of 10 than RHgOAc and slower by a factor of 10 than RHgI . The observation that RHgR reacts more slowly than RHgCl also seems to contradict the postulate⁵ that the rate-determining step for the reaction resembles that for electrophilic substitution. Electrophilic substitution by H^+ is much faster with arylmercury than with phenylmercuric chloride, and the latter is the product of the reaction of dimercury with dilute methanolic HCl .²⁰

Very small changes accompanying changes in S and the slow reactions in hexamethylphosphoramide suggest complete ionization in that solvent, probably with the formation of ion pairs, RHg^+X^- .

The ΔS^\ddagger values reported by Pollard and Westwood⁶ calculated for standard states of an ideal, 1 M solution for the starting state and 1 mole cm^{-3} for the transition state they give values (except for dibenzyl-

G. B. Barlin and D. D. Perrin, *Quart. Rev. (London)*, **20**, 75

H. Zimmer and S. Makower, *Naturwissenschaften*, **23**, 551

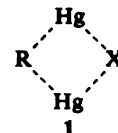
mercury) quite close to that reported here. Diphenylmercury, for example, gives $-57 \text{ cal mole}^{-1} \text{ deg}^{-1}$. (The original values appear to refer to a standard state of 1 mole/20 ml for the starting state and 1 mole/1000 cm^3 for the transition state.) Thus the differences in reactivity commented on above are probably due, in the largest part, to changes in ΔH^\ddagger .

If the changes in the entropy of solvation and the entropy of the metal accompanying the activation process can be neglected, the observed ΔS^\ddagger values are consistent with a transition state in which one translational degree of freedom has become the reaction coordinate. With standard states of 1 mole cm^{-3} for the starting state and 1 mole cm^{-2} for the transition state, the loss of one degree of translational freedom in the latter leads to the entropy shown in eq 14 for a

$$\Delta S^\ddagger = -R \ln (2\pi mkT_e)^{1/2}/h \quad (14)$$

gas.²¹ The symbols have their usual significance. The value of ΔS^\ddagger computed is $-41.6 \text{ cal mole}^{-1} \text{ deg}^{-1}$. The use of 1 M as the standard state for the starting material adds another $-R \ln 10^3$, so that the final calculated value is $-55.3 \text{ cal mole}^{-1} \text{ deg}^{-1}$. The very good numerical agreement between this and the experimental value ($-58.4 \pm 0.7 \text{ cal mole}^{-1} \text{ deg}^{-1}$) is fortuitous. The calculated value would probably be 1–5 $\text{cal mole}^{-1} \text{ deg}^{-1}$ smaller if a proper calculation could be made for the solution.²² Nevertheless the agreement does strongly suggest that considerable translational freedom parallel to the surface is retained by the transition state. If this were lost, a much more negative value would be obtained ($< -100 \text{ cal mole}^{-1} \text{ deg}^{-1}$).²¹

Previous workers²⁻⁵ have favored a four-center, overall transition state, 1, for this reaction, without specifying



whether this stage is reached during the chemisorption or subsequent steps. It now seems unlikely that 1 could be the over-all transition state for the reaction. The strongest argument against it is the relative efficiency of the surface reaction as compared to the homogeneous solution reaction. The simplest models²³ for collisions in solutions give collision rate constants

(21) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, p 398.

(22) The translational entropy in solution is less than that in the gas phase by about $3 \text{ cal mole}^{-1} \text{ deg}^{-1}$ for a molecule of about this molecular weight which does not interact specifically with the solvent. For example, the entropy of solution of I_2 vapor in isooctane is $-3.2 \text{ cal mole}^{-1} \text{ deg}^{-1}$ [J. H. Hildebrand and D. N. Glew, *J. Phys. Chem.*, **60**, 618 (1956)]. Thus, the loss of one degree of translational freedom for such a molecule would lead to an entropy contribution about $1 \text{ cal mole}^{-1} \text{ deg}^{-1}$ less negative than a similar loss from the gas phase. However, the entropy of solution of RHgBr vapor in toluene would be more negative than that of I_2 in isooctane because its entropy of solution from the solid, $5 \text{ cal mole}^{-1} \text{ deg}^{-1}$, is less positive than the entropy of solution of solids which give noninteracting solutions. For example, naphthalene, biphenyl, and diphenylamine all give entropies of solution in benzene of 17 – $18 \text{ cal mole}^{-1} \text{ deg}^{-1}$ [H. Stephen and T. Stephen, "Solubilities of Inorganic and Organic Compounds," The Macmillan Co., New York, N. Y., 1963, pp 1434, 1436, and 1552; K. Suzuki and S. Seki, *Bull. Chem. Soc. Japan*, **28**, 417 (1955); G. Gehlhoff, *Z. Physik. Chem.*, **98**, 252 (1921)]. The exact effect of this on ΔS^\ddagger is impossible to evaluate but $5 \text{ cal mole}^{-1} \text{ deg}^{-1}$ seems like a reasonable upper limit.

(23) E. A. Moelwyn-Hughes, "The Kinetics of Reactions in Solution," Oxford at the Clarendon Press, London, 1947, pp 8–9.

of $33 \text{ l. sec}^{-1} \text{ cm}^{-2}$ for a surface and $\sim 10^{11} \text{ M}^{-1} \text{ sec}^{-1}$ for bimolecular collisions in solution. The pertinent observed rate constants in benzene are $1.2 \times 10^{-8} \text{ l. sec}^{-1} \text{ cm}^{-2}$ for the surface reaction and $0.25 \text{ M}^{-1} \text{ sec}^{-1}$ in solution, so the fraction of successful conversions in the former case is 4×10^{-8} , and, in the latter, 3×10^{-12} . More sophisticated treatment of the collision frequencies²⁴ may substantially alter these numerical values, but the conclusion that the surface reaction is much more efficient is not altered unless the substrate is attracted to the surface in strong preference to the solvent. Considering the solvent structures represented in Table V, this seems quite unlikely. It is hard to see why a transition state like 1 should be more easily formed from liquid mercury than from a mercury atom in solution. The former would seem to require most of the energy necessary to abstract a mercury atom from the liquid (8 kcal mole^{-1}) in addition to most of the energy required by the latter.

It is also hard to see how 1 could be compatible with the requirement that the transition state retains its mobility parallel to the surface, as suggested by ΔS^\ddagger .

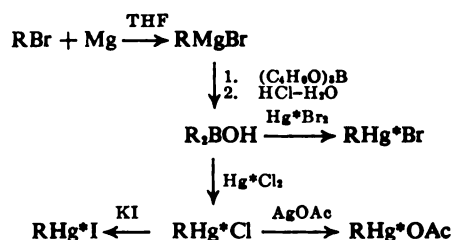
A rate-determining step that is consistent with all the evidence is electron transfer from the substrate to the mercury. This would account for the particular effectiveness of the metal, since its electron affinity must be essentially the same as its work function, $105 \text{ kcal mole}^{-1}$,²⁵ while that of atomic mercury is $30\text{--}40 \text{ kcal mole}^{-1}$.²⁶ There is no definitive experimental evidence excluding 1 as a transition state for a fast exchange step following the chemisorption step, but there is also no evidence strongly supporting it. We prefer the mechanism shown in eq 15–18 because of its analogy with the reversible formation of the mercurous halides at a mercury surface. A definitive conclusion will



have to depend on further experimental results.

Experimental Section

Materials. The general scheme by which the various radioactive mercury compounds were prepared is shown.



Bis(*p*-methoxyphenyl)borinic acid was prepared in 27% yield by the method of Hawthorne.²⁷ It had mp $102\text{--}105^\circ$ (lit.²⁷ 107°).

(24) A. M. North, "The Collision Theory of Chemical Reactions in Liquids," Methuen and Co., Ltd., London, 1964, Chapter 3.

(25) W. B. Hales, *Phys. Rev.*, **32**, 950 (1928).

(26) F. H. Field and J. L. Franklin, "Electron Impact Phenomena and the Properties of Gaseous Ions," Academic Press Inc., New York, N. Y., 1957, p 149.

(27) M. F. Hawthorne, *J. Am. Chem. Soc.*, **80**, 4293 (1958).

The two *p*-methoxyphenylmercuric halides were prepared by the method of Torsell²⁸ from the borinic acid and the appropriate mercuric halide. The latter were labeled simply by mixing them in solution with small amounts of labeled $\text{Hg}(\text{NO}_3)_2$ in aqueous HNO_3 , which is the form in which the ^{203}Hg was obtained. The labeled chloride was obtained in 95% yield and had mp $251.0\text{--}251.5^\circ$, in a sealed, evacuated capillary (lit.²⁸ $249\text{--}250^\circ$). The bromide was obtained in 44% yield and had mp $255\text{--}256^\circ$, in a sealed, evacuated capillary (lit.²⁸ $255\text{--}256^\circ$).

To obtain *p*-methoxyphenylmercuric acetate 0.31 g (9×10^{-4} mole) of the labeled chloride in 60 ml of hot benzene was treated with 0.14 g (8.5×10^{-4} mole) of silver acetate in 80 ml of ethanol (containing just enough water to give a clear solution). A precipitate formed immediately. The reaction mixture was refluxed gently for 15 min to coagulate the precipitate, which was then filtered. The solvent was removed from the filtrate under vacuum. The residual solid was recrystallized from ethyl acetate to give 0.18 g of product (4.9×10^{-4} mole, 54% yield), mp $179.5\text{--}180.5^\circ$, in a sealed, evacuated capillary (lit.²⁸ $178\text{--}179^\circ$).

To obtain the iodide, 0.52 g (1.5×10^{-3} mole) of the radioactive chloride was dissolved in 200 ml of benzene and shaken with four 25-ml portions of a 50% (by weight) solution of potassium iodide in water. The benzene layer was then separated and dried over magnesium sulfate. The solvent was removed under vacuum and the product recrystallized from 30 ml of ethyl acetate to give 0.30 g (0.7 mole, 45% yield) of labeled *p*-methoxyphenylmercuric iodide, mp $237\text{--}238^\circ$ in a sealed, evacuated capillary (lit.²⁸ $237.8\text{--}238.1^\circ$).

The benzene, carbon tetrachloride, and isooctane used in kinetic and solubility studies were of spectrograde quality. The first two were obtained from Mallinckrodt Chemical Works, Inc., the latter from Phillips Petroleum Co. Hexamethylphosphoramide was obtained from Aldrich Chemical Co., and was their best grade. All of these were used without further purification. Methanol was obtained from E. I. duPont de Nemours, & Co., Inc., anisole from Aldrich Chemical Co., nitrobenzene, acetone, and toluene from Eastman Kodak Co., and all were purified by distillation. Triply distilled mercury was used.

Kinetic Procedures. The homogeneous kinetic experiments were initiated by adding a small quantity of a stock solution of RHg^*Br to a solution of Hg^0 . The mixture was held at constant temperature in a thermostat and 10-ml aliquots were removed periodically. Nitrogen gas was bubbled through these vigorously for 5 min , then vapor was passed through a sulfur tower and then into a fume hood. This treatment codistilled about half of the solvent and all of the mercury. In a control experiment, this was several times the length of time necessary to remove all the Hg^0 from a saturated solution in isooctane, as judged by the ultraviolet spectrum. The volume of the demercurated aliquot was then restored to 10 ml , and the radioactivity in half of it was determined with a Nuclear-Chicago DS 5-5 well-type scintillation counter with a thallium-activated sodium iodide crystal detector. A Nuclear-Chicago Model 186 scalar equipped with an automatic timer was used to accumulate a total of at least $10,000$ counts. No experiments were carried out in which the initial radioactivity was less than ten times background.

The technique for measuring heterogeneous rates was very similar to that used to measure the rate of reaction of mercury with iodine, except that the radioactivity of the samples was determined, as described above, instead of analyzing them spectrophotometrically.

Solubility Measurements. For solvents transparent in the ultraviolet, a subsaturated solution of known concentration was prepared and its spectrum determined. This was compared with the spectrum of the saturated solutions to determine their concentration. The saturated solutions were diluted as necessary. For opaque solvents the radioactivity of a solution of known concentration was determined, then the radioactivity of a saturated solution. In each solvent and at each temperature, saturation was approached from both sides; both pure solvent and supersaturated solutions were equilibrated with the crystals. Supersaturated solutions were obtained at higher temperatures. The equilibration was achieved by magnetically stirring a closed flask containing the solution and the crystals at constant temperature until no further change took place.

(28) K. Torsell, *Acta Chem. Scand.*, **13**, 115 (1959).

(29) R. Corsee, P. Dimroth, and R. Schempf, *Chem. Ber.*, **90**, 1337 (1957).

(30) J. C. Sipos, H. Sawatzky, and G. F. Wright, *J. Am. Chem. Soc.*, **77**, 2759 (1955).

Stable Carbonium Ions. XXXIII.^{1a}

Primary Alkoxy-carbonium Ions

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Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. Received January 21, 1967

Abstract: Several primary alkoxy- and alkoxyhalocarbonium ions were directly observed by nmr spectroscopy in the solvent system antimony pentafluoride-sulfur dioxide. Methoxychloro- and methoxyfluorocarbonium ions were found to exist in isomeric forms indicating a rotational barrier around the C-O bond. In the nmr spectra of methoxy- and chloromethoxycarbonium ions nonequivalence of the methylene protons was not observed. Chloromethoxycarbonium ion exhibited a temperature-dependent spectrum because of intermolecular exchange.

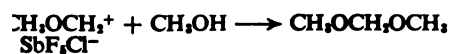
Primary and tertiary alkoxy-carbonium ions were prepared by Meerwein, *et al.*,² by alkylation of esters, and lactones with trimethyloxonium or oxonium tetrafluoroborate or by abstraction of an oxonium ion from acetals and orthoesters. Recently Ramsey and Taft,³ Hart and Tomalia,⁴ and Heinrich,⁵ and Kabuss⁶ reported on the observation (nmr) or isolation of a series of additional secondary and tertiary alkoxy-carbonium ions. We would like to report now our results relating to the observation of stable primary alkoxy- and haloalkoxy-carbonium ions. No primary alkoxy-carbonium ion is known from the literature. The only other long-lived primary carbonium ions reported are oxonium ions.⁷

Experimental and Discussion

Chloromethyl methyl ether is dissolved in antimony pentafluoride diluted with sulfur dioxide, a clear solution is obtained. The pmr spectrum of this solution at -60° (Figure 1) clearly indicates the presence of the methoxycarbonium ion (I).



The nature of I was deduced from the following observations. (1) The pmr spectrum shows subsheilding of both the methylene ($\delta = -9.94$ ppm) and methoxy ($\delta = -5.66$ ppm) protons. (2) The ^1H - ^{13}C coupling, giving rise to a triplet and a doublet, indicates formation of an sp^2 center. (3) Distillation of the solution of I gave a high yield of dimethoxymethane.



Part XXXII: J. M. Bollinger, C. A. Cupas, K. J. Friday, M. L. D. G. A. Olah, *J. Am. Chem. Soc.*, **89**, 156 (1967). (b) Science Foundation Postdoctoral Research Investigator.

Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. J. M. Ann., **632**, 38 (1960); H. Meerwein, V. Hederich, H. Morc. Wunderlich, *ibid.*, **635**, 1 (1960).

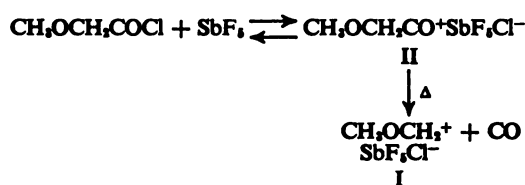
Ramsay and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **88**, 3058

Hart and D. Tomalia, *Tetrahedron Letters*, **3383**, 3389 (1966). Imroth and P. Heinrich, *Angew. Chem.*, **78**, 714 (1966).

Kabuss, *ibid.*, **78**, 714 (1966).

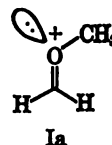
Cupas, M. B. Comisarow, and G. A. Olah, *J. Am. Chem. Soc.*, **88**, 1 (1966).

Ion I could also be observed to arise from the decarboxylation of the methoxyacetyl cation [methoxymethyloxocarbonium ion (II)] which is formed when methoxyacetyl chloride (fluoride) is treated with antimony pentafluoride in sulfur dioxide solution.



If a solution of II is maintained at -60° decarboxylation is very slow and the pmr spectrum of the oxocarbonium ion is observed. Near -20° decarboxylation is very fast and ion I is quantitatively generated.

We had anticipated that in ion I the positive charge will be substantially located on oxygen and therefore a high rotational (inversional) barrier would exist about the methylene-oxygen bond (Ia). Ramsey and Taft³



reported an activation energy of nearly 11 kcal/mole for the coalescence of the two nonequivalent methoxy groups in the dimethoxymethylcarbonium ion, $(\text{CH}_3\text{O})_2\text{C}^+\text{CH}_3$. However, the same authors found only line broadening but not separation, indicative of an observable rotational barrier, in the triethoxy-, dimethoxy-, and diethoxycarbonium ions.

The multiplicity of the absorptions observed for the methoxycarbonium ion, *i.e.*, a quartet and a triplet, would seem to indicate that this ion is freely rotating. This appears unreasonable in view of the 11-kcal activation energy measured by Taft and Ramsey³ for coalescence of the two nonequivalent methoxy groups in dimethoxymethylcarbonium ion and the *cis-trans* isomerism observed by us for the halomethoxycarbonium ions (subsequent discussion). One would anticipate a considerably larger activation energy for rotation in a primary alkoxy-carbonium ion than in a tertiary one. We therefore suggest that the spectrum observed for the methoxycarbonium ion corresponds to an $\text{AA}'\text{X}_2$ spectrum which is deceptively simple and that the observed coupling is an average of the *cis*

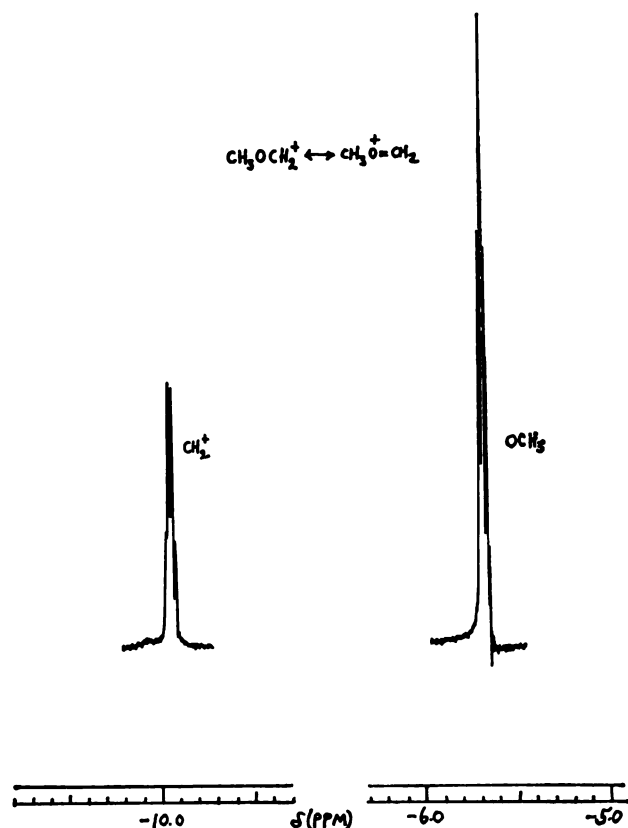


Figure 1.

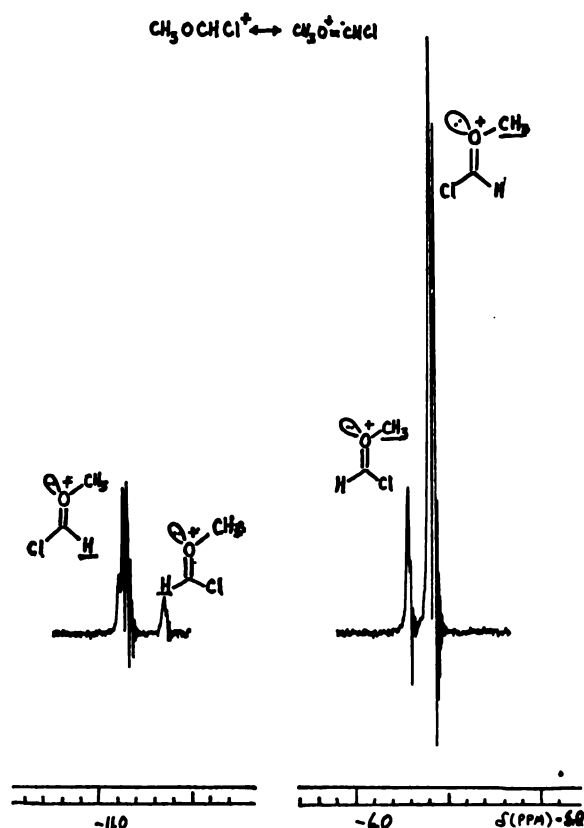


Figure 2.

and *trans* allylic couplings. This interpretation requires that the methyl group and the lone electron pair (see 1a) have the same effect on their respective nearest

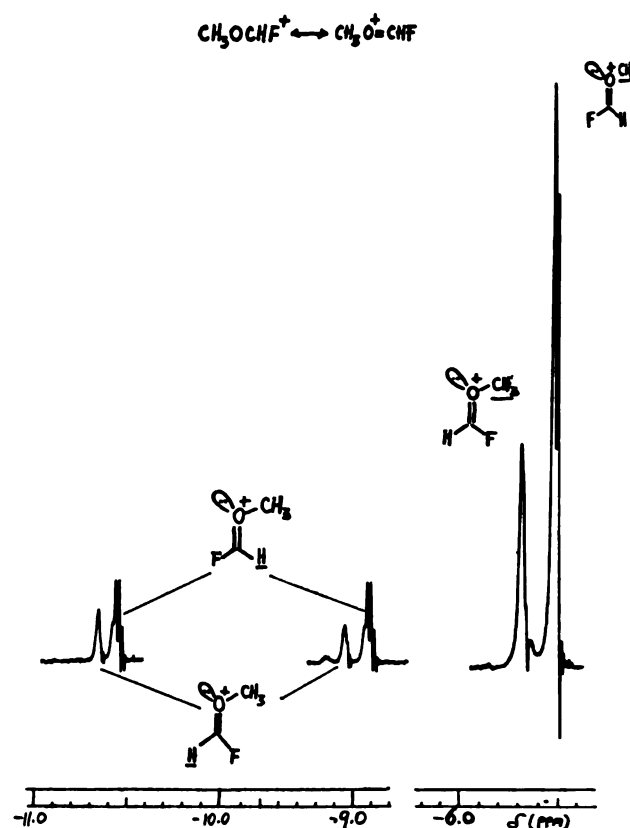


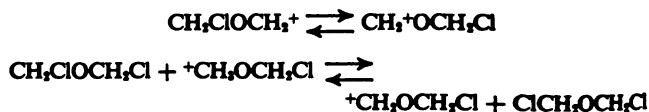
Figure 3.

protons causing the same chemical shift for these two methylene protons.

Similar considerations also apply to chloromethoxycarbonium ion. Bis(chloromethyl) ether in $\text{SbF}_5\text{-SO}_2$ solution is ionized to form the chloromethoxycarbonium ion III. The pmr spectrum of III (Figure 4) at -80°



consists of two triplets at -9.82 and -6.76 ppm, $J_{\text{H-H}} = 1.2$ Hz. This ion is very sensitive to the manner of preparation, and a temperature-dependent spectrum can readily be obtained. This effect is illustrated in Figure 5 showing the coalescence of the CH_2Cl and CH_2 peaks on raising the temperature. Coalescence was also observed simply by adding a small amount of additional bis(chloromethyl) ether. This indicates that in ion III intermolecular exchange may take place (between ion III and un-ionized bis[chloromethyl] ether). Our data do not, however, rule out intramolecular exchange.



It should be mentioned, as in the case of ion I, that there is no noticeable nonequivalence of the methylene protons of ion III. Thus there is not an observable barrier to rotation in the oxonium form of III and IV, although again we believe this to be a result of coincidental chemical shifts and deceptive simplicity.

When α,α -dichloromethyl ether is dissolved in $\text{SbF}_5\text{-SO}_2$ at -60° , the pmr spectrum (Figure 2) indicates

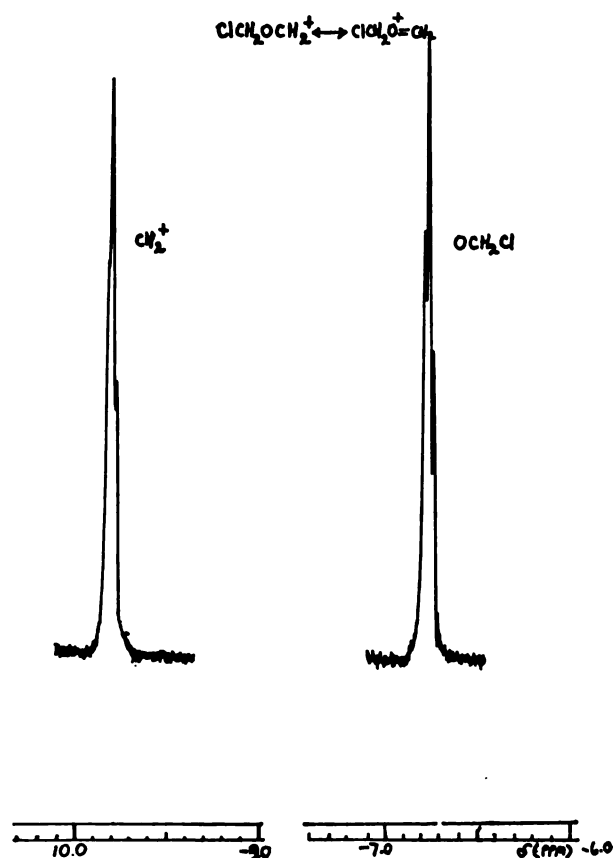
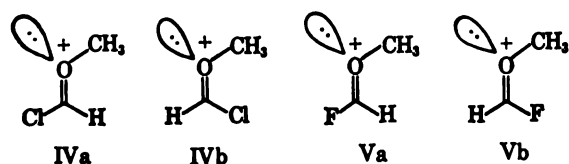


Figure 4.

formation of the methoxychlorocarbonium ion. This ion exists in two conformational forms 'a and b, of which 81% is IVa and 19% is IVb (measured by integration of the pmr spectrum).



red by integration of the pmr spectrum). This assignment is made on the basis of the larger coupling expected for a *cis* allylic coupling.⁸ (We found $J = 1.2$ Hz for the *cis* allylic coupling in IVa and $J = 7$ Hz for the *trans* allylic coupling in IVb). No change in the relative amounts of the two species was found between -40 and -90° .



This interpretation is supported by observation of the methoxyfluorocarbonium ion V prepared by ionization of α,α -difluoromethyl methyl ether⁹ in antimony pentafluoride-sulfur dioxide solution.



The pmr spectrum of V at -40° (the ion was poorly soluble at lower temperatures; near -20° it decomposed with gas evolution), shown in Figure 3, is

⁸ S. Sternbell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

⁹ J. Hine and J. J. Porter, *J. Am. Chem. Soc.*, **79**, 5493 (1957).

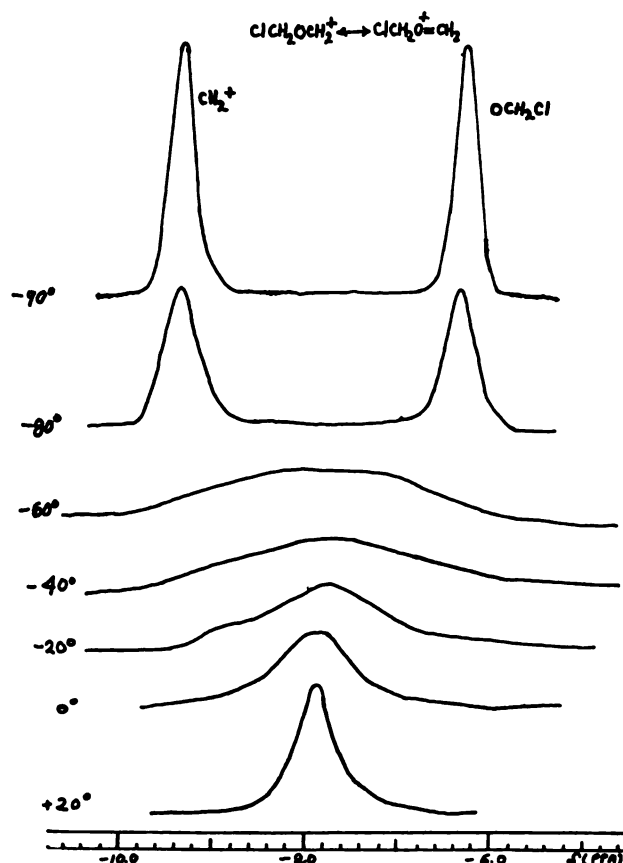


Figure 5.

again a composite of 70% Va and 30% Vb (by integration of both the proton and the fluorine spectra). Again, on the basis of the larger coupling found in Va, this species is assigned the *cis* allylic proton conformation. It is of interest that the fluorine atom does not show detectable coupling with the methoxy group in Va. However, the methoxy group of Vb on expanded sweep width can be seen to be a triplet with 0.7-Hz separations. In this conformation the fluorine atom couples with the methoxy group with the same value as the hydrogen atom. The geminal H-F coupling in both conformations is 98 Hz and provides support for the sp^2 nature of the carbon atom,¹⁰ as do the large downfield shifts of the fluorine atoms observed for both species (CF_3HOCH_3 appears as a doublet, $J_{\text{H-F}} = 75$ Hz, at $+89.7$ ppm; Va appears as a doublet, $J_{\text{H-F}}^{\text{trans}} = 98$ Hz, at -49.9 ppm and Vb appears as a doublet further split into quartets, $J_{\text{H-F}}^{\text{trans}} = 98$ Hz, $J_{\text{H-F}}^{\text{allylic}} = 0.7$ Hz, at -41.8 ppm, all from external FCCl_3 at -40°).

Observations of *cis-trans* isomerism in the halomethoxycarbonium ion shows that structures such as Ia, IVa and b, Va and b, etc., are obviously the important contributing resonance structure of alkoxy ions. On the other hand, the very substantial deshielding of the methylene protons in the methoxy- and chloromethoxycarbonium ions indicates that substantial charge is localized on the methylene carbon atom, and I and III can be considered as stable primary carbonium ions.

(10) H. M. McConnell, C. A. Reilly, and A. D. McLean, *J. Chem. Phys.*, **24**, 479 (1956), find $J_{\text{H-F}} = 81$ Hz in 1,1-dichlorofluoroethylene. G. A. Olah and E. B. Baker (in "Friedel-Crafts and Related Reactions," Vol. III, G. A. Olah, Ed., Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1964, pp 1182-1183) found 182.5 Hz for $J_{\text{H-F}}$ in formyl fluoride.

Table I. Nmr Data of Alkoxy-carbonium Ions*

Starting material in CCl ₄ , internal TMS			Ion in SbF ₅ -SO ₂ (-60°), external TMS in DCCl ₄	
CH ₃ OCH ₂ Cl	3.47 (s), CH ₂ O		I, 5.66 (t), CH ₂ O	<i>J</i> = 1.0 Hz
	5.42 (s), CH ₃		9.94 (q), CH ₃	
ClCH ₂ OCH ₂ Cl	5.58 (s), CH ₂		III, 6.76 (t), CH ₂	<i>J</i> = 1.1 Hz
			9.82 (t), CH ₃	
CH ₃ OCHCl ₂	3.67 (s), CH ₂ O		IVa, 5.60 (d), CH ₂ O	<i>J</i> = 1.2 Hz
	7.33 (s), CH		10.90 (q), CH	
			IVb, 5.72 (d), CH ₂ O	<i>J</i> = 0.7 Hz
			10.66 (q), CH	
CH ₃ OCHF ₂	3.54 (s), CH ₃	<i>J</i> _{H-F} = 75 Hz	Va, 5.46 (d), CH ₂ O	<i>J</i> _{H-F} = 98 Hz
	6.14 (t), CH		9.76 (2q), CH	<i>J</i> _{H-H} = 1.2 Hz
			Vb, 5.64 (t), CH ₂ O	<i>J</i> _{H-F} = 98 Hz
			9.86 (2q), CH	<i>J</i> _{H-H} = 0.7 Hz
				<i>J</i> _{H-F} ^{allylic} = 0.7 Hz

* (s), singlet; (d), doublet; (t), triplet; (q) quadruplet. ^b At -40°.

The pmr data of ions I, III, IV, and V are summarized in Table I. All integrations were in accord with assigned structures.

Experimental Section

All of the halo ethers except α, α -difluoromethyl methyl ether were commercially available and used as obtained. α, α -Difluoromethyl methyl ether was prepared by the method of Hine.⁹

Solutions of the carbonium ions were obtained in the following way. A saturated solution of antimony pentafluoride in sulfur dioxide was prepared (at -10°). Portions (2 ml) of this solution were cooled to -78°, causing some antimony pentafluoride to crystallize from solution. To this suspension was added dropwise with stirring approximately 0.3 g of the appropriate halo ether. Slight warming was required to complete the ionization, whereupon a homogeneous solution resulted with only slight traces of color. Ion concentrations were approximately 10%. These operations were carried out in the laboratory atmosphere. This procedure

provides a simply way to generate carbonium ions in a highly reproducible manner.

Spectra were recorded either on a Varian Model A56-60A spectrometer with external TMS in deuteriochloroform as reference (0.5 ppm has been added to these chemical shifts to correct them to TMS in a capillary as reference) or on a Varian Model HA-60 spectrometer with TMS in a capillary as reference.

Methanolysis of the carbonium ions was accomplished by adding slowly the solution of the carbonium ion in sulfur dioxide to a suspension of methanol and potassium carbonate at -78°. Product isolation was accomplished by drowning the resulting suspension in water and extracting with pentane. Identification of products was made by glpc comparison of retention times with authentic samples and by nmr and infrared spectroscopy. None of the dihalo ethers retained halogen in the quenching experiments.

Acknowledgment. Generous support of the work by grants of the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

Stable Carbonium Ions. XL.^{1a} Protonated Aliphatic Thiols and Sulfides and Their Cleavage to Carbonium Ions

George A. Olah, Daniel H. O'Brien,^{1b} and Charles U. Pittman, Jr.,^{1c}

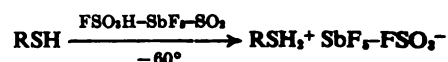
Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. Received January 21, 1967

Abstract: A series of protonated aliphatic thiols and sulfides have been studied in HSO₃F-SbF₅-SO₂ solution. S-protonation was observed at -60° by nmr spectroscopy with negligible exchange rates. At higher temperatures, protonated thiols cleave to carbonium ions. Protonated sulfides, except for tertiary alkyl ones, are resistant to cleavage up to +70°.

We have previously reported the nmr observation of protonated alcohols^{2,3} and ethers.⁴ We wish now to report the observation of S-protonated thiols and sulfides in the extremely strong acid, FSO₃H-SbF₅, at -60° and their cleavage to carbonium ions.

Results and Discussion

Protonated Thiols. Aliphatic thiols are quantitatively protonated in FSO₃H-SbF₅ diluted with SO₂ at -60°.



They show well-resolved nmr spectra with very slow exchange rates. Protonated hydrogen sulfide itself shows a sharp singlet at -6.60 ppm. Protonated methyl thiol (Figure 1) shows the methyl triplet at -2.95 ppm and a SH₂⁺ quartet at -6.45 ppm (*J*_{H-H} = 8.0 cps). Protonated ethyl thiol (Figure 2) shows

(1) (a) Part XXXIX: G. A. Olah and J. Lukas, *J. Am. Chem. Soc.*, **89**, 2227 (1967). (b) National Science Foundation, Postdoctoral Research Investigator, 1966-1967. (c) National Science Foundation, Postdoctoral Research Investigator, 1965.

(2) G. A. Olah and E. Namanworth, *J. Am. Chem. Soc.*, **88**, 5327 (1966).

(3) G. A. Olah, J. Sommer, and E. Namanworth, *ibid.*, in press.

(4) G. A. Olah and D. H. O'Brien, *ibid.*, **89**, 1725 (1967).

Table I. Nmr Chemical Shifts and Coupling Constants of Protonated Thiols at -60° in $\text{HSO}_3\text{F}-\text{SbF}_5-\text{SO}_2$

Thiol	δ , ppm ^a					$J_{\text{H-H}^+}$, cps
	H ₁	H ₂	H ₃	H ₄	SH ₂ ⁺	
HSH					-6.60 (1)	...
1 CH ₃ SH	-2.95 (3) ^b				-6.45 (4)	8.0
2 1 CH ₃ CH ₂ SH	-3.37 (6)	-1.48 (3)			-6.22 (cm)	8.0
3 2 1 CH ₃ CH ₂ CH ₂ SH	-3.40 (cm)	-1.98 (cm)	-1.00 (3)		-6.37 (cm)	8.0
2 1 CH ₃ >CHSH	-3.98 (cm)	-1.73 (2)			-5.93 (2)	7.5
4 3 2 1 CH ₃ CH ₂ CH ₂ CH ₂ SH	-3.47 (6)	~-1.70 (cm)	-1.70 (cm)	-0.90 (3)	-6.45 (3)	7.6
3 2 1 CH ₃ >CHCH ₂ SH	-3.32 (cm)	~-2.25 (cm)	-1.03 (cm)		-6.40 (3)	8.0
3 2b 1 CH ₃ CH ₂ CHSH	-4.08 (6)	a -1.82 (2) b -2.10 (cm)	-1.15 (3)		-6.35 (2)	7.0
CH ₃ 2a (CH ₃) ₂ CSH	...	-1.75 (1)			-6.42 (1)	...
3 2b 1 CH ₃ CH ₂ CSH	...	a -1.75 (1) b -1.97 (cm)	-1.07 (3)		-6.32 (1)	...
CH ₃ 2a						

^a From external capillary of TMS. ^b Multiplicity of peaks shown in brackets; (cm) = complex multiplet.

the methyl triplet at -1.48 ppm, a methylene sextet at -3.37 ppm, and a SH₂⁺ triplet having a complex central peak at -6.22 ppm ($J_{\text{H-H}} = 8.0$ cps). Assignments of the protonated chemical shifts and coupling constants of the protonated thiols studied: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, and *t*-amyl, are summarized in Table I.

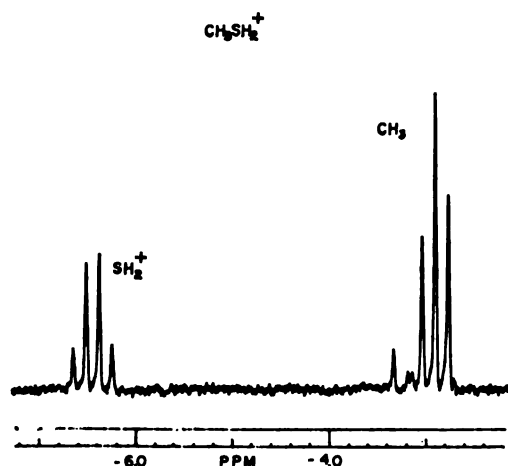


Figure 1.

The protonated thiols are surprisingly stable to increase in temperature when compared to the corresponding protonated alcohols.³ However, the mode of sample preparation is critical. If the sample is prepared by the addition of the diluted, cooled acid to the thiol, simple protonated species are not observed. The nmr spectra indicate that protonated thiols react readily with the excess thiol still present in the solution.

However, when prepared by the addition of thiol to acid, even protonated *t*-butyl thiol shows no appreciable decomposition at -60° . The small peak at -4.0 ppm in the spectrum of protonated *t*-butyl thiol (Figure

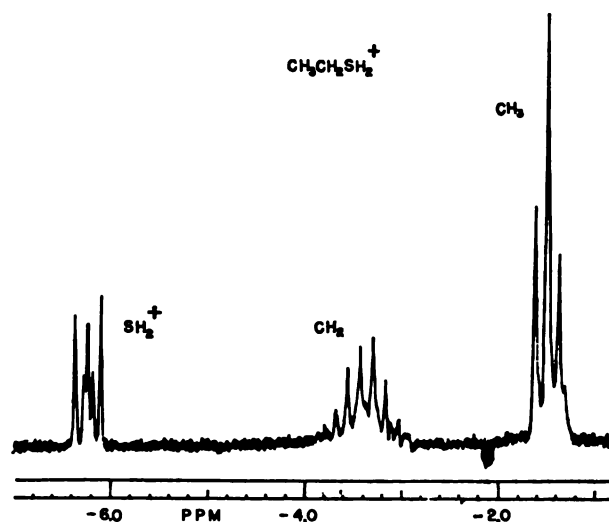


Figure 2.

3) can be attributed to trimethylcarbonium ion and is probably due to cleavage as a consequence of local heating during sample preparation. The intensity of this peak did not increase with time at -60° . In contrast, all attempts to prepare protonated *t*-butyl alcohol results in complete formation of trimethylcarbonium ion even at -70° .

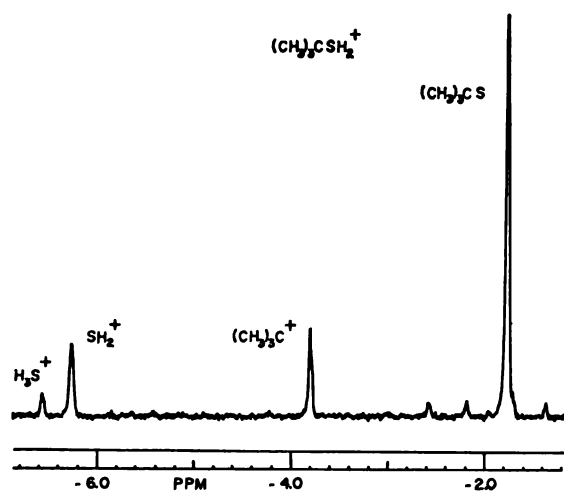


Figure 3.

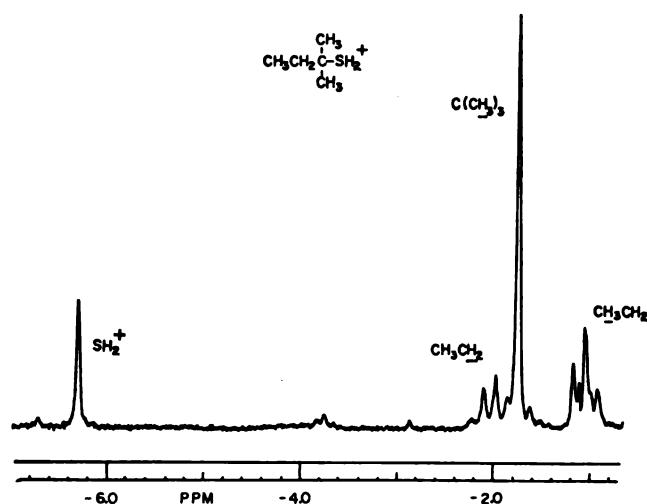
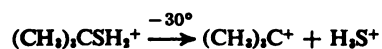


Figure 4.

Protonated *t*-butyl thiol slowly cleaves to trimethyl-



carbonium ion and protonated hydrogen sulfide when the temperature is increased to -30° ($t_{1/2} \approx 15$ min). Protonated *t*-amyl thiol (Figure 4) also cleaves at this temperature to dimethylethylcarbonium ion. The spectrum of this carbonium ion can clearly be seen in Figure 5.⁵

Protonated secondary thiols are stable at higher temperatures. Protonated isopropyl thiol cleaves slowly at 0° in $\text{FSO}_3\text{H-SbF}_5$ (1:1) solution. No well-identified carbonium ion was found in the nmr spectra under these conditions, obviously due to the relative instability of the isopropyl cation at higher temperature giving a complex reaction mixture. Protonated *sec*-butyl thiol cleaves to trimethylcarbonium ion at this temperature.



(5) G. A. Olah, E. B. Baker, J. C. Evans, W. S. Tolgyesi, J. S. McIntyre, and I. J. Bastien, *J. Am. Chem. Soc.*, **86**, 1360 (1964).

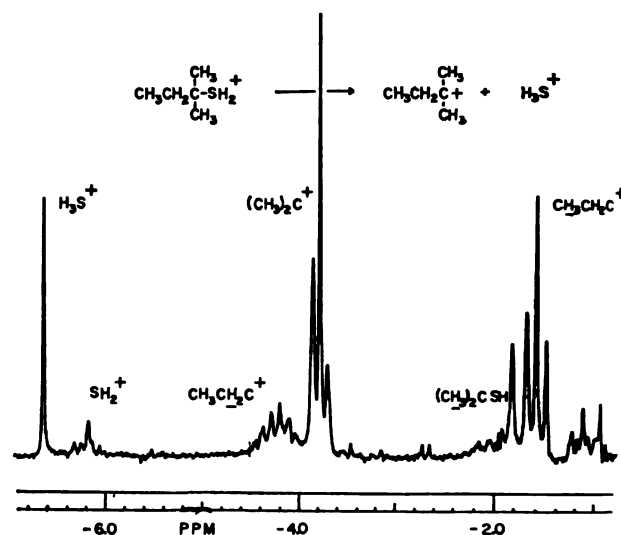


Figure 5.

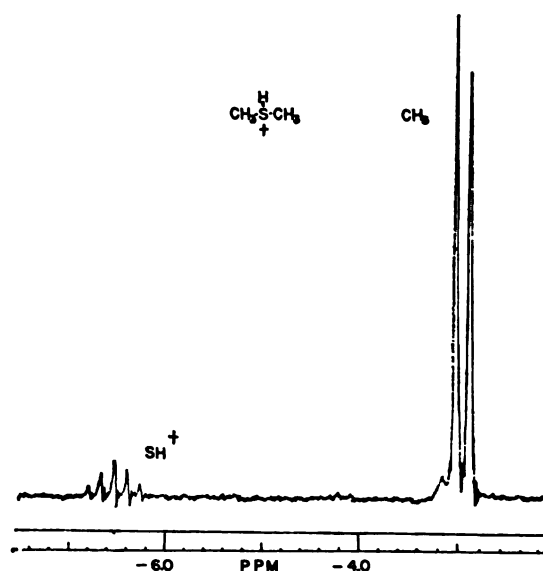
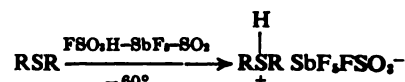


Figure 6.

Protonated primary thiols are stable at much higher temperatures. When prepared at 0° in $\text{FSO}_3\text{H-SbF}_5$ (1:1), protonated *n*-butyl thiol shows slight decomposition to trimethylcarbonium ion attributable to local heating during sample preparation. The intensity of the trimethylcarbonium ion peak did not increase with time at this temperature. Protonated *n*-butyl thiol slowly cleaves to trimethylcarbonium ion only at $+25^\circ$.



Protonated Sulfides. Alkyl sulfides are quantitatively protonated in $\text{FSO}_3\text{H-SbF}_5$ diluted with SO_2 at -60° .



They show well-resolved nmr spectra. Protonated dimethyl sulfide (Figure 6) shows the methyl doublet at -3.08 ppm and the SH^+ septuplet at -6.52 ppm ($J_{\text{H-H}} = 8.0$ cps). Protonated diethyl sulfide (Figure 7) shows the methyl triplet at -1.67 ppm, a complex

Table II. Nmr Chemical Shifts and Coupling Constants of Protonated Sulfides at -60° in $\text{HSO}_3\text{F-SbF}_6\text{-SO}_2$

Sulfide	δ , ppm ^a					$J_{\text{H-SH}^+}$, cps
	H ₁	H ₂	H ₃	H ₄	SH ⁺	
1 (CH ₃) ₃ S	-3.08 (2) ^b				-6.52 (7)	8.0
2 1 (CH ₃ CH ₂) ₂ S	-3.57 (cm)	-1.67			-6.23 (5)	8.0
3 2 1 (CH ₃ CH ₂ CH ₂) ₂ S	-3.33 (cm)	-2.00 (cm)	-1.07 (3)		-6.18 (5)	8.1
2a (CH ₃ >CH) ₂ S	-3.98 (6)	a -1.62 (2) b -1.57 (2)			-5.80 (3)	7.5
2b 2 1a 1b CH ₃ >CHSCH ₃	a -3.89 (cm) b -2.90 (2)	-1.63 (2)			-6.07 (cm)	8.0
4 3 2 1 (CH ₃ CH ₂ CH ₂ CH ₂) ₂ S	-3.33 (cm)	~ -1.70 (cm)	~ -1.70 (cm)	-1.00 (cm)	-6.13 (5)	8.0
3 2a 1 (CH ₃ CH ₂ CH ₂) ₂ S	-3.70 (cm)	a -2.00 (cm) b -1.71 (cm)	-1.10 (3)		-5.73 (cm)	7.7
CH ₃ 2b 2 CH ₃ (CH ₃ C-) ₂ S CH ₃		-1.83 (1)			-5.83 (1)	...
CH ₃ 1 (CH ₃ C-)SCH ₃ CH ₃ 2b CH ₃ 1 2a CH ₃ CSCH<CH ₃ CH ₃	-2.87 (2)	-1.67 (1)			-6.00 (4)	8.0
	-4.05 (cm)	a -1.62 (2) b -1.73 (1)			-6.25 (2)	7.0

^a From external capillary of TMS. ^b Multiplicity of peaks shown in brackets; (cm) = complex multiplet.

multiplet for the methylene hydrogens at -3.57 ppm, and the SH⁺ quintet at -6.23 ppm ($J_{\text{H-H}} = 8.0$ cps). Assignments of derived shifts and coupling constants are summarized in Table II.

The proton on sulfur in the protonated thiols and sulfides is at considerably higher field (-6.52 to -5.80 ppm) than the corresponding proton on oxygen in protonated alcohols and ethers (-9.21 to -7.88 ppm).^{1,2,3} It is worthy of note that protonated hydrogen sulfide appears as a sharp singlet with a similar chemical shift, -6.60 ppm, indicating that the positive charge on protonated sulfur is delocalized and little influenced by alkyl substitution.

Protonated isopropyl sulfide (Figure 8) gave an unexpectedly complex pattern for the methyl hydrogens. It showed a pair of overlapping doublets separated by 3.5 cps at -60° . It is highly unlikely that a preferred conformation can explain this multiplicity since the pair of doublets is still present at $+70^\circ$ in a solution of $\text{HSO}_3\text{F-SbF}_6$ (1:1). A more plausible explanation is the existence of intrinsic asymmetry in the $-\text{HS}^+-\text{R}$ group comparable to that found in ethyl isopropyl sulfoxide, diethyl sulfoxide,⁶ ethyl benzenesulfonate, diethyl acetal,⁷ diethyl sulfite,⁸ and ethyl perfluoro-

isopropanesulfinate.⁹ This asymmetry results in non-equivalent methylene hydrogens in the ethyl groups of the first five listed compounds and nonequivalent

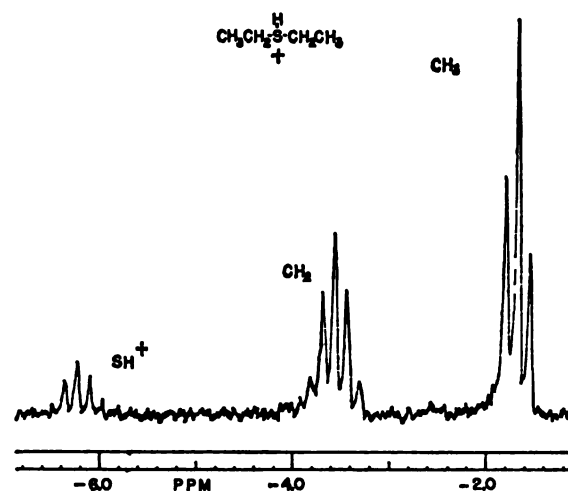


Figure 7.

(8) H. Finefold, *Proc. Chem. Soc.*, 283 (1960); F. Kaplan and J. D. Roberts, *J. Am. Chem. Soc.*, 83, 4666 (1961).

(9) R. M. Rosenberg and E. L. Muettterties, *Inorg. Chem.*, 1, 756 (1962).

(6) T. D. Coyle and F. G. A. Stone, *J. Am. Chem. Soc.*, 83, 4138 (1961).

(7) J. S. Waugh and F. A. Cotton, *J. Phys. Chem.*, 65, 562 (1961).

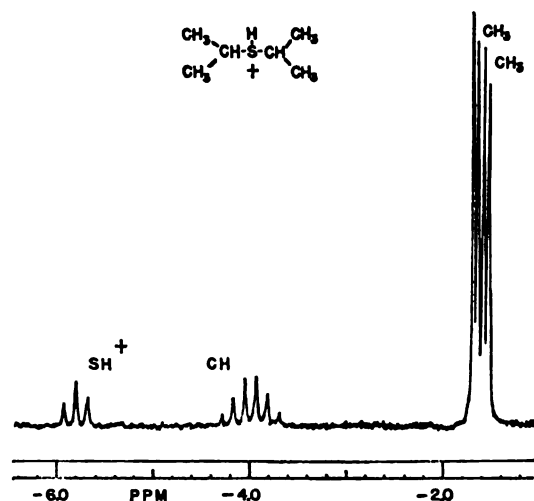


Figure 8.

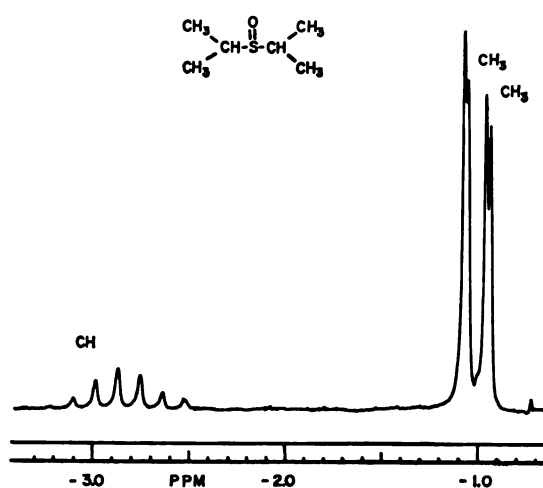


Figure 9.

perfluoromethyl groups in the F^{19} spectrum of ethyl perfluoroisopropanesulfinate. The nmr spectrum of diisopropyl sulfoxide (Figure 9) displays a nonequivalent, overlapping methyl doublets separated by 2.5 cps when dissolved in SO_2 at -60° .

It is particularly noteworthy that nonequivalent methylene hydrogens were observed in the boron hydride addition complex of diethyl sulfide, $(CH_3CH_2)_2S \cdot BH_3$.⁶ This would indicate that the bonding at sulfur in this compound and in the protonated sulfides is qualitatively similar. The existence of this asymmetry further confirms the fact that the exchange of the proton is extremely slow.

In other protonated sulfides where such multiplicity might be observed, protonated methyl isopropyl sulfide gave only one isopropyl methyl doublet; protonated *t*-butyl isopropyl sulfide gave only slight broadening of the isopropyl methyl doublet; and protonated diethyl sulfide gave a complex methylene peak because of the further splitting by the proton on sulfur.

The protonated sulfides are more stable to cleavage than the corresponding protonated ethers² and also more stable than the protonated thiols. Protonated methyl *t*-butyl ether is completely cleaved to trimethylcarbonium ion and protonated methanol upon sample preparation even at -70° . Protonated methyl *t*-butyl

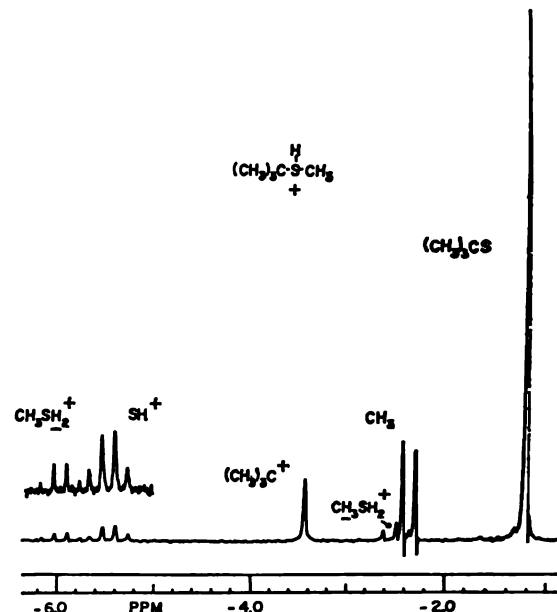


Figure 10.

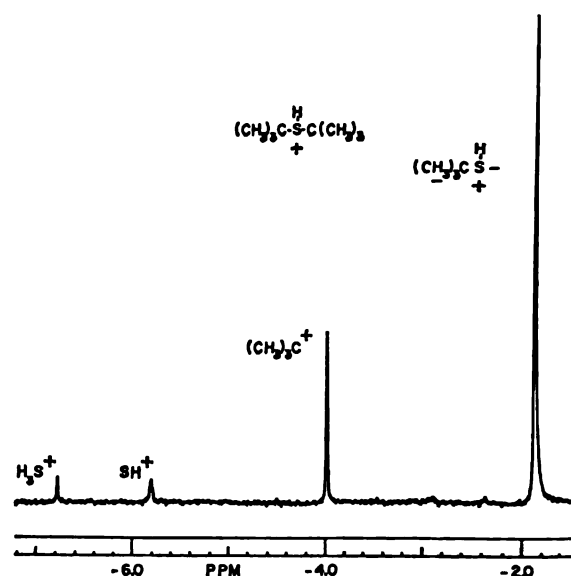
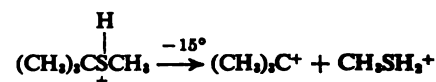
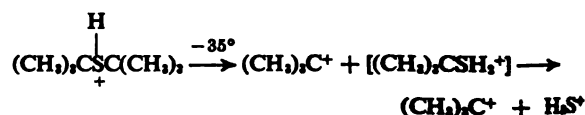


Figure 11.

sulfide is stable at -60° (Figure 10). The initial spectrum shows slight decomposition to trimethylcarbonium ion and protonated methyl thiol probably caused by local heating during sample preparation. No change in peak intensities with time was noted at -60° . When the temperature is increased to -15° , protonated methyl *t*-butyl sulfide very slowly cleaves to trimethylcarbonium ion and protonated methyl thiol.



Protonated di-*t*-butyl sulfide shows very little cleavage at -60° (Figure 11). At -35° it cleaves slowly ($t_{1/2} \approx 1$ hr) to trimethylcarbonium ion and protonated hydrogen sulfide



Protonated secondary sulfides show extraordinary stability toward the strongly acidic medium. Protonated isopropyl sulfide shows no appreciable cleavage up to $+70^\circ$ in a solution of $\text{FSO}_3\text{H-SbF}_5$ (1:1). At this temperature it slowly decomposed. No nmr identifiable products were noted at this elevated temperature.

Experimental Section

Materials. Thiols, symmetrical dialkyl sulfides, isopropyl methyl sulfide, and *t*-butyl methyl sulfide were reagent grade materials and were used without further purification.

sec-Butyl isopropyl sulfide was prepared according to the method of Vecera¹⁰ by the reaction of *sec*-butylthiol in ethoxide-ethanol solution with isopropyl bromide. The product was purified by distillation. The fraction between 139 and 140° was used.

t-Butyl isopropyl sulfide was prepared according to the method of McAllan¹¹ by the reaction of *t*-butyl alcohol in 25% aqueous sulfuric acid with isopropylthiol. The product was purified by distillation. The fraction between 130 and 132° was used.

Isopropyl sulfoxide was prepared by the method of Addison¹² by the reaction of isopropyl sulfide with dinitrogen tetroxide.

(10) M. Vecera, J. Gasparic, D. Snobl, and M. Jurecek, *Chem. Listy*, **50**, 770 (1956); *Chem. Abstr.*, **50**, 15412a (1956).

(11) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **75**, 3627 (1951).

(12) C. C. Addison and J. C. Sheldon, *J. Chem. Soc.*, 2705 (1956).

The product was purified by vacuum distillation. The fraction between 91 and 92° (12 mm) was used. The nmr spectra of the sulfoxide dissolved in sulfur dioxide at -60° is shown in Figure 9.

Nmr Spectra. Varian Associates Model A-56-60A and HA 60-IL nmr spectrometers with variable temperature probes were used for all spectra. Samples of S-protonated thiols and sulfides were prepared by dissolving approximately 1.5 ml of $\text{HSO}_3\text{F-SbF}_5$ (1:1 *M* solution) in an equal volume of sulfur dioxide and cooling to -76° . The thiol or sulfide (approximately 0.2 ml) was dissolved in 1 ml of sulfur dioxide, cooled to -76° , and with vigorous agitation slowly added to the acid solution. Samples prepared in this manner gave nmr spectra which showed no appreciable chemical shift differences with temperature or small concentration variations. The acid was always in excess of the sulfide or thiol as indicated by the large acid peak at -10.2 ppm. Samples undiluted with sulfur dioxide were prepared by cooling the 1:1 *M* acid to 0° and adding, with vigorous agitation, the neat, cooled sulfide or thiol. The nmr spectra of such samples showed a downfield solvent shift of about 0.3 ppm for all peaks because of the absence of sulfur dioxide.

Protonated hydrogen sulfide was prepared by passing gaseous hydrogen sulfide for a short time through a stirred solution of 2 ml of 1:1 $\text{FSO}_3\text{H-SbF}_5$, diluted with 2 ml of sulfur dioxide and cooled to -76° .

Acknowledgment. Generous support of the work by grants of the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

Acid Anhydride-Free Acid Equilibria in Water in Some Substituted Succinic Acid Systems and Their Interaction with Aniline¹

Takeru Higuchi,² Lennart Ebersson, and John D. McRae

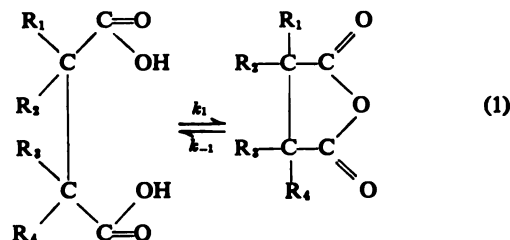
Contribution from the School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706. Received November 7, 1966

Abstract: The rates of formation of cyclic acid anhydrides in aqueous solutions of methyl-substituted succinic acids are shown to increase as expected with the degree of substitution. For the unsubstituted and mono- and di-substituted acids, at least, the estimated equilibrium concentration of the anhydride in the acid solution ranges from 1 to 50 ppm and appears to be largely determined by the rate of formation than by its hydrolysis. The aniline method was not found to be applicable to the tri- and tetrasubstituted acids because of the rapid formation of the corresponding imides.

Recent experimental evidence points to the existence of rather sluggish equilibria in water between certain sterically favored polycarboxylic acids and their corresponding cyclic internal anhydride.³ Although such a process may be expected to be favored by, for example, alkyl substitution⁴ in succinic acid, quantitative evaluation of such an effect had not been widely attempted, particularly on systems in which the relative concentration of the anhydride species would be expected to be low. The present report is concerned with results of an attempt to determine the rates of formation and the relative concentrations of these active species

in aqueous solutions of methyl-substituted succinates at several temperatures.

Direct spectrophotometric determination of the forward rate of reaction 1 as carried out recently⁵ was



not possible in these systems since the relative concentrations of the anhydrides are always much too low to permit convenient determination. For the present purpose, the aniline method developed earlier for studies

(5) L. Ebersson, *Acta Chem. Scand.*, **18**, 1276 (1964).

(1) Supported in part by a grant from the National Institutes of Health, Bethesda, Md., under GM-05830.

(2) Author to whom reprint requests should be directed.

(3) T. Higuchi, T. Miki, A. C. Shah, and A. Herd, *J. Am. Chem. Soc.*, **85**, 3655 (1963).

(4) Recent studies in the glutaric series reflecting effects of this nature have been reported by T. C. Bruice and W. C. Bradbury, *ibid.*, **87**, 4838 (1965).

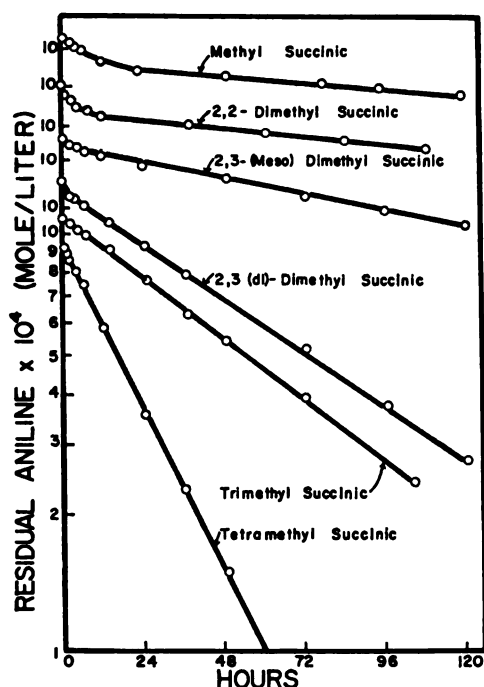
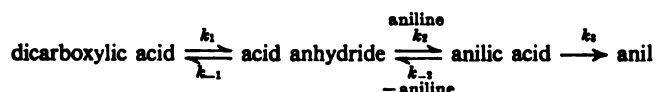


Figure 1. Semilogarithmic plot of aniline concentration as a function of time in several methyl-substituted succinic acid buffers at pH 4.0 and 60°. All buffers were 0.06 *M*.

on the unsubstituted succinate system³ was applied. The method is based on the observation that the formation of anilic acid in aqueous solutions of these dicarboxylic acids and aniline is mediated entirely through intermediate production of the corresponding cyclic anhydride, measurement of the rate of formation of the amide thus affording estimation of both the rate of formation of the anhydride and the equilibrium constant for the cyclization reaction.

Results and Observations

General Behavior of Aniline-Succinate Systems. In Figure 1 the observed residual concentration of aniline in the presence of six methyl-substituted succinate buffers, 0.06 *M* at pH 4.0, is shown as a function of time at 60°. The initial concentration of the amine in each instance was 0.001 *M*. As is evident from the plots, the terminal phase of each reaction exhibited pseudo-first-order reaction kinetics. Since in the trimethyl and tetramethyl systems crystalline precipitates of the corresponding anils were observed, the over-all reaction appears to be



on the basis of previously established chemistry of the succinate system. The initial nonlinearity observed with the mono- and dimethyl systems is presumably due to buildup of the corresponding anilic acid.

If the above rationalization is correct, the indicated equilibrium between the dicarboxylic acid and the anilic acid occurs with increasing facility as the degree of substitution is increased. It is evident in the case of tri- and tetramethyl systems that the initial equilibria are established too quickly to permit convenient measurement of the unidirectional rate, at least at 60°.

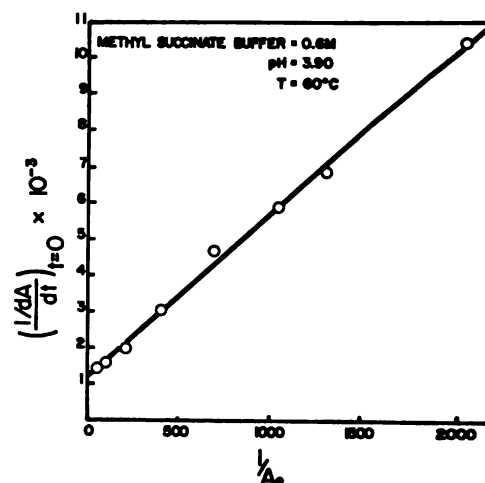


Figure 2. Reciprocal plot of the initial rate of disappearance of aniline in pH 3.90 methylsuccinate buffer (0.6 *M*) at 60° as a function of the reciprocal initial aniline concentration.

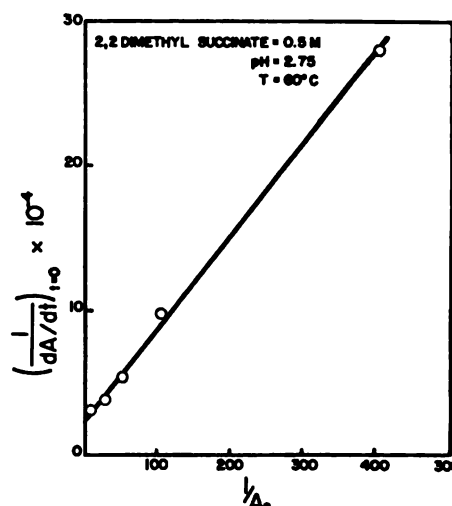


Figure 3. Reciprocal plot of the initial rate of disappearance of aniline in pH 2.75, 2,2-dimethylsuccinate buffer (0.5 *M*), at 60° as a function of the reciprocal initial aniline concentration.

It appeared possible, however, in the remaining four systems to determine the initial rates of loss of aniline in the manner previously described for estimating the k_1 values for these acids.

Estimation of k_1 . The absolute rate of formation of the postulated acid anhydride species for monomethyl- and two dimethyl-substituted succinic acids was estimated by determining the limiting initial rate of reaction with excess aniline in these systems. The reciprocal of initial rates was plotted *vs.* the reciprocal of initial aniline concentrations to give plots such as those represented by Figures 2 and 3 for the methylsuccinate and 2,2-dimethylsuccinate buffer systems, respectively. The limiting initial rate represented by the intercept of such plots can be used to calculate k_1 . The values of k_1 obtained in this manner are shown in Figure 4 plotted in the usual Arrhenius manner against $1/T$, the actual range of temperature being 40–70° for the monomethylsuccinic system and 50–80° for two dimethylsuccinic systems. Measurement was not attempted in the case of the *meso*-dimethylsuccinate system because of the low solubility of the acid and because of

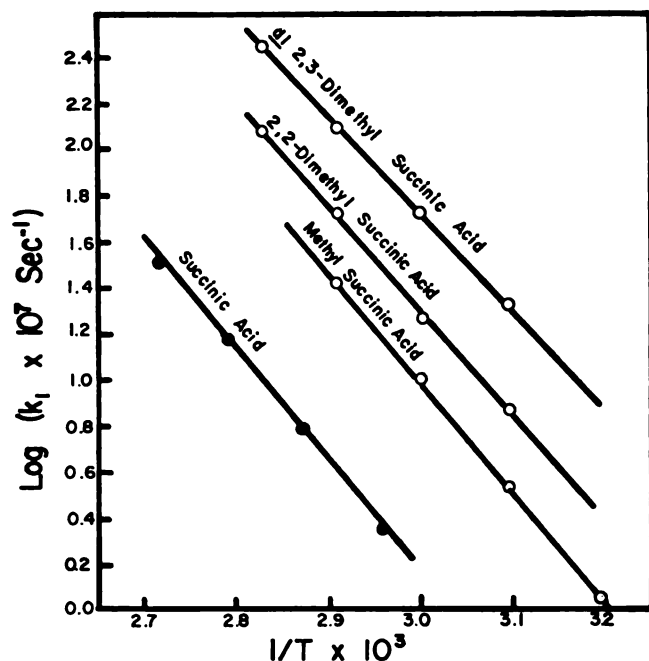


Figure 4. Arrhenius plots of k_1 , the anhydride formation constant for four anhydrides.

its limited availability. Data for the unsubstituted succinic acid obtained earlier³ are also included for comparison purposes. In Table I numerical values obtained at 60° are given, together with E_a , the energies of activation estimated from the Arrhenius plots. Eyring's ΔH^\ddagger would differ from these by 0.66 kcal/mole. Entropies of activation have been calculated for k_1 at 60° and are also included in Table I.

Table I. Rate of Cyclic Anhydride Formation in Water at 60°

Acid	$k_1 \times 10^7$ sec ⁻¹	E_a , kcal/ mole	$-\Delta S^\ddagger$, eu
Succinic	1.5	22.2	25.2
Methylsuccinic	9.9	21.7	22.9
2,2-Dimethylsuccinic	18.2	21.1	23.4
2,3-dl-Dimethylsuccinic	52.5	19.6	25.7

Estimation of K_1 ($=k_1/k_{-1}$). The equilibrium constants for the cyclization step can be readily estimated from the k_1 values since the reverse reactions have been studied by Eberson.⁶ In Table II the constants, or equivalently the fraction of these acids present at these temperatures in their respective anhydride forms at equilibrium, are listed.

Table II. Equilibrium Constant for Anhydride Formation

Temp, °C	$K_{eq} \times 10^6$ (k_1/k_{-1})			
	Succinic	Methylsuccinic	2,2-Dimethylsuccinic	2,3-dl-Dimethylsuccinic
95	21	130	340	600
75	10	60	165	320
50	4 ^a	19.5	56	130
25	1 ^a	5.5 ^a	16 ^a	49 ^a

^a Extrapolated values.

(6) L. Eberson, *Acta. Chem. Scand.* 18, 534 (1964).

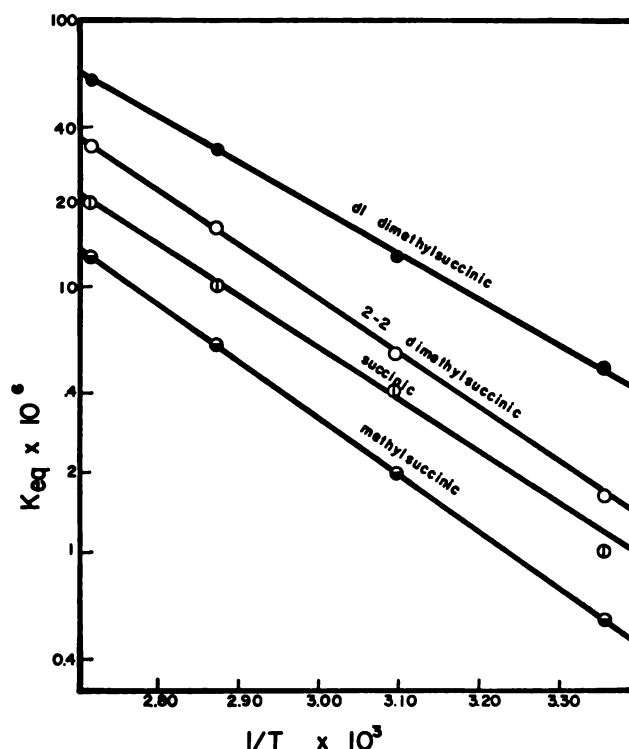


Figure 5. Equilibrium constant for formation of cyclic anhydride in water plotted against $1/T$.

The values shown in the table for succinic acid require some explanation since the extrapolated constant at 25° of 1×10^{-6} differs significantly with that of 0.2×10^{-6} reported earlier.³ In making the earlier estimate, the rate constants (k_1) obtained experimentally at 95, 85, 75, and 65° for succinic acid were considered to form a curved rather than a linear Arrhenius plot, the nonlinear extrapolation yielding a rather rough estimate for K_{eq} of 2×10^{-7} at 25°. The slight departure from linearity is evident for the point shown in Figure 4. If, however, we assume that the line is more or less linear as are others of the series, the equilibrium constant at 25° for succinic comes out to be approximately 1×10^{-6} . The magnitude of the uncertainty introduced by extrapolation reflects the relatively high activation energy for the reaction. The higher equilibrium value for succinic anhydride would reduce the free energy of its hydrolysis from -9250 cal/mole recently calculated from our earlier data by Jencks, *et al.*,⁷ to -8310 cal/mole.

The equilibrium constants given in Table II are shown plotted in Figure 5 against $1/T$. The enthalpic changes for cyclization of the four acids shown do not appear to differ significantly, the mean indicated heat of the reaction being of the order of 9 kcal/mole.⁸ The plot for succinic acid appears to support the higher extrapolated value of the equilibrium value at 25° since it falls essentially on the line.

Evaluation of k_2 . Determinations of k_2 , the rate constant for reaction between free aniline and anhydride,

(7) W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Am. Chem. Soc.*, 88, 4464 (1966).

(8) The observed lack of dependence on methyl substitution is at variance with the conclusion drawn from calorimetric measurements (J. B. Conn, G. B. Kistiakowsky, R. M. Roberts, and E. A. Smith, *ibid.*, 64, 1747 (1942)). These were, however, carried out on solid anhydrides and involved guesses as to heats of fusion. The mean value of 9 kcal is in reasonable agreement with the mean of the calorimetric estimates.

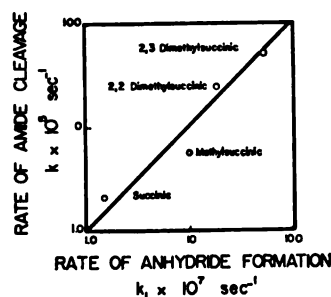


Figure 6. Plot of rates of hydrolysis of succinanic acids against rates of anhydride formation from corresponding acids.

were performed for five methyl-substituted succinic anhydrides. These determinations were made at 20, 25, and 30° at pH 4.65 using a 0.05 *M* buffer composed of an acid-salt system corresponding to the anhydride studied. The values of k_2 obtained at 25°, based on free aniline concentration at the chosen pH, are shown in Table III. Check runs on methylsuccinic anhydride and aniline at pH 3.30 and 3.90 at 25° yielded results which agreed with that obtained at higher pH. The apparent heat of activation, E_a , for the formation of all the anilic acids was found to be essentially the same, about 4.6 ± 0.3 kcal/mole.

Table III. Comparison of Rate of Reaction with Aniline, k_2 , with Rate of Hydrolysis, k_{-1} , at 25°

Acid anhydride	$k_2, M^{-1} \text{ sec}^{-1}$	$k_{-1} \times 10^3, \text{ sec}^{-1}$
Succinic	19.3	2.64
Methylsuccinic	15.3	3.65
2,2-Dimethylsuccinic	5.3	2.84
<i>dl</i> -2,3-Dimethylsuccinic	9.2	3.95
<i>meso</i> -2,3-Dimethylsuccinic	13.4	5.73

General Discussion

It is apparent from the data presented that substitution of methyl groupings for methylene hydrogens in succinic acid markedly increases the cyclization tendency as expected. The order and magnitude of the observed rate enhancement essentially parallel that recently reported for formation of the same anhydrides from the corresponding succinanic acids,⁹ as is evident from the log-log plot of the specific rate constants as shown in Figure 6. Since the reverse hydrolytic reaction rates represented by k_{-1} in Table III are relatively unaffected by methyl substitution, the equilibrium points appear to be largely determined by the formation rate.

Experimental Section

Equipment and Reagents. Mineral oil baths regulated to 0.05° were used for the kinetic runs to determine k_1 . All final determinations of residual aniline were carried out spectrophotometrically

on a Cary Model 11 MS spectrophotometer. The adjustment and determinations of pH were made with a Beckman pH meter with an expanded scale.

Aniline was freshly distilled and kept under nitrogen. The methyl-substituted succinic acids used have been previously described.⁸ The anhydrides were prepared by treating the corresponding acids with excess acetyl chloride and recrystallizing from anhydrous diethyl ether or diethyl ether-petroleum ether (bp 30–60°) mixtures. All other chemicals used were reagent or analytical grade.

Procedure for Kinetic Runs to Determine k_1 . The several 0.5 or 0.06 *M* buffers at the desired pH also contained aniline in various concentrations. The ionic strength was adjusted to 1.0 with sodium chloride. These solutions were filled into glass ampoules of appropriate capacity, sealed under nitrogen, and then immersed in a thermostated mineral oil bath at the desired temperature. Ampoules were periodically withdrawn as samples and chilled to quench the reaction, after which a measured volume was withdrawn, made strongly alkaline with concentrated sodium hydroxide solution, and extracted with three portions of chloroform to remove residual aniline. The aniline concentration in the chloroform extract was determined spectrophotometrically at 287 $m\mu$. This procedure is essentially that reported earlier³ except that sampling times were generally more frequent with the methyl-substituted succinic acids than with succinic acid since the former reacted more rapidly with aniline.

The dissociation constants employed in calculating k_1 values were obtained potentiometrically in systems at 70° and in acid concentration conditions identical with those used in the rate studies. The values obtained are given as compound (molarity), pK_1 , pK_2 ; succinic acid (0.5), 4.4, 4.8; methylsuccinic acid (0.6), 3.75, 5.15; 2,2-dimethylsuccinic acid (0.5), 3.80, 6.0; *dl*-2,3-dimethylsuccinic acid (0.5), 3.75, 5.65.

Procedure for Determination of k_2 . These rate constants were determined in a conventional manner in a thermostated Cary Model 11 spectrophotometer. The reactions carried out directly in the photometer cell were made pseudo first order with respect to anhydride by using anhydride in 40-fold excess over the aniline concentration, with the latter having a zero-time concentration of about 2.5×10^{-4} *M*. The anhydride was first introduced into the reaction cell in varying amounts of dioxane such that the final dioxane concentration ranged from 3.2 to 19.2% on a volume basis. The aniline was next introduced in a 0.05 *M* buffer composed of the acid-salt system corresponding to the anhydride being studied in the reaction. The composition of the solution in the reference cell was identical except for the omission of anhydride. The increase in absorbance at 235 $m\mu$ was used to follow the reaction rate. Semi-logarithmic plots of the equilibrium value of the absorbance minus the value of the absorbance at time t , $A_\infty - A_t$, gave good first-order plots over several half-lives, and the resulting rate constants were then extrapolated to zero dioxane concentration. The second-order constants were calculated from these rate values on the basis of the anhydride concentration employed and the estimated value of f_2 , the fraction of unprotonated aniline in the solution at the pH and temperature of the reaction.

The dissociation constant of aniline was determined spectrophotometrically at 20, 25, and 30° in the presence of buffers of the same concentration as used in the studies to determine k_2 . The pK_a' of aniline determined in this manner was 4.81, 4.74, and 4.69, respectively, at 20, 25, and 30°.

In these studies, a buffer effect was noted on both k_2 and, when determining the pK_a' of aniline, the fraction of total aniline present as the free amine. Increasing buffer concentration caused a decrease in both the value of k_2 and in the fraction of free amine present, the magnitude of the effect being comparable in both cases. Since it is the free amine form that is postulated as the reactive species with the acid anhydrides, the decrease of the concentration of this form would be expected to reflect itself in a corresponding decrease in k_2 . However, at concentrations of 0.05 *M* buffer, the values of k_2 obtained differ by about only 2% or less from buffer-free values, and the values in Table III for k_2 are uncorrected for buffer effects.

(9) T. Higuchi, L. Ebersson, and A. K. Herd, *J. Am. Chem. Soc.*, **88**, 3805 (1966).

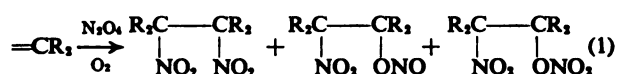
The Products and Stereochemistry of Reactions of Dinitrogen Tetroxide with $\Delta^{9,10}$ -Octalin, Norbornene, Cyclooctatetraene, 6,6-Diphenylfulvene, and Indene

Harold Shechter, John J. Gardikes,^{1a} Thomas S. Cantrell,^{1b,c} and George V. D. Tiers^{1d}

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio, and the Central Research Department, Minnesota Mining and Manufacturing Company, St. Paul, Minnesota. Received December 19, 1966

Abstract: $\Delta^{9,10}$ -Octalin and dinitrogen tetroxide in ethyl ether in the presence of oxygen yield *trans*-9,10-dinitrodecalin (II) and 10-nitro-9-decalyl nitrate (III). Norbornene and dinitrogen tetroxide give, after hydrolysis and chromatography, *exo,cis*- (IX, major) and *trans*- (X, minor) 2,3-dinitrobicyclo[2.2.1]heptanes and 2-hydroxy-3-nitrobicyclo[2.2.1]heptane (stereochemistry unestablished). Cyclooctatetraene and dinitrogen tetroxide result in the formation of 5,8-dinitro-1,3,6-cyclooctatriene (XXII) of probable *trans* stereochemistry. The mechanisms of these reactions are consistent with homolytic addition of dinitrogen tetroxide or nitrogen dioxide to the olefinic centers to give vicinal nitrocycloalkyl radicals which then react selectively with the nitrating agent(s) from the more sterically accessible direction. Reaction of 6,6-diphenylfulvene and dinitrogen tetroxide leads to 4-benzhydrylidene-*cis*-3,5-dinitrocyclopentene (XXIX), 2-nitro-6,6-diphenylfulvene (XXX), and 2,5-dinitro-6,6-diphenylfulvene (XXXI). Indene and dinitrogen tetroxide and subsequent aqueous hydrolysis yield *cis*-2-nitro-1-indanol (XXXVI). The *cis* stereochemistry of the products derived from addition of dinitrogen tetroxide to 6,6-diphenylfulvene and to indene may indicate that with rigid planar cycloolefins (charge transfer) coordination with dinitrogen tetroxide, and subsequent collapse to *cis* adducts, becomes an important reaction mechanism.

Dinitrogen tetroxide reacts with olefins (eq 1) in ether or ester-type solvents and in the presence of oxygen to give vicinal dinitro compounds, nitro nitrites, nitro nitrates.² These reactions involve coordina-



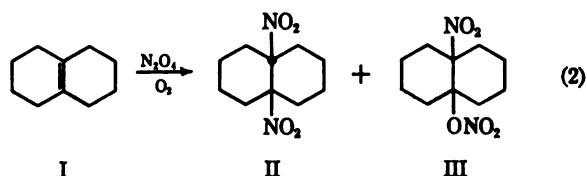
tion of dinitrogen tetroxide with the electron-donor olefins and subsequent homolytic addition of the nitrating agent(s) to the olefins.² Dinitrogen tetroxide adds stereoselectively to a number of olefins and cycloolefins. Cyclohexene and cyclopentene give both *cis* and *trans* products.³ 1-Methylcyclohexene yields 1-methyl-*trans*-2-nitrocyclohexyl nitrite exclusively.³ *cis*- and *trans*-stilbenes and dinitrogen tetroxide give mixtures of the *dl*- and *meso*-dinitro adducts in a 3:2 ratio and the *threo* and *erythro* nitro nitrites in a 2:1 ratio.⁴ It has been suggested that the major stereoisomeric adducts are formed more rapidly because the structure of the transition state for homolytic reaction involves an intermediate nitroalkyl radical ($\text{R}_2\dot{\text{C}}-\text{CR}_2\text{NO}_2$) in which the nitrating agent (NO_2 , N_2O_4) resembles the reagents and thus attack occurs at the greater rate from the more accessible direction.^{2,4a,5}

(a) The studies of reactions of dinitrogen tetroxide with $\Delta^{9,10}$ -octalin and norbornene have been abstracted in part from the Ph.D. dissertation of J. J. Gardikes, The Ohio State University, Columbus, Ohio, 1960. This research was supported by the Office of Naval Research. (b) The investigations of dinitrogen tetroxide with cyclooctatetraene, 6,6-diphenylfulvene, and indene were effected by T. S. Cantrell, Ph.D. Dissertation, The Ohio State University, Columbus, Ohio, 1964. (c) National Science Foundation Cooperative Fellow, 1962 and 1963–1964, and National Science Foundation Graduate Fellow, 1962–1963. (d) The nuclear magnetic resonance spectra of *cis*- and *exo,trans*-2,3-dinitrobicyclo[2.2.1]heptanes and *exo,cis*- and *trans*-2,3-diacetamidobicyclo[2.2.1]heptanes were studied by G. V. D. Tiers of the Minnesota Mining and Manufacturing Co., St. Paul, Minn. (e) H. Shechter, *Record Chem. Progr.*, 25, 55 (1964). (f) J. C. D. Brand and I. D. R. Stevens, *J. Chem. Soc.*, 629 (1958). (g) H. Shechter and J. J. Gardikes, *J. Am. Chem. Soc.*, 81, 5420 (1959); (h) T. Stevens, *ibid.*, 81, 3593 (1959).

In the present study the stereochemistry of addition of dinitrogen tetroxide to $\Delta^{9,10}$ -octalin, bicyclo[2.2.1]heptene-2, cyclooctatetraene, 6,6-diphenylfulvene, and indene has been investigated. The principal objectives of this research are to evaluate possible charge-transfer and steric effects in reactions of dinitrogen tetroxide with the particular olefins. The chemistry of the products of these reactions has also been determined.

Discussion

$\Delta^{9,10}$ -Octalin. Addition of $\Delta^{9,10}$ -octalin (I) in ethyl ether to dinitrogen tetroxide in ethyl ether at -20° in the presence of oxygen (eq 2) yields *trans*-9,10-dinitrodecalin (II, 76% conversion of I) as the principal product; small amounts of 10-nitro-9-decalyl nitrate (III, eq 2; stereochemistry unknown) were isolated (see Experimental Section) in certain experiments. Upon inverting the order of addition of reactants at 0° in the

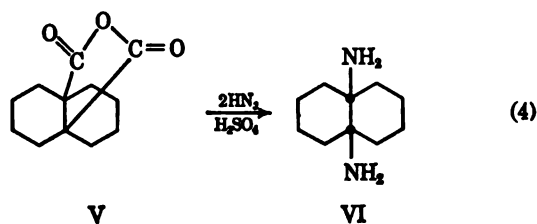
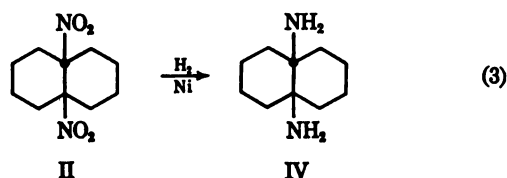


absence of oxygen, *trans*-9,10-dinitrodecalin (II, 74%) is also obtained. The order of addition of reagents does not significantly affect the types and stereochemistry of the products formed. When oxygen is passed rapidly through the reaction mixture, there is a significant change in the course of addition and 10-nitro-9-decalyl nitrate (III) is a major product.

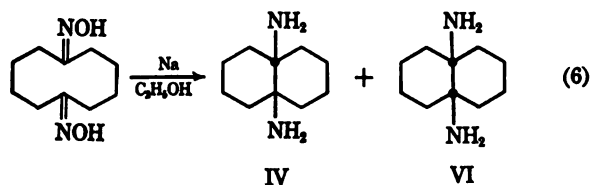
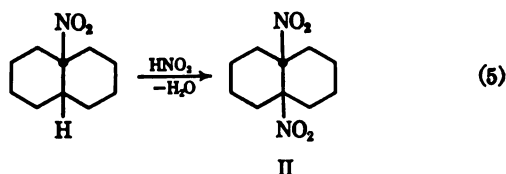
The stereochemistry of *trans*-9,10-dinitrodecalin (II) was assigned upon its hydrogenation (eq 3) over Raney

(5) Reaction of *trans*-stilbene with dinitrogen tetroxide to give *dl*-1,2-dinitro-1,2-diphenylethane and *threo*-1-(2-nitro-1,2-diphenylethyl) nitrite as the principal products may be formally classified as that in which *cis* addition is preferred.^{4a}

nickel to *trans*-9,10-diaminodecalin (IV, 97% yield) and subsequent conversion to *trans*-9,10-diacetamidodecalin and *trans*-9,10-diaminodecalin dipicrate. The assignment of structure of *trans*-9,10-diaminodecalin (IV) was made after synthesis of *cis*-9,10-diaminodecalin (VI) and *cis*-9,10-diacetamidodecalin by reaction of *cis*-decalin-9,10-dicarboxylic anhydride (V) with hydrazoic acid⁶ and sulfuric acid (eq 4) and subsequent acetylation of the product. The stereochemical assign-

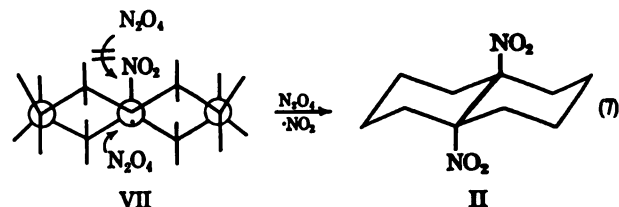


ments of structure of II, IV, and VI are in agreement with previous intuitive assignments for these products as obtained from (1) nitration of *cis*- and *trans*-decalins⁷ and *trans*-9-nitrodecalin^{7c} (eq 5) and (2) reduction of 1,6-cyclodecanedione dioxime with sodium and ethyl alcohol⁸ (eq 6).



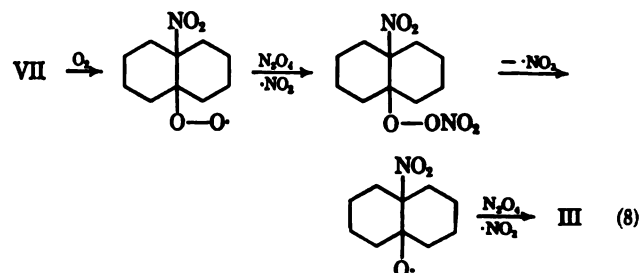
The formation of *trans*-9,10-dinitrodecalin (II) from $\Delta^{9,10}$ -octalin indicates that dinitrogen tetroxide adds to the unsaturated center by a *trans* process. The stereochemical results thus exclude a concerted or bimolecular reaction involving coordinative *cis* attack of dinitrogen tetroxide on the carbon-carbon double bond. Synthesis of *trans*- (II) rather than *cis*-9,10-dinitrodecalin may be interpreted in terms of a homolytic addition process involving initial formation of the 10-nitro-9-decalyl radical (VII) and subsequent exchange with dinitrogen tetroxide or electron pairing with nitrogen dioxide. On the basis that radical pairing or exchange processes involve small activation energies and are usually exothermic, it is anticipated that the structure of the transition state for reaction of the 10-

nitro-9-decalyl radical (VII) with the nitrating agent is close to reactants and will reflect the trigonal (sp^3) character of the tertiary radical which results in partial flattening of each of the fused cyclohexane rings from their chair forms. In the reaction of the 10-nitro-9-decalyl radical (VII) to give the *trans* adduct (II, eq 7), a maximum of four partial 1,3 interactions with the



nitrating agent will be involved, whereas for formation of the *cis*-dinitro adduct, there will be three more prohibitive 1,2 interactions, one of which is with a bulky nitro group.⁹ It is also of note that the generation and fate of VII in the present system are identical with that proposed for liquid-phase nitration of *trans*-9-nitrodecalin to II.^{7c}

10-Nitro-9-decalyl nitrate (III) can be made a minor or major reaction product by the amount of oxygen introduced during addition. Its structure was assigned from its quantitative and infrared analyses and upon consideration of its probable origin. 10-Nitro-9-decalyl nitrate (III) may possibly arise (eq 8) from addition of oxygen to the 10-nitro-9-decalyl radical (VII), reaction of the 10-nitro-9-decalylperoxyl radical with dinitrogen tetroxide or nitrogen dioxide, homolytic decomposition of 10-nitro-9-decalyl pernitrate, and exchange or electron pairing of the resulting 10-nitro-9-decalyloxy radicals with the nitrating agent(s).¹ An additional or alternate source of III may be reaction of VII with nitrogen trioxide ($\cdot NO_3$).²



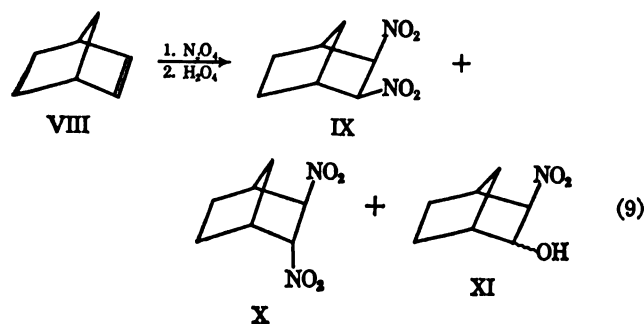
Norbornene. Reaction of norbornene (VIII) with dinitrogen tetroxide in ethyl ether at 0°, rapid aqueous hydrolysis of the initial adducts, and chromatography of the products on silica gel (eq 9) results in formation of *exo,cis*-2,3-dinitrobicyclo[2.2.1]heptane (IX, 22% conversion of VIII; mp 108°), *trans*-2,3-dinitrobicyclo[2.2.1]heptane (X, 12%; mp 127°), and 2-hydroxy-3-nitrobicyclo[2.2.1]heptane (XI, 33%; stereochemistry unestablished). There is net isomerization of IX to X on chromatography; however, under conditions of near-kinetic control involving rapid chromatography and minimal handling of the products, the principal

(6) Schmidt reactions of hydrazoic acid with carboxylic acids give amines with retention of configuration: H. Wolff, *Org. Reactions*, 3, 307 (1946).

(7) (a) S. Nametkin and O. Madaeff-Ssitscheff, *Ber.*, 59, 370 (1926); (b) W. Huckel and M. Blohm, *Ann.*, 502, 114 (1933); (c) H. Shechter and D. Brain, *J. Am. Chem. Soc.*, 85, 1806 (1963).

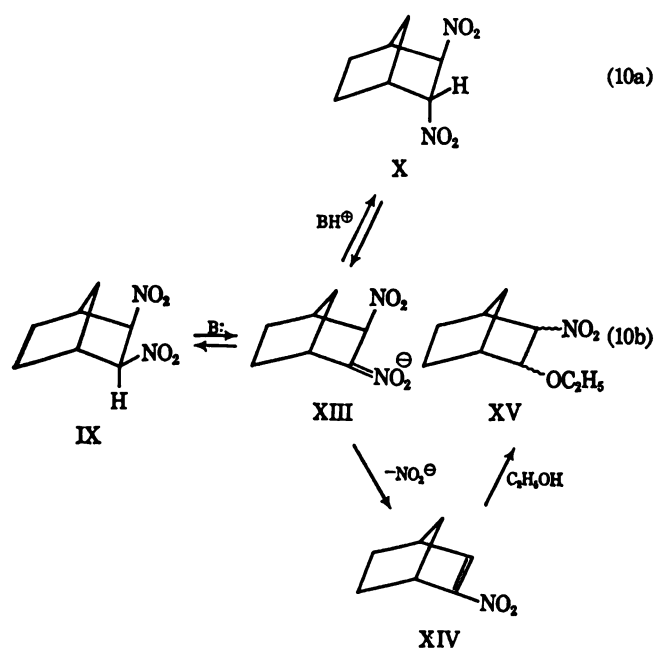
(8) P. A. Plattner and J. Halstkamp, *Helv. Chim. Acta*, 27, 200 (1944).

(9) (a) The relative thermodynamic stabilities of *cis*- and *trans*-9,10-dinitrodecalins are not known. *trans*-Decalin is 2.1 kcal more stable than is *cis*-decalin;^{9b} however, *cis*-9-methyldecalin derivatives are slightly more stable than are *trans*-9-methyldecalin derivatives.^{9a} *cis*-9-Decalylcarboxylic acid is also thermodynamically more stable than the *trans* isomer.^{9d} (b) G. F. Davies and E. C. Gilbert, *J. Am. Chem. Soc.*, 63, 1585 (1941); (c) A. Ross, P. A. S. Smith, and A. S. Dreiding, *J. Org. Chem.*, 20, 905 (1955); (d) R. E. Pincock, E. Grigat, and P. D. Bartlett, *J. Am. Chem. Soc.*, 81, 6332 (1959).



dinitro adduct was of *exo,cis* (IX) rather than of *trans* (X) stereochemistry. *endo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (XII) was not found.

The gross structures of IX and X were indicated from their analyses and infrared properties; that the adducts are related stereochemically was established by isomerization of X to IX¹⁰ (eq 10a) on chromatography or by the action of catalytic quantities of piperidine, cyclohexylamine, sodium methoxide, and potassium *t*-butoxide. The fact that addition of dinitrogen tetroxide



to VIII occurs without carbon-skeleton rearrangement¹¹ is demonstrated by oxidation of IX and X with alkaline potassium permanganate to *cis*-1,3-cyclopentenedicarboxylic acid in excellent yields. Behavior of IX as a vicinal dinitro compound which will undergo base-catalyzed elimination of nitrous acid (eq 10b) is indicated by its reaction with equivalent amounts of sodium ethoxide to give 2-ethoxy-3-nitrobicyclo[2.2.1]heptane (XV, stereochemistry unknown).

The stereochemistries of IX and X are assigned on the basis of their chromatography properties and their dipole moments. The nuclear magnetic resonance of IX and X and of their derivatives in which there has been no stereochemical alteration about the functional

(10) This appears to be the first recorded example of base-catalyzed isomerization of a vicinal dinitro compound. Such dinitro compounds are usually converted to conjugated nitroolefins by bases. In the present system isomerization of the vicinal dinitro compound may be allowed because collapse of XIII to XIV is a relatively slow process because of the strain involved.

(11) Possibly anticipated if addition of dinitrogen tetroxide occurred by an electrophilic process.

centers corroborate the structural assignments.¹² The evidence for the structures of IX and X is as follows.

It has been previously observed that rigid cyclic compounds having dinitro groups in *cis* positions are much more strongly adsorbed¹³ than are their corresponding *trans* isomers. The enhanced adsorptive properties of such *cis* derivatives have been attributed to their greater dipole moments and to the relatively favorable steric circumstances for interaction of the polar nitro groups with the adsorbent.¹³ Chromatography of the vicinal dinitro products of the present research revealed quickly that the adduct melting at 108° is more strongly adsorbed on silica gel than is the isomer of 127° melting point. The assignments initially made are that the isomers melting at 108 and 127° are the *exo,cis* (IX) and the *trans* (X) adducts, respectively. The stereochemical designations are compatible with the dipole moments subsequently determined for IX (6.1 D.) and X (3.4 D.).¹⁴

The structures of IX and X also agree with their nuclear magnetic resonance properties. The spectrum of the isomer melting at 108° (IX) shows, *inter alia*, a doublet of area 2 at τ 5.09 ($J \sim 2$ cps) attributable only to the hydrogens on the carbon atoms C-2 and C-3 containing the nitro groups. The observed equivalence of these hydrogens indicates that IX is either the *exo,cis* or *endo,cis* isomer. The corresponding hydrogens in the isomer melting at 127° (X) exhibit significantly different chemical shifts, appearing at τ 4.52 (pair of doublets, $J \sim 4$ cps) and τ 4.93 (pair of doublets, $J \sim 3.9$ cps, $J \sim 1.4$ cps);¹⁵ X, therefore, possesses the *trans* stereochemistry.

The hydrogen signals at C-7 provide evidence for the assignment of the *cis* nitro groups of IX as *exo* rather than *endo*. The apical hydrogens (C-7) of X occur as a complex multiplet overlapping the signals of the C-5 and C-6 methylenes at τ 8–8.5. In the spectrum of IX, on the other hand, one apical hydrogen is half of a broadened AB quartet at τ 7.45; the other half is partially masked by the C-5 and C-6 methylenes at τ 8.4 but appears to occur at *ca.* τ 8.56. The low-field position of one hydrogen at C-7 in IX is consistent with its location as *syn* to the two *exo* nitro groups. Models reveal that the nitro groups of IX are probably parallel to each other and perpendicular to the C-2–C-3 bond; the *syn* C-7 hydrogen is thus in the deshielding region. An effect of the magnitude found in IX would not be expected from proximity to only one nitro group (as in the *trans* isomer) or for the *endo,cis*-dinitro adduct.

trans-2,3-Diacetamido[2.2.1]heptane, mp 272–274°, has been previously prepared.¹⁶ A chemical proof of

(12) Efforts to resolve either of the 2,3-dinitrobicyclo[2.2.1]heptanes by reaction of insufficient brucine, α -phenethylamine, and potassium menthylate were unsuccessful.

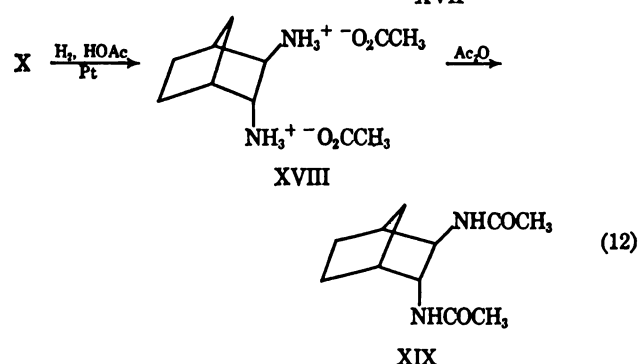
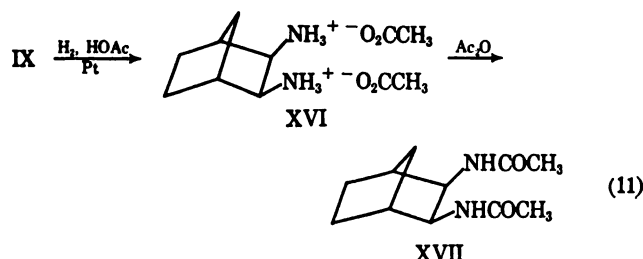
(13) D. B. Miller, Ph.D. Dissertation, The Ohio State University, 1957.

(14) The theoretical moments of IX and X as calculated using simple trigonometric methods involving vector addition of group moments are 6.3 and 2.2 D., respectively. It is not yet clear why the observed value for X is somewhat greater than that calculated. The enhanced dipole moment obtained for X does not affect the stereochemical assignments given to IX and X.

(15) The coupling constants are consistent with those previously observed in norbornane systems; see P. Laszlo and P. von R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1171 (1964); E. I. Snyder and B. Franzus, *ibid.*, **86**, 1166 (1964).

(16) (a) From *trans*-2,3-bicyclo[2.2.1]heptanedicarboxylic acid and from dimethyl *endo,cis*-2,3-bicyclo[2.2.1]heptanedicarboxylate. (b) K. Alder and G. Stein, *Ann.*, **514**, 211 (1934). (c) C. S. Inglessis, Ph.D. Dissertation, Clark University, 1959.

the stereochemistry of compounds IX and X was initiated. Hydrogenation of IX and X over platinum in glacial acetic acid¹⁷ gives the corresponding diamines as isolated in near-quantitative yields as dibasic acetates (XVI and XVIII, eq 11 and 12). Reactions of XVI and XVIII with acetic anhydride (eq 11 and 12) yield



the corresponding diacetylated derivatives, *exo,cis*-2,3-diacetamidobicyclo[2.2.1]heptane (XVII, mp 272° uncor; 83% yield) and *trans*-2,3-diacetamidobicyclo[2.2.1]heptane (XIX, mp 280° uncor; 84% yield). A mixture of XVII and XIX results in melting point depression.

Since there are only small differences in melting points for the diacetamido derivatives prepared previously¹⁸ and presently, it is not possible to make structural assignments on such evidence.¹⁸ The nuclear magnetic resonance for XVII and XIX are decisive, however, and corroborate the stereochemical assignments given IX and X. In the spectrum of XVII (in trifluoroacetic acid) the equivalent hydrogens at C-2 and C-3 appear as a broadened doublet at τ 5.64; in the spectrum of XIX the hydrogens at C-2 and C-3 are nonequivalent and occur as separate unresolved multiplets at τ 5.81 and 6.23. Thus XIX is assigned the *trans* structure and XVIII the *cis* for reasons analogous to that discussed for the nuclear magnetic resonance of IX and X.

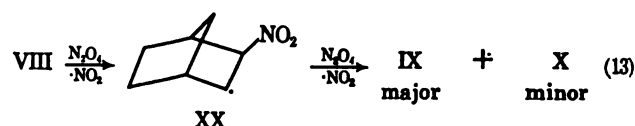
Isolation of IX as the major dinitro adduct from dinitrogen tetroxide and VIII indicates that the principal stereochemical path involves *exo-cis* addition. *exo-cis* processes involving free-radical mechanisms have been observed in reactions of *p*-thiocresol,^{19a} ethyl bromoacetate,^{19b} and bromotrichloromethane,^{19c} respectively, with VIII, and in homolytic reaction of hydrogen bromide and 2-bromo-2-norbornene.^{19d} The major stereochemical path in the present system thus may be

(17) The acidic solvent is necessary to prevent isomerization during the reductions.

(18) Authentic XIX was no longer available from ref 16c and its synthesis is laborious.

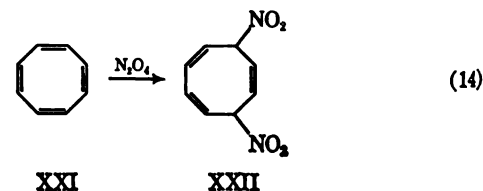
(19) (a) S. J. Cristol and G. D. Brindel, *J. Am. Chem. Soc.*, **76**, 5699 (1954); (b) J. Weinstock, Abstracts, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., 1955, p 190; (c) V. A. Rollen, *Dissertation Abstr.*, **19**, 960 (1958); (d) N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 623 (1960).

interpreted in terms of a homolytic process involving sterically preferred *exo* attack on VIII by the nitrating agent to give the *exo*-3-nitro-2-norbornyl radical (XX, eq 13), and subsequent exchange with dinitrogen tetroxide or electron pairing with nitrogen dioxide from the more accessible directions (eq 13). An alternate possibility is that a portion of the *exo,cis* product (IX) is formed *via* coordination of the olefinic center of VIII with dinitrogen tetroxide from the lesser hindered direction (*exo*) and subsequent *cis* addition. Systems in which this latter mechanism appears to be important have been found and will be discussed in this paper.



The 2-hydroxy-3-nitrobicyclo[2.2.1]heptane (XI) obtained from VIII and dinitrogen tetroxide is presumably derived from hydrolysis of 2-(3-nitrobicyclo[2.2.1]heptyl) nitrites. The structure of XI is confirmed by its analysis and infrared absorption (see Experimental Section), its oxidation by basic potassium permanganate to *cis*-1,3-cyclopentenedicarboxylic acid, and its conversion by acetic anhydride to 2-acetoxy-3-nitrobicyclo[2.2.1]heptane²⁰ in 70% yield. The stereochemistry and isomeric composition of XI were not determined. It is probable that XI is a mixture of *exo,cis*-2-hydroxy-3-nitro and *endo*-2-hydroxy-*exo*-3-nitro isomers.

Cyclooctatetraene. Dinitrogen tetroxide and cyclooctatetraene (XXI) in ethyl ether at -70° give 5,8-dinitro-1,3,6-cyclooctatriene (XXII, eq 14) in >34% yield; other products formed decompose rapidly at room temperature and cannot be handled readily.²¹



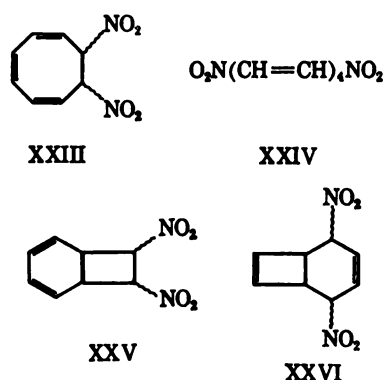
Use of inverse addition techniques or excess XXI does not improve the yield of XXII or result in other tractable products. XXII decomposes rapidly and often violently in 1–2 hr; its ability to be handled is generally improved when it is purified.

From its analysis and spectral properties the product of reaction of XXI and dinitrogen tetroxide must be a 1:1 dinitro adduct. Its probable structure includes XXII, 1,2-dinitro-3,5,7-cyclooctatriene (XXIII), 1,8-dinitro-1,3,5,7-octatetraene (XXIV), derivatives of bi-

(20) (a) Ethanolic solutions of 2-acetoxy-3-nitrobicyclo[2.2.1]heptane and of IX in excess base give ultraviolet absorption with maxima at 245 $m\mu$; the extinction coefficients (max) are 11,310 and 11,428, respectively. Since salts of primary and secondary nitro compounds usually absorb at 229–235 $m\mu$ with $\lambda_{\text{max}} \sim 11,000$, it is believed that the bathochromic shifts in absorption of the present bicyclic nitronates result from the diminished π -bond order of the C–N bonds in these strained ground states in excitation processes involving further diminution of the π order. (b) F. T. Williams, P. W. K. Flanagan, W. J. Taylor, and H. Shechter, *J. Org. Chem.*, **30**, 2674 (1965).

(21) Adducts such as 1,2-dinitro-3,5,7-cyclooctatriene (XXIII) and 1-nitro-2-nitro-3,5,7-cyclooctatriene are expected to isomerize to unstable products such as 1,8-dinitro-1,3,5,7-octatetraene (XXIV) and 1-nitro-8-nitro-1,3,5,7-octatetraene. Multiple addition of dinitrogen tetroxide to these rearrangement products and to XXI also probably occurs.

[4.2.0]octadiene (XXV and XXVI), and those containing phenyl or cycloheptatriene groups.²² The



violet spectrum of the present adduct exhibits no maximum but only a shoulder at 240–245 mμ strong end absorption; its infrared spectrum indicates strong bands for nitro groups (6.46 and 7.48 μ) saturated carbon but none for aromatic nuclei or isolated nitroolefins. The spectral properties of the compound strongly suggest that it is a 1,3,6-octatriene.²³ Its ultraviolet spectrum is very similar to that of 5,8-bis(2-cyano-2-propyl)-1,3,6-cyclooctatriene, the product of 1,4-homolytic addition of 2-cyano-2-propyl radicals and XXI.²⁴

The nuclear magnetic resonance of the adduct clearly indicates benzenoid, cycloheptatriene, and bicyclo[4.2.0]octadiene structures. The absence of aryl hydrogen signals at τ 2.5–3.0 eliminates any benzene derivative; the lack of resonance in the τ 5.0–6.5 region indicates the absence of tertiary hydrogen on carbons which do not bear nitro groups, thus ruling out any bicyclooctadiene or cycloheptatriene structures. The complex absorption in the τ 7.7 region is consistent with the structure assigned XXII.

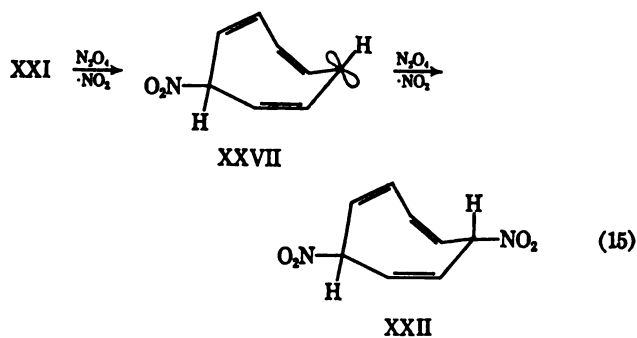
Direct experimental evidence is available on the stereochemistry of XXII; its instability precludes determination of its dipole moment. *cis*-Bimolecular addition of dinitrogen tetroxide on XXI appears unlikely because of steric features of the cyclooctatetraene ring. The stereochemistry of XXII is probably *trans* because 4-nitro-2,5,7-cyclooctatrien-1-yl radical (XXVII), a presumed intermediate, will strongly reflect a stereochemistry in which the nitro group is quasi-equatorial rather than quasi-axial, and subsequent reaction with the nitrating agent can proceed most readily in the quasi-equatorial direction.²⁵

4-Diphenylfulvene. Addition of dinitrogen tetroxide to 6,6-diphenylfulvene (XXVIII) in ethyl ether in the absence of oxygen and subsequent hydrolysis of initial products (eq 16) give 4-benzhydrylidene-

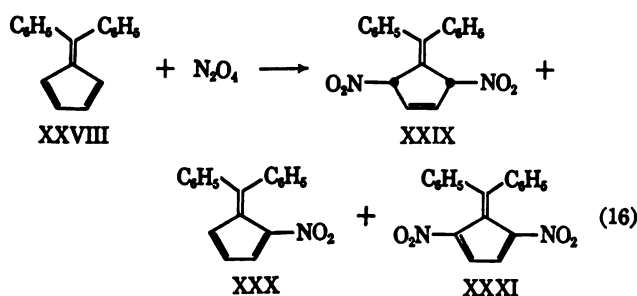
For a summary of the types of structures derivable by addition to cyclooctatetraene, see R. A. Raphael in "Nonbenzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, Inc., New York, 1959, Chapter 10.

1,3,5-Cyclooctatriene, bicyclo[4.2.0]octadiene, and cycloheptachromophores possess strong absorption maxima in the 265–275 mμ; see M. Kamlet and H. Ungnade, Ed., "Organic Electronic Data," Vol. I and II, Interscience Publishers, New York, N. Y., 1963.

J. L. Kice and T. S. Cantrell, *J. Am. Chem. Soc.*, **85**, 2298 (1963). When the nitro group is quasi-equatorial in XXVII or if the stereochemistry is *cis* (one of the nitro groups must take an axial position), models reveal that severe steric interference will occur between the quasi-equatorial nitro group and the carbon atoms of the ring.



cis-3,5-dinitrocyclopentene (XXIX, 22–28%), 2-nitro-6,6-diphenylfulvene (XXX, 2–4%), and 2,5-dinitro-6,6-diphenylfulvene (XXXI, 9–12%). Inverse addition of the reagents in the absence of oxygen at 0° yields the same product but in different proportions: XXIX (14–16%), XXX (1–2%), and XXXI (15–16%). There is considerable oxidation and polymerization of XXVIII by dinitrogen tetroxide. Direct addition using 10–15% excess XXVIII leads to the highest yields of

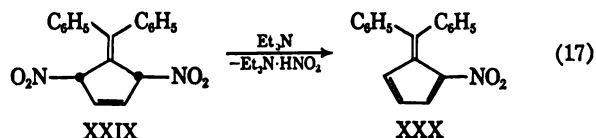


tractable products: XXIX (45–52%), XXX (3–4%), and no XXXI.

The elemental analysis, molecular weight, and absorption spectra of 4-benzhydrylidene-*cis*-3,5-dinitrocyclopentene (XXIX), a white solid, are consistent with its structure. The infrared absorption bands of XXIX at 6.42 and 7.31 μ are characteristic of saturated secondary nitro groups. Its ultraviolet spectrum exhibits a shallow maximum at 250 mμ (ϵ 10,200)^{26a} and is similar to that of 1,1-diphenylethylene [λ_{\max} 251 mμ (ϵ 12,000)]; its absorption is quite different from that of 3-benzhydrylidene-3,5-dinitrocyclopentene [λ_{\max} 290 mμ (ϵ 19,000)].^{26b} It is thus apparent that XXIX possesses the 1,1-diphenylethylene chromophore and is the product of 1,4 addition of dinitrogen tetroxide across the five-membered ring of XXVIII. The stereochemistry of XXIX is assigned on the basis of its dipole moment. The calculated moments for the *cis* and *trans* isomers of 4-benzhydrylidene-3,5-dinitrocyclopentene are 5.60 and 0.98 D., respectively. The moment determined experimentally is 5.71 D., nearly identical with that anticipated for XXIX. Products obtained under relatively mild conditions were searched for 4-benzhydrylidene-*trans*-3,5-dinitrocyclopentene, but none was found. Some may have been formed initially and subsequently transformed to XXX and XXXI. Even if such an unlikely circumstance leads exclusively to the XXX and XXXI isolated, these products are formed in such minor amounts that it can be concluded that addition of dinitrogen tetroxide to XXVIII occurs primarily by a *cis* reaction path.

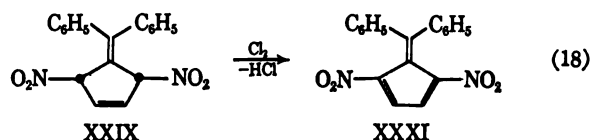
(26) (a) E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 2014 (1950); (b) J. L. Kice and F. M. Parham, *J. Am. Chem. Soc.*, **80**, 3792 (1958).

2-Nitro-6,6-diphenylfulvene (XXX) is a brick red solid. Its infrared spectrum shows bands for a conjugated nitro group at 6.61 and 7.40 μ . Its ultraviolet spectrum exhibits maxima at 374, 290, and 254 $m\mu$ (ϵ 23,500, 11,100, and 12,000) and is similar in shape to that of XXVII with a bathochromic shift of *ca.* 50 $m\mu$. Further evidence for the structure of XXX is that it is obtained in 63% yield by treating XXIX with triethyl-

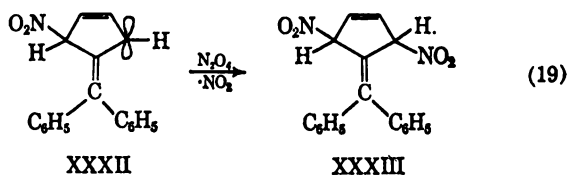


amine in benzene (eq 17). When triethylamine is added to a reaction mixture of XXVIII and dinitrogen tetroxide (without hydrolysis), XXX is isolated in 55% yield.

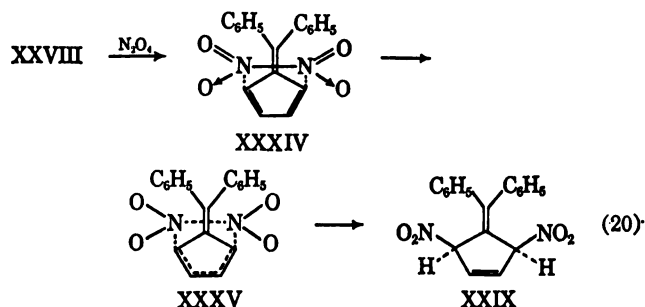
2,5-Dinitro-6,6-diphenylfulvene (XXXI), an orange solid, has infrared absorption for conjugated nitro groups at 6.69 and 7.53 μ . Its ultraviolet absorption maxima at 399 and 308 $m\mu$ (ϵ 29,000 and 12,700) are shifted bathochromically as anticipated upon comparison with that of XXX. The structure of XXXI is established chemically upon effecting its synthesis from XXIX by chlorination in warm chloroform (eq 18).



The result of particular interest in the present system is that the major (or sole) initial product of reaction of XXVIII and dinitrogen tetroxide is derived from *cis* rather than *trans* 1,4 addition. The stereochemistry is unexpected on the basis of stepwise homolytic addition of nitrogen dioxide and subsequent stereochemical control since attack of the nitrating agent from the lesser hindered side of the intermediate nitrocycloalkenyl radical XXXII will yield the *trans* adduct XXIII (eq 19).



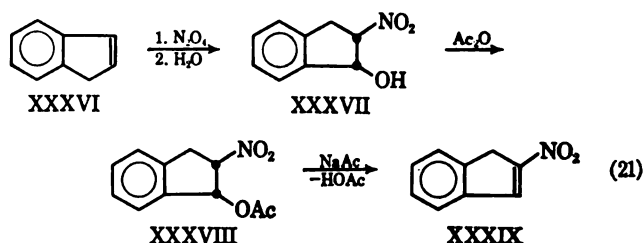
It is possible that the *cis*-dinitro compound XXIX is formed *via* a process in which the dinitrogen tetroxide first forms a charge-transfer or addition complex with the diene system of XXVIII (eq 20). Dinitrogen



tetroxide does give 1:1 adducts with benzene, mesityl-

ene, and nitrobenzene which are believed to be derived from orbital overlap²⁷ of the π -electron systems of the compounds with dinitrogen tetroxide. Coordination of dinitrogen tetroxide and XXVIII as indicated (eq 20) may indeed occur since the cyclopentadienyldiene moiety is a rigid and electron-rich planar π system. Formation and collapse *via* XXXIV and XXXV may thus possibly be favored because the process allows maximum overlap and minimal steric restriction of the reactants.

Indene. Addition of dinitrogen tetroxide in ethyl ether to indene (XXXVI) in ethyl ether at 0° and subsequent hydrolysis of the initial products gives *cis*-2-nitro-1-indanol (XXXVII, eq 21) as the only well-defined product. Major reactions result in amorphous



products and black resins^{28a} containing nitro groups. Inverse addition enhances formation of intractables^{28b} and decreases the nitroindanol XXXVII. Attempts to convert the primary products advantageously to 2-nitroindene (XXXIX) by treatment of the reaction mixture with triethylamine were unsuccessful.

The gross structure of 2-nitro-1-indanol (XXXVII) is derived from its analytical and spectral properties (infrared bands at 6.50 and 2.98 μ for nitro and hydroxyl groups) and its conversion (eq 21) to *cis*-1-acetoxy-2-nitroindane (XXXVIII) and to 2-nitroindene (XXXIX), a previously established structure,²⁹ by reaction with acetic anhydride and subsequent elimination by sodium acetate.

The stereochemistry of XXXVIII, and consequently of XXXVII, is assigned on the basis of the nuclear magnetic resonance properties of the hydrogen atoms at C-3. The nuclear magnetic resonance of a number of 1,2-disubstituted indanes of known stereochemistry has been recently determined.³⁰ For the *trans* compounds containing either electronegative or electropositive substituents, the signals due to the hydrogens at C-3 occur as quartets with differences of chemical shifts of 23–44 cps; the methylene hydrogens, however, of the corresponding *cis* isomers absorb as doublets at very nearly the same field, the difference in chemical shifts being only 0–3 cps for the compounds studied. In the spectrum of XXXVIII, the methylene hydrogens absorb as doublets centered at τ 6.37 ($J = 7.4$ cps) and 6.40 ($J = 7.0$ cps) with a difference of 2 cps. On the basis of the generalization reported,³⁰ the stereochemistries of XXXVII and XXXVIII are assigned as *cis*.

That the sole tractable product of reaction of indene (XXVI) and dinitrogen tetroxide is derived from *cis* addition is not in agreement with a stepwise homolytic

(27) C. C. Addison and J. C. Sheldon, *J. Chem. Soc.*, 1941 (1956).

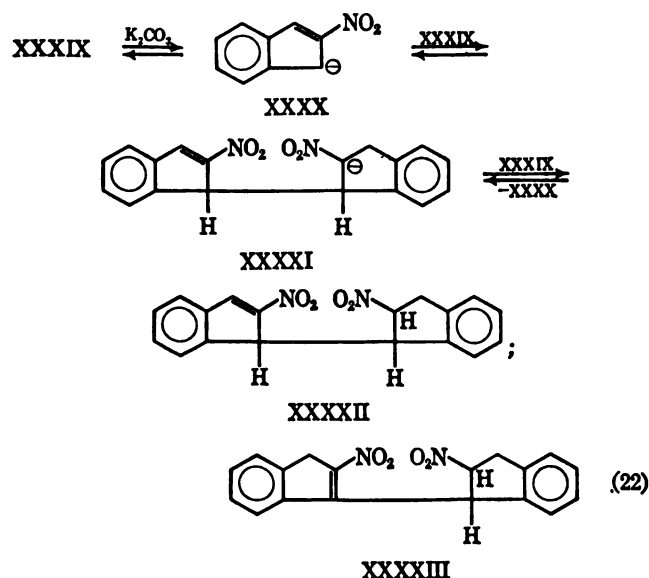
(28) (a) Indene is polymerized by free-radical or electrophilic reagents.^{28b} (b) "Encyclopaedia of Organic Chemistry," Vol. 12A, Elsevier Publishing Co., Inc., New York, N. Y., 1948, p 101.

(29) O. Wallach and E. Beschke, *Ann.*, 336, 2 (1904).

(30) W. E. Rosen, L. Dorfman, and M. Linfield, *J. Org. Chem.*, 29, 1723 (1964).

process; attack of the nitrating agent from the preferred direction by such a mechanism would give the *trans* adduct. As has been suggested for reaction of XXVIII and dinitrogen tetroxide, the *cis* stereochemistry of XXXVII may result from initial coordination of dinitrogen tetroxide with XXXVI, a nearly flat rigid cycloolefin having considerable π electron activity, and subsequent intramolecular collapse with minimum reorganization. It is of note that the *cis* stereochemistry of reaction of dinitrogen tetroxide and indene (XXXVI) is analogous to that observed for addition of performic acid³⁰ and of deuterium bromide³¹ to XXXVI. It has been suggested that the latter reaction occurs by a classical carbonium ion process involving ion pairs. It is conceivable that reaction of dinitrogen tetroxide with XXXVII (and with XXVIII) involves collapse of an initial π adduct *via* an intimate ion pair process or *via* transition states having considerable cationic rather than homolytic character.

cis-1-Acetoxy-2-nitroindane (XXXVIII) is also of interest in that it is converted by potassium carbonate to 1-(2-nitro-1-indenyl)-2-nitroindane (XXXII, eq 22), the product of self-Michael addition of 2-nitroindene



(XXXIX). Analytical, molecular weight, and spectral data allow the structural assignment of XXXII. The infrared spectrum of XXXII has strong bands at 6.47 and 6.66 μ indicating the presence of both conjugated and unconjugated nitro groups. Maximum ultraviolet absorption of XXXII occurs at the same wavelength as does 2-nitroindene (XXXIX; 338 $m\mu$) but of only one-half the intensity. The adduct is assigned structure XXXII rather than as the isomer XXXXIII on the basis that the nmr spectrum showed only one methylene signal of intensity 2.

Experimental Section

Reaction of $\Delta^9,10$ -Octalin (I) with Dinitrogen Tetroxide. Inverse Addition. $\Delta^9,10$ -Octalin mixture³² (68 g, 0.277 mole of I, n_D^{20} 1.4938)

(31) M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 2248 (1963).

(32) (a) The I used was a mixture of $\Delta^9,10$ -octalin (I, 55.4%), $\Delta^1,9$ -octalin (28%), and decalin (16.6%) prepared by reduction of naphthalene with lithium in ethylamine.^{33b} The presence of $\Delta^1,9$ -octalin complicated separation and identification of the products of reaction with dinitrogen tetroxide but did not affect the principal stereochemical objectives of

in ethyl ether (250 ml) was added dropwise to dinitrogen tetroxide (138 g, 1.5 moles) in ethyl ether (750 ml) at -20° . Oxygen was passed through the reaction mixture only while the octalin was added. The mixture was then kept between -10 and 20° for 45 hr. A bluish crystalline solid was filtered which, after having been washed with a small quantity of cold ethyl ether and air dried, was identified as *trans*-9,10-dinitrodecalin (II, 33.4 g), mp 150 – 159° . After the reaction solution had been poured on ice, washed with water, 10% aqueous sodium bicarbonate, and water, dried over magnesium sulfate, and concentrated, additional II (16.0 g) was obtained, mp 149 – 159° . The total II isolated was 49.4 g (0.217 mole). Recrystallization of II from hot ethanol gave 47.7 g of pure material (76% conversion of I to II, mp 168° cor, lit.⁷ 164°).

Complete evaporation of the ethereal filtrate left a yellow oil (50.6 g) from which no solid could be crystallized. Distillation of an aliquot of the material allowed separation of decalin,³³ n_D^{20} 1.4695, equivalent to 11.3 g (0.083 mole) in the evaporated filtrate. The remaining material exhibited absorption for olefin, nitro (6.47 μ), and nitrate (6.13 μ) groups; its various components could not be adequately resolved (see subsequent Experimental Section) because of their drastic decomposition upon chromatography on silica gel or on vacuum distillation.

In a similar experiment in which oxygen was bubbled through the mixture for the entire reaction period, a solid of different composition was obtained. From this solid, after several recrystallizations from alcohol, was isolated II, mp 161 – 164° , and an analytically pure product, 9-nitro-10-nitrodecalin (III), mp 122 – 124° , of unknown stereochemistry (probably *trans*). The infrared spectrum of III exhibits absorptions for a nitro group at 6.45 μ and for nitrate at 6.13 and 7.8 μ .

Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 49.17; H, 6.60; N, 11.45. Found: C, 49.31; H, 6.41; N, 11.45.

Direct Addition. Dinitrogen tetroxide (13.8 g, 0.15 mole) in ethyl ether (75 ml) was added in 1 hr at 0° to $\Delta^9,10$ -octalin reagent^{33a} (13.6 g, 0.055 mole of I) in ethyl ether. After 8 hr, II precipitated (6.1 g), mp 155 – 160° , and was filtered. The filtrate was handled as described previously to give additional II (3.7 g), decalin, and nitro derivatives.³⁴

Reduction of *trans*-9,10-Dinitrodecalin (II). *trans*-9,10-Diaminodecalin (IV), *trans*-9,10-Diacetamidodecalin, and *trans*-9,10-Diaminodecalin Dipicrate. *trans*-9,10-Dinitrodecalin (II, 2.0 g, 0.0088 mole) in 15% absolute ethanol in benzene (50 ml) was hydrogenated over Raney nickel (45 psi) at room temperature for 6 hr. Filtration of the catalyst and evaporation of the solvents gave crude *trans*-9,10-diaminodecalin (IV, 1.435 g, 0.0085 mole), mp 65 – 67° , 96.6% conversion of II. Pure IV was obtained as white needles upon one recrystallization from cold ethyl ether, mp 70° , lit.⁷ 70° . *trans*-9,10-Diacetamidodecalin (white crystals) prepared from reaction of IV with acetic anhydride and 10% sodium hydroxide melted above 360° ; the *trans*-9,10-diaminodecalin dipicrate prepared melted at 262 – 264° , lit.⁸ 262 – 264° .

Synthesis of *cis*-9,10-Diaminodecalin (VI) and *cis*-9,10-Diacetamidodecalin. Sodium azide (1.95 g, 0.03 mole) in concentrated sulfuric acid (25 ml) was added dropwise to a stirred mixture of decalin-9,10-dicarboxylic anhydride (2.08 g, 0.01 mole, mp 89 – 91° , lit.³⁴ mp 95 – 96°) and fuming sulfuric acid at 56 – 60° . After 7 hr, evolution of gas had ceased, and the reaction mixture was cooled and poured on ice. The solution was made basic and then extracted several times with ethyl ether. The ether extract was dried over magnesium sulfate and evaporated to give crystalline *cis*-9,10-diaminodecalin (VI, 0.4 g, 0.0024 mole), mp 41° , lit.⁸ 41° , 24.0%

this study. (b) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955); W. G. Dauben, E. C. Martin, and G. J. Fonken, *J. Org. Chem.*, **23**, 1205 (1958); A. S. Hussey, J. F. Sauvage, and R. H. Baker, *ibid.*, **26**, 256 (1961); see R. A. Benkeser and E. M. Kaiser, *ibid.*, **29**, 955 (1964).

(33) Its infrared spectrum and refractive index are essentially identical with that of authentic decalin.

(34) A considerable portion of the noncrystalline product, as separated by chromatography on silica gel, is soluble in excess sodium hydroxide. The ultraviolet absorption of an alkaline solution of this material in ethanol shows a minimum at 234 $m\mu$ and a maximum at 283 $m\mu$ (λ_{max} 9700) analogous to that of conjugated nitroanates.^{35b} The ultraviolet absorption and the nuclear magnetic resonance of this material indicate the presence of a carbon-carbon double bond and a $CHNO_2$ function. It is probable that a constituent of the reaction product is 1-nitro- $\Delta^9,10$ -octalin. For further experiments on the products, see ref 1a.

(35) K. Alder and K. H. Backendorf, *Ber.*, **71**, 2199 (1938).

conversion of decalin-9,10-dicarboxylic anhydride. Reaction of VI with acetic anhydride and 10% sodium hydroxide yielded *cis*-9,10-diacetamidodecalin, mp 243°, lit.⁸ 242°.

Reaction of Norbornene (VIII) with Dinitrogen Tetroxide. Dinitrogen tetroxide (4.6 g, 0.6 mole) in ethyl ether (200 ml) was added in 2 hr at 0–5° to norbornene (VIII, 37.6 g, 0.4 mole) in ethyl ether (500 ml). After 4 hr the mixture was poured into water (500 ml), stirred for 0.5 hr, and washed quickly with 5% aqueous sodium bicarbonate (400 ml),²⁸ dilute hydrochloric acid, and water. After the ether solution was evaporated, the oily residue was stirred several hours with water (three 400-ml portions). The water-insoluble oil was redissolved in ether, dried over magnesium sulfate, evaporated to about 200 ml, and cooled with ice. The white solid which separated was filtered, washed with a small quantity of cold ether, air dried, and then identified as *exo,cis*-2,3-dinitrobicyclo[2.2.1]heptane (IX, 7.7 g), mp 108°, infrared absorption for an aliphatic nitro group at 6.45 μ .

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.04. Found: C, 45.47; H, 5.46; N, 15.09.

The remaining ethereal filtrate was evaporated and the yellow residue (28.8 g) chromatographed on silica gel (G. F. Smith Co., 3.5 \times 21 cm) prewashed with 1:1 Skellysolve B–methylene chloride (200 ml). The following eluents were used: 1:1 Skellysolve B–methylene chloride (1200 ml), methylene chloride (1000 ml), and 4:1 methylene chloride–ethyl acetate (500 ml). Seven equal fractions (about 400 ml) were collected. Fractions 1 (16.7 g) and 2 (2.3 g) show identical spectra for a mixture of IX and X. Fractions 3 (0.5 g), 4 (1.0 g), 5 (2.4 g), 6 (1.7 g), and 7 (3.5 g), though different, show bands for hydroxyl, nitro, and carbonyl (5.8 μ) groups; their principal component is 2-hydroxy-3-nitrobicyclo[2.2.1]heptane (XI).

Fraction 1 (1.0-g aliquot) was rechromatographed on silica gel (V_{200} = 160 ml) prewashed with Skellysolve B (200 ml).²⁷ The following solvents were used: Skellysolve B (150 ml), 4:1 Skellysolve B–methylene chloride (150 ml), 3:2 Skellysolve B–methylene chloride (150 ml), 3:2 methylene chloride–Skellysolve B (150 ml), and methylene chloride (100 ml). Ten fractions (1'–10') of approximately 70 ml each were collected. Fractions 1' and 2' contained only a small amount of product (0.03 g); this material exhibited bands for nitro (6.48 μ) and possibly nitrate (6.12 μ) groups. Fractions 3'–5' yielded a white solid, *trans*-2,3-dinitrobicyclo[2.2.1]heptane (X, 0.46 g), mp 127–130°.

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.04. Found: C, 45.03; H, 5.43; N, 15.21.

The total amount of X in fractions 1 and 2 is 8.73 g, 0.047 mole, 11.8% conversion of VIII. Fractions 6'–10' yielded *exo,cis*-2,3-dinitrobicyclo[2.2.1]heptane (IX, 0.46 g), mp 108–110°; the amount of IX calculated in fractions 1 and 2 is 8.7 g. The total amount of IX isolated from the reaction is 16.4 g, 0.008 mole, 22% conversion of VIII.

From the aqueous washes of the initial reaction product after addition of sodium chloride, extraction with ether, drying of the ether extracts over magnesium sulfate, and vacuum evaporation of the ether, was isolated crude 2-hydroxy-3-nitrobicyclo[2.2.1]heptane (XI, 20.6 g, 0.131 mole, 33% conversion of VIII).²⁸ Distillation of VIII at greatly reduced pressures resulted in its extensive decomposition. The proof of structure of XI is described in subsequent experiments.

Oxidation of IX, X, and XI to Cyclopentane-*cis*-1,3-dicarboxylic Acid with Potassium Permanganate. To a solution of potassium permanganate (3.16 g, 0.02 mole) in water (50 ml) was added *exo,cis*-2,3-dinitrobicyclo[2.2.1]heptane (IX, 1.86 g, 0.01 mole). The mixture was warmed on a steam bath for 2 hr and then kept at 25–30° for 4 hr. The manganese dioxide was filtered, the solu-

tion was acidified, further traces of manganese dioxide were filtered, and finally the solution was extracted several times with ether. The ether solution was dried over magnesium sulfate and evaporated; the white solid (mp 118°) obtained was washed with a small quantity of cold Skellysolve F–ether, air dried, and then identified as cyclopentane-*cis*-1,3-dicarboxylic acid (1.01 g, 0.0064 mole), mp 120°, no depression by an authentic sample, 64% conversion of IX.

By procedures essentially identical with that described, X and XI were each oxidized by potassium permanganate to cyclopentane-*cis*-1,3-dicarboxylic acid, mp 118°, no depression by an authentic sample.

2-Acetoxy-3-nitrobicyclo[2.2.1]heptane. Concentrated sulfuric acid (five drops) was added to XI (8.4 g, 0.53 mole) in acetic anhydride (25 ml). The reaction mixture became hot and was heated (about 50°) further for 1.5 hr, and then stored at 25–30° for 24 hr. The resulting black solution was poured into water (100 ml), and the mixture stirred for 0.5 hr. After the mixture had been extracted with ether, the combined ether extracts were washed with 5% aqueous sodium bicarbonate, water, dilute aqueous hydrochloric acid, and water, dried over magnesium sulfate, and evaporated. The yellow oil obtained was distilled at reduced pressure to give 2-acetoxy-3-nitrobicyclo[2.2.1]heptane (7.4 g, 0.37 mole), bp 92–93° (0.3 mm), n_D^{20} 1.4807, 70% conversion.

Anal. Calcd for $C_{11}H_{13}NO_4$: C, 54.24; H, 6.58; N, 7.04. Found: C, 54.01; H, 6.51; N, 7.19.

Isomerization of *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX) with Piperidine. *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX, 1.86 g, 0.01 mole) in ethyl ether (160 ml) was treated with piperidine (0.21 g, 0.0025 mole) in ether (20 ml). A solid formed immediately upon addition of piperidine. After 5 min the mixture was filtered; the ether solution was washed with water, excess aqueous hydrochloric acid, and water, and dried over magnesium sulfate and the solvent evaporated. The white solid isolated upon recrystallization from Skellysolve B was *trans*-2,3-dinitrobicyclo[2.2.1]heptane (X, 1.20 g, 0.00645 mole), mp 127°, 64.5% conversion of IX.

Attempted Isomerization of *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX) with Pyridine. *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX, 0.93 g, 0.005 mole, in ethyl ether (80 ml) was treated with pyridine (0.2 g, 0.0025 mole). There was no precipitation. After 5 min the ether solution was washed with water, excess aqueous hydrochloric acid, and water, dried over magnesium sulfate, and evaporated. All of the starting material was recovered, mp 108°; its infrared absorption spectrum was identical with that of authentic IX.

Attempted Thermal Isomerization of *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX). *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX, 0.5 g), mp 108°, was heated slowly to 160° (20 min) and then allowed to cool to room temperature. Upon heating IX slowly turned red and sublimed. Both the sublimed and recovered solids gave the same melting point, 106°; their infrared spectra were identical with the starting material.

Reaction of *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX) with Sodium Ethoxide. Sodium methoxide (1.62 g, 0.03 mole) was added portionwise to *exo,cis*-2,3-dinitrobicyclo[2.2.1]heptane (IX, 5.58 g, 0.03 mole) in absolute ethanol (50 ml) and stored for 0.5 hr. The resulting yellow mixture was poured in water (200 ml) and extracted with ether. After the extract had been washed with water, dilute acid, and water, dried over magnesium sulfate, and evaporated, the remaining oil was distilled. A colorless fraction (1.5 g, 27% yield) which analyzed for 2-ethoxy-3-nitronorbornane was obtained, bp 63–64° (0.3 mm), n_D^{20} 1.4748, infrared absorption bands for nitro (6.49 μ) and possibly ether (9.16 μ) groups; there was no absorption for a carbon–carbon double bond.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 58.35; H, 8.16; N, 7.56. Found: C, 58.37; H, 8.35; N, 7.77.

Reduction of *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX). *exo,cis*-2,3-Dinitrobicyclo[2.2.1]heptane (IX, 1.86 g, 0.01 mole) in glacial acetic acid (50 ml) was hydrogenated over platinum (45 psi) at room temperature for 24 hr. After the catalyst had been filtered, the mixture was frozen, and the solvent sublimed under reduced pressure. A white ether-insoluble, water-soluble solid was obtained which begins melting at 110°. After having been washed with ether and air dried, the total solid weighed 2.36 g, 96% conversion of IX; based on the diacetate salt of *exo,cis*-2,3-diaminobicyclo[2.2.1]heptane (XVI). Treatment of the salt with picric acid in ethanol gave the dipicrate of *exo,cis*-2,3-diaminobicyclo[2.2.1]heptane, mp 245°.

Anal. Calcd for $C_{11}H_{16}O_4N_4$: C, 39.05; H, 3.45; N, 19.17. Found: C, 39.59; H, 3.43; N, 18.50.

(36) Prolonged treatment (24 hr) of IX and X in ethyl ether with 5% aqueous sodium bicarbonate gave oils which exhibit absorption for hydroxyl and nitro groups.

(37) When large amounts of IX (4.7 g) are chromatographed on silica gel (3.5 \times 20 cm) with Skellysolve B, there is some isomerization to X; this isomerization is not observed when a small amount (1.0 g) of IX is chromatographed on a similar column. Solutions of IX and X in ethyl ether and in methylene chloride upon standing for long periods turn yellow. The infrared spectra of the yellow solids isolated upon evaporation of the solvents, however, show no change of IX and X. There is depression in melting point upon mixing IX with X.

(38) The XI in fractions 3–7 is not included in the per cent conversion reported; the value thus quoted is believed to be minimal. In other experiments in which the initial reaction mixture was extracted thoroughly with water, the conversion of VIII to XI is considerably greater than 40%.

is of *exo,cis*-2,3-Diacetamidobicyclo[2.2.1]heptane (XVII). The diacetate salt of *exo,cis*-2,3-diaminobicyclo[2.2.1]heptane (XVI) (0.74 g, 0.003 mole) and acetic anhydride (5 ml) was stirred overnight.³⁰ The solution was cooled, the white solid precipitated was filtered, the solvents were evaporated, and the solid was washed with cold acetone. The combined solids on recrystallization from hot acetone yielded pure *exo,cis*-amidobicyclo[2.2.1]heptane⁴⁰ (XVII, 0.56 g, 2.48 × 10⁻³ mole), mp 272°, 82.6% conversion.

Calcd for C₁₁H₁₈N₂O₂: C, 62.81; H, 8.63; N, 13.32. Found: C, 62.66; H, 8.79; N, 13.17.

Isomerization of *trans*-2,3-Dinitrobicyclo[2.2.1]heptane (X). *trans*-2,3-Dinitrobicyclo[2.2.1]heptane (X, 1.86 g, 0.01 mole) in glacial acetic acid (50 ml) was hydrogenated over platinum (45 psi) at 100°C for 24 hr. After filtering the catalyst and freeze-drying the solvent under reduced pressure, a white, water-soluble solid was obtained which began to melt at 18°. After the solid had been washed with ether and air-dried, the weight was 2.30 g, 94% conversion of X assuming the product to be the diacetate salt of *trans*-2,3-diaminobicyclo[2.2.1]heptane (XVIII).

Isomerization of *trans*-2,3-Diacetamidobicyclo[2.2.1]heptane (XIX). The diacetate salt of *trans*-2,3-diaminobicyclo[2.2.1]heptane (XVIII, 0.74 g, 0.003 mole) and acetic anhydride (5 ml) was stirred overnight.⁴⁰ The mixture was cooled, the white solid precipitated was filtered, the solvents were evaporated, and the solid was washed with cold acetone. The combined solids on recrystallization from hot acetone yielded pure *trans*-2,3-diaminobicyclo[2.2.1]heptane (XIX, 0.57 g, 2.52 × 10⁻³ mole), 84% conversion.

Calcd for C₁₁H₁₈N₂O₂: C, 62.81; H, 8.63; N, 13.32. Found: C, 62.72; H, 8.52; N, 13.27.

Reaction of Cyclooctatetraene (XXI) and Dinitrogen Tetroxide. Dinitrogen tetroxide (9.2 g, 0.100 mole) in ethyl ether (25 ml) was stirred for 1 hr to stirred cyclooctatetraene (XXI, 10.4 g, 0.100 mole) in ether (150 ml) at -70 to -78° under nitrogen. The solution was allowed to warm to -20° and then stirred at this temperature for 1 hr. The now orange solution was filtered to give crude 1,3,6-cyclooctatriene (XXII, 6.4 g, 0.33 mole, 33%) which was washed twice with cold ether. Darkening of crude material occurred rapidly and the compound was purified by the following procedure, working as rapidly as possible. The crude XXII was dissolved in ca. six parts of oxygen-free ethyl acetate, and ethyl ether was added; the mixture was faintly turbid. The solution was then cooled, 15°, then at -78°. Two recrystallizations in this manner gave XXII (3.22 g, 0.0164 mole, 16.4%) as white prisms, mp 10°C, which turned yellow on standing at room temperature for 1 hr, and which decomposed violently after standing for 1 hr to overnight. The compound could be recrystallized overnight at -20° with little visible change, but some decomposition had nevertheless occurred and spectral and analytical data were performed immediately on freshly crystallized material.

Calcd for C₈H₈N₂O₄: C, 48.97; H, 4.08; N, 14.27. Found: C, 48.66; H, 4.22; N, 14.11.

Infrared spectrum of XXII shows strong bands at 6.45, 7.47, 10.5, 12.8, 13.16, and 14.23 μ. Its ultraviolet spectrum displays no true maximum, but a strong end absorption, with a shoulder at 240–245 mμ.

The nmr spectrum of XXII consists of a doublet centered at τ 3.74 (area 2, hydrogens on C-2 and C-3, J = 7.4 cps) overlapping at τ 3.74 (area 2, hydrogens on C-6 and C-7), a broad doublet at τ 4.16 (area 2, hydrogens on C-5 and C-8), and an additional multiplet at τ 4.3–4.5 (area 2, H on C₁ and C₄).

The ethereal filtrate from the reaction was evaporated at 10° to give a red oil which fumed and turned to a black tar when it stood at 0°. Use of the inverse addition technique or the addition of XI gave no other tractable product, nor was the yield of XXII proved.

Reaction of 6,6-Diphenylfulvene (XXVIII) with Dinitrogen Tetroxide. Normal Addition, Equimolar Quantities of Reactants. Dinitrogen tetroxide (0.92 g, 0.010 mole) in ethyl ether (10 ml) was stirred in 1 hr to a stirred solution of 6,6-diphenylfulvene (XXVIII, 2.30 g, 0.010 mole, freshly crystallized) in ethyl ether (60 ml) under nitrogen; the solution of XXVIII in ethyl ether had

formation of the product appeared to have taken place during the first few minutes after mixing.

There was depression in melting point upon mixing with *trans*-2,3-diaminobicyclo[2.2.1]heptane (XIX). The infrared spectra of the product showed some differences in absorption in the fingerprint region.

previously been flushed thoroughly with nitrogen. The mixture was stirred at 0° for 1 hr. The pale yellow solid formed was filtered, washed with cold ether, and air dried. The crude 4-benzhydrylidene-*cis*-3,5-dinitrocyclopentene (XXIX, 0.33 g, 0.0010 mole, mp 158° dec) was recrystallized from benzene or chloroform. Pure XXIX was obtained as white prisms, mp 165° dec.

Anal. Calcd for C₁₈H₁₄N₂O₄: C, 67.07; H, 4.35; N, 8.70. Found: C, 66.82; H, 4.41; N, 8.63.

Compound XXIX possesses an ultraviolet absorption maximum at 250 mμ (ε 10,200). Its nuclear magnetic resonance spectrum shows a singlet at τ 2.79 (area 10, aromatic hydrogens) and a pair of narrow doublets at τ 3.21 and 3.44 (J = 1.2 cps) representing the olefinic and methine hydrogens, respectively. It displays strong infrared absorption at 6.42, 7.29, 11.86, 12.52, 13.09, 13.31, and 14.12 μ.

The ethereal filtrate was washed with water, 5% aqueous sodium bicarbonate, 5% hydrochloric acid, and water and then dried. Cooling the solution at 5° gave 2,5-dinitro-6,6-diphenylfulvene (XXXI) as a red solid (0.36 g, 0.0011 mole), mp 225° dec. Recrystallization from ethyl acetate yielded pure XXXI as brilliant orange needles, mp 228° dec, which shows strong infrared bands at 6.37, 6.69, 7.52, 10.49, 13.17, and 14.18 μ. Its ultraviolet spectrum exhibits maxima at 374 and 308 mμ (ε 29,000 and 12,700).

Anal. Calcd for C₁₈H₁₂N₂O₄: C, 67.50; H, 3.74; N, 8.75. Found: C, 67.24; H, 3.83; N, 8.48.

The ether was evaporated from the filtrate. The residue was chromatographed on silica gel (24 × 260 mm) and eluted with hexane (100 ml), 9:1 hexane-methylene chloride (200 ml), 4:1 hexane-methylene chloride (200 ml), 2:1 hexane-methylene chloride (200 ml), 1:1 hexane-methylene chloride (150 ml), methylene chloride (200 ml), 8:1 methylene chloride-ethyl acetate (200 ml), and 2:1 methylene chloride-ethyl acetate (300 ml). Twenty-four fractions were collected and evaporated. Fractions 1–5 contained a dark red oil which crystallized on standing in the cold or on seeding. Recrystallization from 10% benzene-hexane gave 2-nitro-6,6-diphenylfulvene (XXX) as tiny brick red prisms, mp 111–113° dec (0.08 g, 0.0003 mole).

Anal. Calcd for C₁₈H₁₂NO₂: C, 78.61; H, 4.73; N, 5.10. Found: C, 78.46; H, 4.98; N, 5.36.

XXX has strong infrared bands at 6.32, 6.40, 6.69, 7.40, 7.58, 12.80, 13.16, and 14.23 μ. Its ultraviolet absorption maxima are at 374, 290, and 254 mμ (ε 23,500, 11,100, and 12,000).

Fractions 6–17 contained XXIX contaminated with XXXI. Recrystallization from benzene gave purer XXIX as off-white prisms (0.40 g, total 0.73 g, 0.00230 mole). Fractions 18–24 contained a red-black tar (1.86 g) which resisted crystallization and which exhibited infrared bands at 2.9 (broad), 6.41, 6.59, and 7.40 μ. Reaction of 6,6-diphenylfulvene (XXVIII) with dinitrogen tetroxide in ethyl ether thus yielded XXIX (0.0023 mole, 23% yield), XXX (0.0003 mole, 3% yield), and XXXI (0.0011 mole, 11% yield). Two additional experiments performed in the manner described gave similar results: XXIX (26 and 28%), XXX (2 and 4%), and XXXI (8.5 and 10%) were formed in the indicated yields.

Inverse Addition. A solution of XXVIII (2.30 g, 0.010 mole) in ethyl ether (50 ml, flushed with nitrogen) was added at 0° to stirred dinitrogen tetroxide (0.92 g, 0.010 mole) in ethyl ether (40 ml). The addition required 30 min, after which the solution was stirred for 1 hr. Filtration gave XXIX (0.27 g, 0.0084 mole) which was washed with cold ether. The combined ethereal filtrate and washings were washed with 5% sodium bicarbonate, 5% hydrochloric acid, and water, dried, and cooled to 5°. There was thus obtained XXXI (0.22 g, 0.00069 mole) identified by its melting point and its infrared spectrum. The solution was concentrated to ca. 40 ml and then cooled; additional XXXI (0.29 g, total XXXI: 0.51 g, 0.0016 mole, 16% yield) was obtained.

The mother liquors were evaporated and the residue was chromatographed on silica gel (British Drug House, Ltd., 24 × 250 mm). The column was eluted with 200 ml each of hexane, 9:1 hexane-methylene chloride, 6:1 hexane-methylene chloride, 3:1 hexane-methylene chloride, 2:1 hexane-methylene chloride, and methylene chloride. The 9:1 hexane-methylene chloride fractions gave XXX (~1%). The 3:1 and 2:1 hexane-methylene chloride fractions yielded, on evaporation, additional XXIX (0.24 g, total XXIX: 0.51 g, 0.0016 mole, 16% yield). The reaction of XXVIII with dinitrogen tetroxide in ethyl ether, adding the fulvene to the dinitrogen tetroxide, thus gave XXIX (16% yield). A second experiment conducted in the described manner gave XXIX (14%), XXX (1%), and XXXI (15%); the results are similar to that of the first experiment.

Normal Addition, Excess XXVIII. Dinitrogen tetroxide (12.4 g, 0.135 mole) in ethyl ether (35 ml) was added in 1 hr under nitrogen to a stirred solution of XXVIII (34.5 g, 0.150 mole) in ethyl ether (700 ml) at 0°. The mixture was stirred at 0° for 1.5 hr and then filtered. The crude XXIX (3.41 g) was washed twice with cold ether and air dried. The combined ethereal washings and filtrate were washed with water, dried, and concentrated to ca. 400 ml. Cooling to 5° gave additional crude XXIX (7.47 g). The mother liquor was concentrated to ca. 125 ml and cooled again. There was obtained a total of 11.87 g of an orange solid which was mainly XXIX contaminated with a little XXX. Further concentration and cooling of the mother liquors gave only red tar. The final crop of orange solid obtained above was ground and triturated with 4:1 hexane-benzene. The yellow residue, crude XXIX (11.03 g, total crude XXIX: 21.91 g, 0.0682 mole, 50% yield), was combined with the two crops obtained earlier and the whole recrystallized from chloroform-ethyl acetate (charcoal) to give pure XXIX, mp 165° dec. The total yield of pure XXIX was 20.0 g (0.062 mole, 46% based on dinitrogen tetroxide).

The benzene-hexane washings from the trituration of the third crop of XXIX were evaporated to give XXX (0.66 g, 0.0024 mole, 1.4% based on dinitrogen tetroxide). The reaction of dinitrogen tetroxide with excess XXVIII in ethyl ether at 0° thus gave XXIX (46% yield) and XXX (1.4% yield). Two additional experiments repeated as indicated gave analogous results: XXIX (45 and 52%) and XXX (1 and 3.5%).

Reaction of 4-Benzhydrylidene-*cis*-3,5-dinitrocyclopentene (XXIX) with Triethylamine. A solution of 4-benzhydrylidene-*cis*-3,5-dinitrocyclopentene (XXIX, 0.50 g, 0.00155 mole) and triethylamine (0.20 g, 0.0020 mole) in benzene (15 ml) was refluxed under nitrogen for 15 min. The dark red solution was evaporated to dryness under reduced pressure. The residue was taken up in a small amount of benzene and chromatographed on neutral alumina (20 × 200 mm, activity II). The column was eluted with hexane (100 ml) and 6:1 hexane-benzene (300 ml). A broad red band which moved down the column with the benzene-hexane was collected and evaporated to dryness. The residue was dissolved in warm 10% benzene-hexane (3 ml). On cooling the solution at -15°, 2-nitro-6,6-diphenylfulvene (XXX) crystallized as tiny dark red prisms, mp 111-113° dec; a total of 0.27 g (0.00098 mole, 63% yield) was obtained.

Conversion of 4-Benzhydrylidene-*cis*-3,5-dinitrocyclopentene (XXIX) to 2,5-Dinitro-6,6-diphenylfulvene (XXXI). 4-Benzhydrylidene-*cis*-3,5-dinitrocyclopentene (XXIX, 0.62 g, 0.00193 mole) was dissolved in boiling chloroform (25 ml) and a stream of chlorine was passed through the refluxing solution for 2 hr. The solvent was then evaporated and the red semicrystalline residue was chromatographed on silica gel (20 × 220 mm). Elution with 2:1 hexane-methylene chloride gave an orange solid identified as 2,5-dinitro-6,6-diphenylfulvene (XXXI, 0.19 g, 0.00058 mole, 31%) by its infrared spectrum.

Reaction of 6,6-Diphenylfulvene (XXVIII) and Dinitrogen Tetroxide and Subsequent Treatment with Triethylamine. A solution of 6,6-diphenylfulvene (XXVIII, 4.60 g, 0.020 mole) in ethyl ether (150 ml) was flushed with nitrogen, and dinitrogen tetroxide (1.70 g, 0.0185 mole) in ethyl ether (10 ml) was added at 0° under nitrogen. The addition required 40 min, after which the mixture was stirred for 20 min; triethylamine (2.2 g, 0.022 mole) was then added, and the mixture was stirred at 0° for 0.5 hr and at room temperature for 2 hr.

After the mixture had been evaporated to ca. 10 ml, it was chromatographed on neutral alumina (30 × 300 mm, activity II). Elution with 20% ether-hexane (400 ml) developed a deep red zone, leaving a dark brown zone at the top of the column. The red zone was eluted with 20% ether-hexane and the solvent evaporated. The residue was recrystallized from 20% benzene-hexane at -15°

to give 2-nitro-6,6-diphenylfulvene (XXX, 2.91 g, 1.04 moles, 52%), mp 111° dec.

Reaction of Dinitrogen Tetroxide with Indene (XXXVI). Dinitrogen tetroxide (18.4 g, 0.02 mole) in ethyl ether (40 ml) was added in 1 hr to a stirred solution of indene (XXXVI, 24.0 g, 0.21 mole) in ethyl ether (200 ml) at 0° in the absence of oxygen. The solution was stirred for 1.5 hr and filtered. The polymeric white solid formed (0.81 g) was washed with cold ether and air dried. The substance melted with decomposition over a broad range, exhibited the behavior of polymers, and was not further studied.

The filtrate was washed with water, dried, and concentrated to ca. 50 ml. Cooling to 5° and trituration with hexane resulted in partial crystallization. The solid, after having been washed with cold 1:2 ether-hexane, weighed 6.5 g. The mother liquor was combined with the wash liquid, reconstituted, and cooled to -15°. A second crop of 2-nitro-1-indanol (XXXVII, mp 115-117°) was obtained which weighed 1.7 g; total yield, 8.2 g (0.046 mole, 23%). Two recrystallizations from ethyl acetate gave pure XXXVII as white silky needles, mp 117-118°.

Anal. Calcd for C₉H₉NO₂: C, 60.51; H, 5.02; N, 7.84. Found: C, 60.88; H, 5.15; N, 7.82.

Chromatography of the mother liquor on silica gel and elution with various solvents gave only brown gums. Use of the inverse addition technique gave increased amounts of the polymer and greatly decreased yields of nitro alcohol.

Acetylation of 2-Nitro-1-indanol (XXXVII). Sulfuric acid (three drops) was added to 2-nitro-1-indanol (XXXVII, 4.00 g, 0.022 mole) in acetic anhydride (75 ml). The solution was stored at room temperature overnight and then poured into ice water (300 ml). The suspension was stirred for 1 hr and extracted with ether. The combined ethereal extracts were washed with 5% sodium bicarbonate and water, dried, and evaporated to dryness. The residue crystallized on scratching and was recrystallized twice from ethanol (charcoal) to give 1-acetoxy-2-nitroindane (XXXVIII, 4.34 g, 0.0194 mole, 87%) as large colorless prisms, mp 62-63°.

Anal. Calcd for C₁₁H₁₁NO₄: C, 59.75; H, 4.98. Found: C, 60.22; H, 4.91.

Conversion of 1-Acetoxy-2-nitroindane (XXXVIII) to 2-Nitroindene (XXXIX). A solution of 1-acetoxy-2-nitroindane (XXXVIII, 2.00 g, 0.009 mole) in ethyl ether (40 ml) was refluxed over sodium acetate (0.3 g) for 35 hr. The solution was filtered, washed twice with water, dried, and evaporated to give a yellow solid residue. Recrystallization from benzene gave 2-nitroindene (XXXIX, 1.04 g, 0.0066 mole, 73%) as stout yellow needles, mp 139-140°. The ultraviolet spectrum of XXXIX showed $\lambda_{\text{max}}^{\text{CHCl}_3}$ 336 and 241 m μ (ϵ 26,000 and 35,000). The nmr spectrum showed, in addition to the aromatic hydrogen signals at τ 2.4-2.8, a triplet of area 1 at τ 2.11 (vinyl hydrogen), and a doublet of area 2 at τ 6.08 (methylene hydrogens); $J = \sim 1.4$ cps.

Preparation of 1-(2-Nitro-1-indenyl)-2-nitroindane (XXXIII) from 1-Acetoxy-2-nitroindane (XXXVIII). A solution of 1-acetoxy-2-nitroindane (XXXVIII, 0.90 g, 4.1 mmoles) in ethyl ether (20 ml) was refluxed over potassium carbonate (0.70 g, 7.8 mmoles) for 3 hr. The dark brown solution was filtered while still warm. The residue was extracted twice with ether, and the extracts were combined with the filtrate. The combined ether solution was treated with charcoal, filtered, and evaporated to give a brown oil which partially solidified on trituration with 1:1 benzene-hexane. Recrystallization of the solid from 1:1 benzene-hexane gave 1-(2-nitro-1-indenyl)-2-nitroindane (XXXIII, 0.16 g, 0.51 mmole, 22%) as tiny, dull yellow prisms, mp 193-194° dec. The compound exhibited strong infrared bands at 6.47 and 6.66 μ ; the ultraviolet spectrum shows λ_{max} 338 m μ (ϵ 11,000).

Anal. Calcd for C₁₃H₁₄N₂O₄: C, 67.92; H, 4.41. Found: C, 68.16; H, 4.31.

Solvolysis of 6-Bicyclo[3.1.1]heptyl Tosylates¹

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Abstract: The acetolysis and ethanolysis of *exo*- and *endo*-6-bicyclo[3.1.1]heptyl tosylates have been studied. The tosyl group must occupy the pseudo equatorial position on a cyclobutane ring in order to permit a high degree of participation. The *endo:exo* ratio was about 10%. Using the rate of borohydride reduction of the corresponding ketone as a model, both epimers appeared to react at an accelerated rate. The products of the reactions have been determined; the *endo* isomer gives mainly the 2-norcaranyl acetates, whereas the *exo* isomer gives a variety of products. The ratio of the products is not significantly solvent dependent.

We have previously shown that *endo*-5-bicyclo[2.1.1]hexyl tosylate undergoes acetolysis at a rate 10⁶ faster than the *exo* isomer.³ The remarkably high *endo:exo* ratio has prompted us to investigate two series of isomeric cyclopropylcarbinyl, cyclobutyl, and allylcarbinyl derivatives.⁴ We now wish to report on the part of this investigation which deals with the bicyclo[3.1.1]heptanes. The syntheses of the compounds to be discussed are reported elsewhere.⁵

The rates of solvolysis of *endo*-6-bicyclo[3.1.1]heptyl tosylate (I) and of the *exo* isomer II were determined in glacial acetic acid and in two ethanol-water mixtures. In all cases, the reactions proceeded to completion; no internal return was noted. The data are summarized in Table I.

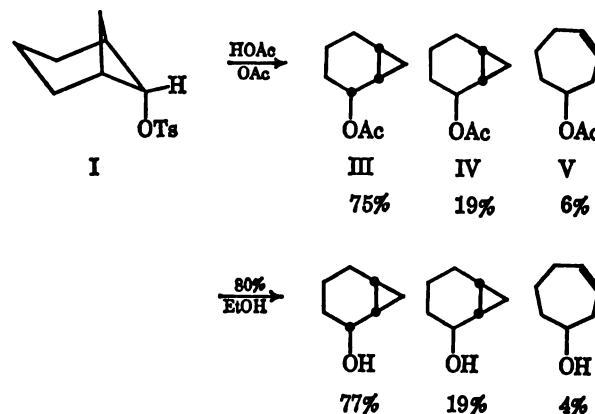
Table I. Rates of Solvolysis of 6-Bicyclo[3.1.1]heptyl Tosylates

Tosylate	Solvent	Temp, °C	<i>k</i> , sec ⁻¹	Δ <i>H</i> ‡, kcal/mole	Δ <i>S</i> ‡, eu
<i>endo</i>	HOAc	17.0	1.70 × 10 ⁻³	20.1	+2
		32.0	9.90 × 10 ⁻³		
		25.0	4.44 × 10 ⁻³ *		
	80% EtOH	25.0	2.40 × 10 ⁻³		
	95% EtOH	25.0	4.61 × 10 ⁻³		
<i>exo</i>	HOAc	97.7% EtOH	2.92 × 10 ⁻³ *	28.5	+4
		115.0	8.84 × 10 ⁻³		
		130.0	3.61 × 10 ⁻⁴		
		120.0	1.43 × 10 ⁻⁴ *		
	80% EtOH	25.0	1.01 × 10 ⁻³ *		
		120.0	2.47 × 10 ⁻⁴		
		97.7% EtOH	2.73 × 10 ⁻³		

* Extrapolated values.

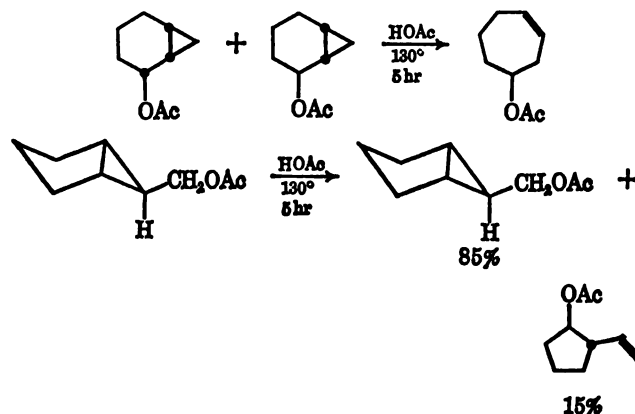
The products of the solvolyses were determined by isolation of the product mixtures followed by vpc separation and identification of individual components by comparison of the nmr and infrared spectra with those of authentic samples. The result, in the case of the *endo* isomer, was fairly simple (see Scheme I). In the ethanolysis experiment, the alcohols were identified by treatment of the reaction mixture with acetyl chloride followed by separation of the acetates. The

Scheme I



ethers were not separated and identified as such, but the vpc curve for the ether mixture was quite similar to that for the acetate mixture (except at shorter retention times) suggesting that the ethers were formed in about the same ratio. The ether:alcohol ratio was 88:12.

The solvolyses of the *exo* isomer led to more complex product mixtures. The data are summarized in Table II. Since the reaction conditions for acetolysis (5 hr, 130°) might lead to further reactions of the products initially formed, the stability of the products was investigated. A mixture of *cis*- and *trans*-2-norcaranyl acetates was found to isomerize to 4-cycloheptenyl acetate. *exo*-Bicyclo[3.1.0]hexane-6-methyl acetate (VII) was found to be partially converted to *trans*-2-vinylcyclopentyl acetate under the reaction conditions.



In the solvolysis in 80% ethanol, the ratio of ethers to alcohols was 30:70. In the absence of base, the 2-norcaranols were converted to 4-cycloheptenol, and

(1) This investigation was supported by the Army Research Office, Durham, and forms part of the Ph.D. Thesis of B. A. H., 1966.


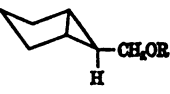
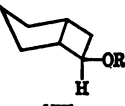

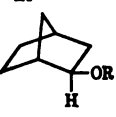
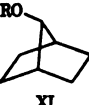
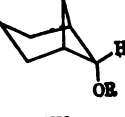
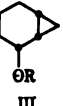
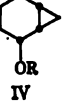
(2) National Institutes of Health, Predoctoral Fellow, 1963-1966.

(3) K. B. Wiberg and R. Fcnoglio, *Tetrahedron Letters*, 1273 (1963).

(4) Some of the results of this investigation are given in K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963); K. B. Wiberg and A. J. Ashe, III, *Tetrahedron Letters*, 1553, 4245 (1965).

(5) K. B. Wiberg and B. A. Hess, Jr., *J. Org. Chem.*, **31**, 2250 (1966).

Table II. Products of the Solvolysis of *exo*-Bicyclo[3.1.1]heptyl Tosylate

Product	Obsd product compositions,* %			Cor compositions,* %	
	HOAc (R = Ac)	80% EtOH (R = H)	80% EtOH HO ⁻ (R = H)	HOAc	80% EtOH
	17	36	14	15	15
	14	..	23	16	25
	7	9	11	7	12
	51	37	3	5	3
	4	6	8	4	9
	7	10	8	7	9
	1	2	8
	20	37	21
	5	9	5

* Corrected for isomerization under the reaction conditions and for the S_N2 reaction.

bicyclo[3.1.0]hexane-6-methanol was completely converted to *trans*-2-vinylcyclopentanol. The compounds were, however, stable under the reaction conditions when a slight excess of base was added to the solvent. When this was done, the S_N2 product, *endo*-6-bicyclo[3.1.1]heptanol, increased in amount.

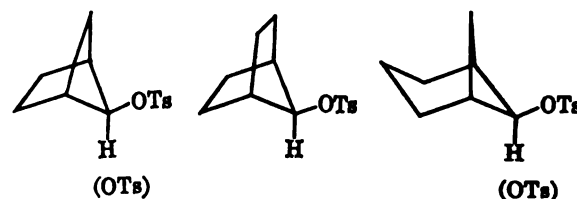
It is possible to correct the observed data to take into account the isomerization reactions, making only the assumption that most of the cycloheptenyl acetate found in the acetolysis experiments arose from the norcaranyl acetates. This does not appear unreasonable in view of the results of the ethanolysis experiments. The corrected data are included in Table II.

Having presented the experimental data, we may now consider their significance. The *endo* isomer I is over a million times as reactive as the *exo* isomer II, indicating

that the rate acceleration characteristic of cyclobutyl derivatives requires that the leaving group occupy the pseudo equatorial position.⁶ This conclusion had also been reached in our previous study of the 5-bicyclo[2.1.1]hexyl tosylates.³

A comparison of the kinetic data for acetic acid and for aqueous ethanol permits an estimation of the Winstein *m* and *N* values.⁷ The *Y* value for 97.7% ethanol corresponds to that for glacial acetic acid. For the solvolysis of I, *m* was 0.56 and *N* was 0.66; whereas for II, *m* was 0.59 and *N* was 0.19. The last value is based on *Y* values determined at 25° whereas the rates of reaction were measured at 120°. The unusually low value of *N* is probably a result of not using *Y* values for 120°. The low values of *N* demonstrate that the reactions are limiting solvolyses, and the values of *m* are of a reasonable magnitude for such a process.

It is of interest to try to relate the rates of solvolysis with those of other compounds. At first, it appeared to us that 7-norbornyl derivatives would provide an adequate model in view of the similarity in structure.



It is generally recognized that there is a correlation between the C-C-C bond angle at the reaction site and the rate of solvolysis.⁸ The angle for 7-norbornyl derivatives is 94°,⁹ whereas that for bicyclo[3.1.1]heptyl derivatives must be less than 88°. ¹⁰ Thus, on this basis one might expect the latter to react more slowly than 7-norbornyl.

However, Brown has suggested that 7-norbornyl derivatives may for some reason be abnormal, since the rate of solvolysis of the tosylate is less than that of any other tosylate which has been studied, and since the rate of borohydride reduction of 7-norbornanone is greater than that of any other ketone which has been studied.¹¹ We may ask if there should be any structural factor which would lead to anomalous rates of reaction.

The important factor in these reactions is the *difference* in destabilization due to bond angle deformation between the tetrahedral and trigonal structures. Here, 7-norbornyl derivatives would be anticipated to be significantly different from monocyclic compounds. With cyclobutyl derivatives, for example, the tetrahedral structure has a bond angle⁶ of about 87.8°, whereas the trigonal structure (cyclobutanone)¹² has an angle of

(6) Cyclobutane deviates from planarity by 35° (P. N. Skancke, Thesis, Oslo, 1960) leading to positions for substituents which are analogous to axial and equatorial positions of a cyclohexane ring.

(7) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948); S. Winstein, E. Grunwald, and H. W. Jones, *ibid.*, **73**, 2700 (1951).

(8) H. C. Brown and M. Gerstein, *ibid.*, **72**, 2926 (1950); P. von R. Schleyer and R. D. Nicholas, *ibid.*, **83**, 182 (1961); cf. C. S. Foote, *ibid.*, **86**, 1853 (1964); P. von R. Schleyer, *ibid.*, **86**, 1854 (1964), where the correlation was made with the infrared carbonyl frequencies rather than bond angles.

(9) Dr. G. Dallinga, private communication.

(10) The C-C-C bond angle in cyclobutane is 87.8° and that in bicyclo[2.1.1]hexane is 84.5°.

(11) H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).

(12) A. Bauder, F. Tank, and H. H. Günthard, *Helv. Chim. Acta*, **46**, 1453 (1963).

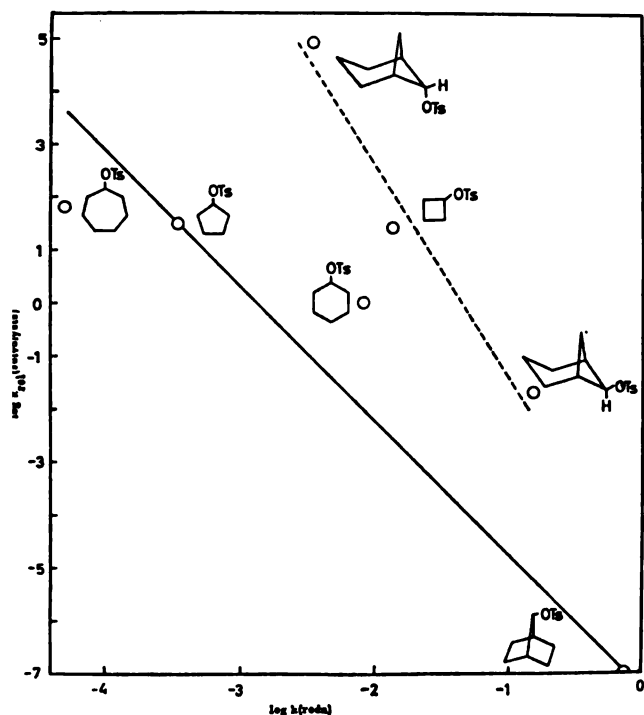


Figure 1. Relationship between rates of solvolysis and rates of borohydride reduction of the corresponding ketones. The solid line joins cyclopentyl with 7-norbornyl; the dashed line indicates the results with the cyclobutyl derivatives.

90.5°. Thus, the angle has increased significantly on going to the ketone, relieving some of the strain associated with the formation of a trigonal center. With norbornyl derivatives, however, the angle at the methylene bridge is constrained by the two-carbon wings and probably cannot change significantly on going from the alcohol to the ketone. Thus, despite the larger angles in 7-norbornanol and 7-norbornanone as compared to cyclobutanol and cyclobutanone, the increase in strain is probably greater for the former than for the latter.

The bicyclo[*n*.1.1]alkane derivatives would be expected to be intermediate in strain increase between cyclobutyl and 7-norbornyl compounds. This postulate could be tested if the heats of hydrogenation of the ketones to the alcohols were known. Unfortunately, these values are not as yet available. As a result, we have adopted the suggestion of Brown and Muzzio¹¹ that the rates of borohydride reduction of the ketones provide a model for the effect of converting a tetrahedral center to trigonal. The rate of reduction of bicyclo[3.1.1]heptanone-6 was determined giving a rate constant of $1.4 \times 10^{-1} \text{ sec}^{-1}$ at 0°. As expected, the rate is between those for cyclobutanone and 7-norbornanone. The reaction led to 97.5% of *endo*-6-bicyclo[3.1.1]heptanol and 2.5% of *exo*-6-bicyclo[3.1.1]heptanol, giving the partial rate factors for *endo* and *exo* attack of 3.5×10^{-3} and $1.5 \times 10^{-1} \text{ sec}^{-1}$, respectively. The data required for a correlation with rates of solvolysis are summarized in Table III.

The rates of acetolysis are compared with the rates of borohydride reduction in Figure 1. Brown and Muzzio¹¹ have suggested that a line drawn through 7-norbornyl and cyclopentyl "would provide a reasonably satisfactory locus" for most of the compounds they examined. Such a line is drawn in the figure; the deviations (± 2 log units) for cyclohexyl and cycloheptyl

Table III. Rates of Acetolysis and Borohydride Reduction

Ring	Solvolysis k , 25°	k_{rel}	Reduction ^a k , 0°
Cyclobutyl	3.0×10^{-3}	27 ^b	1.33×10^{-3} ^c
Bicyclo[3.1.1]heptyl			
<i>exo</i> -6	1.0×10^{-3}	0.021	1.5×10^{-1}
<i>endo</i> -6	4.44×10^{-3}	91,000	3.5×10^{-3}
Norbornyl-7		10^{-7} ^c	7.5×10^{-1} ^d
Cyclohexyl	4.88×10^{-3}	1.00 ^d	8.1×10^{-3} ^e
Cyclopentyl	1.58×10^{-3}	32.4 ^d	3.5×10^{-4} ^e

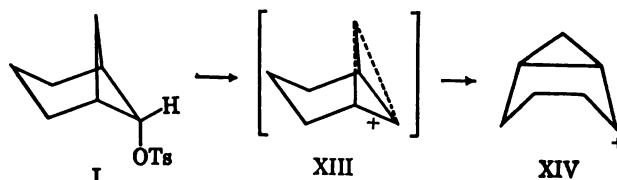
^a Partial rate factors. ^b J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951); H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956). ^c S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955). ^d S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *ibid.*, **74**, 1127 (1952). ^e H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957). ^f H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).

derivatives perhaps suggest the uncertainty inherent in the correlation.

The three species of present interest, *endo*-6-bicyclo[3.1.1]heptyl, cyclobutyl, and *exo*-6-bicyclo[3.1.1]heptyl have acetolysis rates which are greater than expected by 6.0, 4.3, and 3.3 log units, respectively. Thus, using Brown's criterion, all appear to undergo solvolysis at accelerated rates.

The magnitude of the rate acceleration for cyclobutyl is in accord with other data. It has been found that the replacement of the α -hydrogen by methyl in secondary alcohol derivatives normally produces a rate increase by a factor of about 5×10^4 .¹² In the case of cyclobutyl, methyl substitution increases the rate by only a factor of about 10^2 .¹⁴ If there were no special stabilization of the tertiary derivatives, the rate acceleration for cyclobutyl itself would be $\sim 5 \times 10^2$. This, of course, is a minimum value since 1-methylcyclobutyl derivatives may also react at a somewhat increased rate.¹⁵

The very large rate acceleration observed with *endo*-6-bicyclo[3.1.1]heptyl tosylate indicates a bridged activated complex. One may write the structure XIII and ask whether this represents the activated complex for a rearrangement to a more stable ion XIV, or whether it is an intermediate in the reaction and is stabilized by virtue of electron delocalization.



The 2-norcaranyl derivatives are very reactive in solvolytic reactions suggesting that the ion XIV is probably well stabilized in the fashion of cyclopropylcarbinyl cations.¹⁶ The stabilization is particularly

(13) H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 5008 (1964).

(14) H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952); J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5034 (1951).

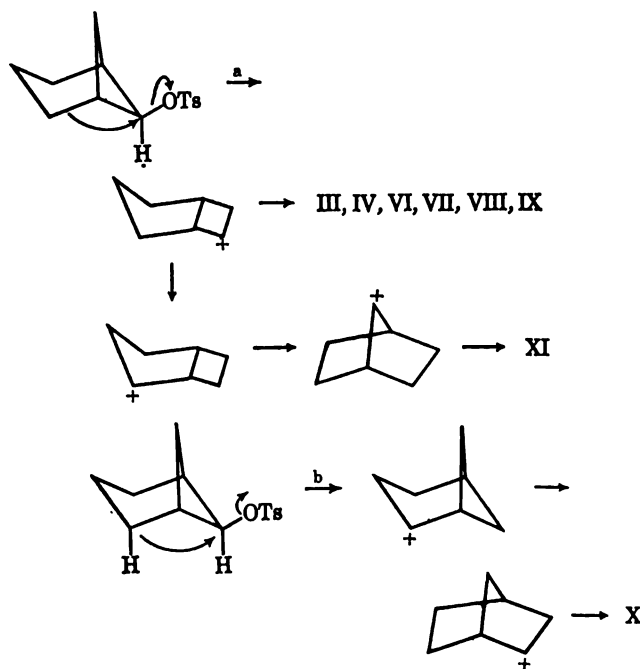
(15) The correlation of acetolysis rates with carbonyl frequencies¹⁵ does not appear to be particularly useful with cyclobutyl derivatives because of the lack of correlation of vibrational frequency with bond angle. Thus: cyclobutanone, 1791 cm^{-1} ; 6-methylbicyclo[3.2.0]heptan-6-one, 1776 cm^{-1} ; bicyclo[3.1.1]heptan-6-one, 1775 cm^{-1} .

(16) (a) Cyclopropylcarbinyl intermediates: Wiberg and Ashe, see ref 4; P. von R. Schleyer and G. van Dine, *J. Am. Chem. Soc.*, **88**, 2321 (1966). (b) Stable cyclopropylcarbinyl ions: N. Deno, H. G. Richey, Jr., J. S. Liu, J. D. Hodge, J. J. Houser, and M. J. Wisotsky, *ibid.*, **84**, 2016 (1962); C. V. Pittman and G. Olah, *ibid.*, **87**, 2998 (1965); N. C. Deno, J. S. Liu, J. O. Turner, O. N. Lincoln, and R. E. Fruit, *ibid.*, **87**, 3000 (1965).

favorable since XIV is both cyclopropylcarbinyl and secondary. Since little thermochemical evidence is available concerning the relative energies of the classical cyclobutyl and the cyclopropylcarbinyl cations, it is not possible to estimate if the observed effect can be rationalized in terms of such a driving force. If the rate acceleration for *endo*-6-bicyclo[3.1.1]heptyl tosylate is taken as 10^6 , this corresponds to a stabilization of the activated complex by about 8.3 kcal/mole. The driving force would have to be greater than this amount since the driving force cannot be fully realized in the activated complex.

One possible way in which to obtain evidence dealing with the above question is to examine the possibility of trapping an intermediate using an ion in solution. In some cases, this has been accomplished using halide ion,¹⁷ azide ion,¹⁸ and methoxide ion.¹⁹ An attempt was made to capture an intermediate ion using azide ion in acetic acid, and chloride ion in acetone. No chloride or azide corresponding to I was obtained²⁰ and olefin was the major product in acetone solution. Thus, the question remains unresolved at the present time. We shall, however, return to this question at a later time.

The solvolytic behavior of the *exo*-tosylate II is also of some interest in view of its apparent higher than expected reactivity. The products of the reaction may be derived *via* a series of carbonium ion reactions.



The carbon participation path, a, might be expected to give a modest rate acceleration since a 1,3-bridged cyclobutane is probably somewhat destabilized in comparison to a 1,2-bridged cyclobutane.²¹ In the absence of thermochemical data, it is difficult to estimate the magnitude of the possible rate factor.

(17) S. Winstein, A. Ledwith, and M. Hojo, *Tetrahedron Letters*, 341 (1961).

(18) H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.*, **86**, 120 (1964).

(19) H. Tanida, T. Teruji, and T. Irie, *ibid.*, **88**, 864 (1966).

(20) See, however, the reaction of *endo*-5-bicyclo[2.1.1]hexyl tosylate with chloride ion⁴ in which unrearranged *endo*-chloride was the major product.

(21) This conclusion is not at all certain and is in the process of being tested. If the conclusion is incorrect, there would be no apparent driving force for rearrangement to XV.

The products of the reaction are, however, not in accord with the above formulation. First, the acetolyses of *exo*- and *endo*-bicyclo[3.2.0]heptyl-6 tosylates have been investigated²² and neither gives bicyclo[3.2.0]heptyl-6 acetate or 7-norbornyl acetate as a product. However, both are formed in the present case. It seems likely that they are not formed *via* the 6-bicyclo[3.2.0]heptyl cation. Second, it is difficult to see why the product composition should be essentially unchanged on going from acetic acid to aqueous ethanol as solvent if the reaction involves a series of rearrangement steps. In these cases, one usually intercepts the ions at an earlier stage with the more nucleophilic aqueous ethanol as compared to acetic acid.

The simplest explanation for the rate acceleration and for the solvolysis products suggests that the products are derived from one principal intermediate which is stabilized in part by electron delocalization and in part by some strain relief resulting from the longer bonds in the "nonclassical" intermediate. The reactions may be formulated as in Scheme II. It can be seen that this intermediate provides a reasonable path for the formation of both bicyclo[3.2.0]heptyl-6 and 7-norbornyl derivatives. We do not consider that the data are such that they force one to accept a "nonclassical" intermediate. However, such an intermediate provides a simple, economical explanation for all of the data.

Experimental Section

Acetolysis of *endo*-Bicyclo[3.1.1]heptyl-6 Tosylate. Into a set of about 15 test tubes was accurately measured increasing amounts of standard sodium acetate in acetic acid. The final volume in each was adjusted to 10 ml with anhydrous acetic acid. Several drops of brom phenol blue in acetic acid was added to each tube as an indicator. The test tubes were stoppered, placed in a constant temperature bath, and allowed to equilibrate for 15 min. *endo*-Bicyclo[3.1.1]heptane-6 tosylate (300 mg) was dissolved in approximately 3 ml of carbon tetrachloride. A 200- μ l portion of this solution was transferred with stirring to a test tube using a Hamilton 250- μ l syringe. Zero time was taken at the completion of addition, and the time for the indicator change was recorded. The process was repeated for each test tube, covering a range of 10–90% reaction. This method eliminated the problem of the time required to dissolve the tosylate in the reaction solvent, and permitted reactions with a half-life as short as 30 sec to be studied.

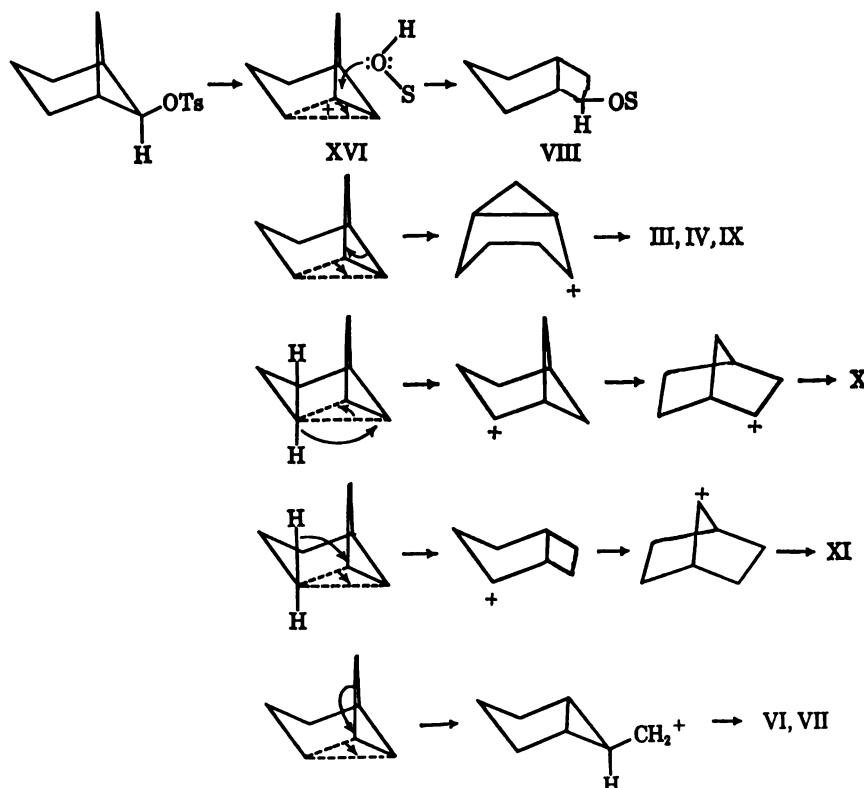
Ethanolsolysis of *endo*-Bicyclo[3.1.1]heptyl-6 Tosylate. Two ethanol–water mixtures were prepared having 79.95 and 95.00% ethanol by volume (the former had a density of 0.84930 at 25.0°, and the latter had 0.80321). The experiments were carried out as described above except that the base solution was prepared by dissolving sodium in the alcohol–water mixture and standardizing against hydrochloric acid solution by titration.

Acetolysis of *exo*-Bicyclo[3.1.1]heptyl-6 Tosylate. Solutions of the tosylate were prepared by weighing the tosylate into a volumetric flask and diluting to 50 ml with glacial acetic acid containing approximately 1% acetic anhydride and sufficient sodium acetate to neutralize the *p*-toluenesulfonic acid formed. Portions (3.3 ml) of the solution were placed in ampoules, and the ampoules were sealed. The ampoules were placed in a constant temperature water bath and were allowed to equilibrate. They were removed at known times, cooled rapidly to room temperature, and broken open; 3 ml of the solution was removed for titration with standard sodium acetate in glacial acetic acid. Brom phenol blue was used as the indicator.

Ethanolsolysis of *exo*-Bicyclo[3.1.1]heptyl-6 Tosylate. The ethanolysis was carried out in the same manner as the acetolysis runs using 79.95 and 97.75% ethanol. The latter had a density of 0.79371 at 25°.

(22) F. F. Nelson, Ph.D. Thesis, University of Wisconsin, 1960.

II



Acetolysis Studies. a. *endo*-Bicyclo[3.1.1]heptyl-6 Tosylate. A solution of 0.5 g of the tosylate (containing 20–30% of the *exo* isomer) in acetic acid containing a small excess of sodium acetate was allowed to stand for 15 min at room temperature. The mixture was diluted with an equal volume of water and extracted with portions of pentane. The pentane solution was washed with 2.5% sodium bicarbonate solution, and again with water. After drying, distillation gave 150 mg of a clear liquid, and residue. The latter was shown by nmr to be *exo*-bicyclo[3.1.1]heptyl-6 tosylate. The distillate was examined by vpc using a Carbowax column at 148°. The first component (19.5 min) was 4-acetoxycycloheptene, and the second component (21.5 min shoulder at 22.5 min) was a 4:1 mixture of *endo*- and *exo*-norbornyl acetates. Both components were identified by comparison with authentic samples.

In the acetolysis was carried out in the absence of acetate ion, amount of 4-acetoxycycloheptene increased at the expense of the norbornyl acetates.

Ethanolysis of *endo*-Bicyclo[3.1.1]heptyl-6 Tosylate. A solution of 0.6 g of the tosylate in 50 ml of 80% ethanol containing 120 mg of sodium acetate was allowed to stand for 8 min at room temperature. The reaction mixture was worked up as described above, and the mixture of ethers and alcohols was dissolved in pyridine and cooled. To this solution was added 2.0 g of acetyl chloride. After 10 minutes, 6 ml of water was added, and the mixture was extracted with two 20-ml. portions of pentane. The pentane solution was washed with two portions of dilute hydrochloric acid, two portions of water, and two portions of 5% sodium bicarbonate solution. After drying, the pentane was removed, and distillation residue gave 0.2 g of a mixture of ethers and acetates. Vpc analysis indicated that the acetate products were the same as from acetolysis. The ether:acetate ratio was 88:12.

***exo*-Bicyclo[3.1.1]heptyl-6 Tosylate.** A solution of 2.0 g of tosylate in 160 ml of anhydrous acetic acid containing 0.027 g of sodium acetate was heated in a sealed flask at 120° for 1 hr. It was cooled, diluted with 200 ml of water, and extracted with 175-ml portions of pentane. The pentane solution was washed with three 250-ml portions of 2.5% sodium bicarbonate solution and with water. After drying, distillation of the solvent

gave 1.0 g of products. Vpc analysis using a Carbowax column at 140° indicated four components. The first component (8 min, 17%) was *trans*-2-vinylcyclopentyl acetate;²³ the second (10 min, 7%) was 7-norbornyl acetate; the third (11 min, 11%) was a mixture of *exo*-bicyclo[3.2.0]heptyl-6 acetate and *exo*-norbornyl acetate; and the fourth (14 min, 65%) was a mixture of 4-acetoxycycloheptene²³ and *exo*-bicyclo[3.1.0]hexane-6-methyl acetate.²³ The last mixture could be separated using an XF-1150 column. All components were identified by comparison with authentic samples.

d. Ethanolsolysis of *exo*-Bicyclo[3.1.1]heptyl-6 Tosylate. The reaction was carried out essentially as described above, and the products were converted to acetates using acetyl chloride in pyridine. The ratio of ethers to acetates was 30:70. The acetates were the same as found in the acetolysis, but in a different ratio.

Bicyclo[3.1.1]heptanone-6. A solution of 5 g of *exo*-bicyclo[3.1.1]heptanol-6, 11.2 g of aluminum *t*-butoxide, and 19.1 g of benzoquinone in 570 ml of anhydrous ether was heated to reflux for 12.5 hr. The ether was removed by distillation, and the volatile material was collected at 0.3 mm. The latter was separated by vpc using a 1/8 in. DEGS column at 140°. The ketone with a retention time of 8 min was collected giving 1.3 g (26%). It had an infrared carbonyl band at 1775 cm⁻¹.

Reduction of Bicyclo[3.1.1]heptanone-6. The rate of reduction by sodium borohydride was determined at 0° in isopropyl alcohol solution as described by Brown and Muzzio.¹¹ The concentration of ketone was 0.00506 M, and of borohydride 0.00190 M. Assuming a 1:4 stoichiometry, good second-order kinetics were observed with $k = 1.4 \times 10^{-1}$ sec.

The product of the reduction was converted to acetates using pyridine and acetyl chloride. The acetates were isolated by vpc using a DEGS column at 140° (retention time 7.5 min). The nmr spectrum of the mixture indicated a strong triplet τ 5.31 for the $-CHOAc$ proton of the *endo* isomer and a weak doublet at τ 5.69 for the corresponding proton of the *exo* isomer.⁵ The ratio of the areas of the two bands indicated 97.5% *endo* and 2.5% *exo* acetates.

(23) An authentic sample was kindly supplied by Dr. A. J. Ashe.

Aminolysis of Esters. I. Kinetics and Mechanism in Anhydrous Dioxane¹

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Abstract: The kinetics of aminolysis of 11 phenyl esters by various amines have been studied spectrophotometrically under pseudo-first-order conditions in anhydrous *p*-dioxane. The following relationships were found: $k_{\text{obsd}} = k_2(\text{amine}) + k_3(\text{amine})^2$ for the reaction of phenyl dichloroacetate with *n*-butylamine and 3-methoxy-*n*-propylamine, and for the reaction of phenyl difluoroacetate with *n*-butylamine; $k_{\text{obsd}} = k_2(\text{amine})$ for the reaction of phenyl dichloroacetate with *N*-methyl-*n*-butylamine, piperidine, *N,N*-dimethyl-1,3-propanediamine, and *N,N,N'*-trimethyl-1,3-propanediamine, and for the reaction of phenyl difluoroacetate with piperidine and *N*-methyl-*n*-butylamine; $k_{\text{obsd}} = k_2(\text{amine}) + k_3(\text{amine}) + k_3'(\text{amine})(\text{Et}_3\text{N})$ for the reaction of phenyl dichloroacetate and *n*-butylamine where catalytic amounts of triethylamine were added. A series of reactions in cyclohexane was performed, and only third-order kinetics were detected. Rate constants for the reaction of ten different aliphatic esters with *n*-butylamine were correlated by the Taft equation, $\log(k/k_0) = \rho^*\sigma^* + \delta E_s$.

Although much information is available in the literature concerning the aminolysis and ammonolysis of esters, essentially none exists in aprotic solvent systems. Reactions of this type have been extensively investigated in aqueous solution.⁴ Organic solvents have been used by other investigators, but these have been either alcohols,⁵ glycols, dioxane-water, or dioxane-alcohol.⁶

The present study undertakes kinetic studies of this reaction in anhydrous dioxane, in order to establish the order of reaction in this solvent, and to determine whether the same observation of general base catalysis with primary amines, such as has been well established in aqueous solution,^{4a} is obtained. It was also desired to examine the effect of structure of the acyl portion of the ester, in the hope of shedding more light on the mechanism of this reaction in aprotic solvents.

Experimental Section

Materials. *p*-Dioxane was Matheson Coleman and Bell Spectroquality reagent grade solvent. Its purity was checked by infrared, ultraviolet, and vapor phase chromatographic analyses.

Difluoroacetic acid was purchased from K and K Laboratories; distillation at atmospheric pressure gave a distillate of boiling range 125–134°. This corresponds to the boiling point of a 10% water-acid azeotrope.⁷

Sodium phenolate was prepared by reaction of phenol (Fisher Scientific Co., purified by distillation) with sodium in anhydrous benzene.

Amines. *n*-Butylamine, *N*-methyl-*n*-butylamine, 3-methoxy-*n*-propylamine, and *N,N*-dimethyl-1,3-propanediamine were purchased from Matheson Coleman and Bell. Piperidine and triethylamine were obtained from Eastman Organic Chemical Co. The amines were purified by storing overnight over sodium hy-

dride pellets and then distilling at atmospheric pressure from fresh sodium hydroxide pellets using a 15-in. Vigreux column. The fraction having a constant boiling point was collected and stored in an amber glass bottle over fresh sodium hydroxide pellets.

N,N,N'-Trimethyl-1,3-propanediamine was prepared from 3-chloro-*N,N*-dimethyl-*n*-propylamine hydrochloride (Matheson Coleman and Bell), 20 g (0.11 mole), which was dissolved in 100 ml of distilled water. A solution of 40% aqueous methylamine (Matheson Coleman and Bell), 77.5 g (ca. 1.1 moles), was added, and the mixture was refluxed gently for 6 hr. The cooled reaction mixture was treated with solid potassium hydroxide until some solid remained undissolved. The amine layer which separated was removed, the aqueous layer was extracted several times with ether, and the ether extracts were added to the diamine. The ether solution was washed with saturated sodium hydroxide solution, dried over anhydrous sodium sulfate, and the ether removed on a water bath. The residue was distilled through a 10-in. Vigreux column to give 7.0 g (55% yield) of colorless liquid product.

The degree of purity of each amine was determined by acid-base titration and was checked by vapor phase chromatographic analysis. In the former method, a known weight of the amine dissolved in a known excess of standard hydrochloric acid was titrated against a standard solution of sodium hydroxide using methyl red (pH 4.4–6.2) as an indicator. In the latter method, an F & M Model 720 gas chromatograph with a 3-ft Carbowax column was used. For all amines, a clean single peak was obtained, indicating almost 100% purity.

Refractive indices, boiling points, and infrared spectra were also determined for the amines. A common absorption band between 2900 and 3000 cm⁻¹ corresponding to methyl and methylene stretch was observed. The physical constants and degree of purity of the individual amines are listed as follows: *n*-butylamine, bp 77–77.5°, *n*_D²⁰ 1.3976, 99.9% pure (lit.⁷ bp 77°; *n*_D²⁰ 1.4010); *n*-methyl-*n*-butylamine, bp 90–91°, *n*_D²⁰ 1.3997, 100.0% pure (lit.⁷ bp 90–99°, *n*_D²⁰ 1.4018); 3-methoxy-*n*-propylamine, bp 116–118°, *n*_D²⁰ 1.4315, 100.0% pure (lit.⁸ bp 118°, *n*_D²⁰ 1.4182); *N,N*-dimethyl-1,3-propanediamine, bp 132–133°, *n*_D²⁰ 1.4315, 99.8% (lit.⁹ bp 130–133°); piperidine, bp 104–105.5°, *n*_D²⁰ 1.4500, 99.9% pure (lit.⁷ bp 106°, *n*_D²⁰ 1.4530); triethylamine, bp 88–89°, *n*_D²⁰ 1.4003, 99.9% pure (lit.¹⁰ bp 89–90° *n*_D²⁰ 1.4003); and *N,N,N'*-trimethyl-1,3-propanediamine, bp 140–143°, *n*_D²⁰ 1.4275, 99.8% pure (lit.¹¹ bp 140–142°).

Esters. **Phenyl Dichloroacetate.** Dichloroacetyl chloride (prepared from Matheson Coleman and Bell dichloroacetic acid by the method of Brown¹²), 14.4 g (0.098 mole), and 7.8 g (0.083 mole) of phenol were placed in a 150-ml, ground-joint, round-

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(2) United Arab Republic Government Fellow for 1960–1965.

(3) To whom requests for reprints should be sent.

(4) See, for example, (a) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 104 (1966); (b) L. R. Fedor, T. C. Bruce, K. L. Kirk, and J. Meinwald, *ibid.*, **88**, 108 (1966), and references listed therein.

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bottomed flask with a water condenser, and the mixture was refluxed until evolution of HCl gas ceased (about 5 hr). The mixture was dissolved in excess hot petroleum ether and filtered. The white solid ester which crystallized on cooling the filtrate was recrystallized from petroleum ether to give 13.4 g (80% yield) of the crystalline solid, melting at 48–49° (lit.¹³ mp 38.5–49.5°). The infrared spectrum of an emulsion of this solid in Nujol showed absorption bands at 1775 (C=O stretch), 1600 (C=C stretch), 1497 (aromatic H—C=C stretch), and 1200⁻¹ cm⁻¹ (C—C=C stretch).

Phenyl Difluoroacetate. Into a 200-ml, three-necked, round-bottomed flask fitted with condenser, dropping funnel, and thermometer, was introduced 8 g (0.07 mole) of sodium phenolate. To this, 7.3 g of the water–acid azeotrope (0.067 mole of difluoroacetic acid) was added. The mixture was stirred with a magnetic stirrer while cooling to 10° in a crushed ice–salt bath. From the dropping funnel, 5.5 g (0.036 mole) of phosphorus oxychloride was added portionwise to maintain the temperature at 10° (the excess POCl₃ was used to consume the water present in the azeotrope). After the addition was complete, the reaction mixture was allowed to warm to room temperature and heat was gently applied while stirring until evolution of HCl gas ceased. After 2 hr, the flask was cooled, and the reaction mixture was extracted with ether. After removal of ether with a water aspirator, the liquid residue was distilled (23 mm), and the fraction having bp 88–92° was collected and refractionated twice to give 7.0 g of a colorless liquid, bp 90–91° (23 mm), n_D^{25} 1.4617, d_4^{25} 1.262 g/cc. *Anal.* Calcd for C₈H₆F₂O₂: C, 55.81. Found: C, 55.6. The infrared spectrum of a liquid sample showed absorption bands at 1790 (C=O stretch), 1600 (C=C stretch), 1500 (aromatic H—C=C stretch), 1215 (O—C=C stretch), and 1115 cm⁻¹ (F₂C—) (not reported in the literature).

Phenyl Trichloroacetate. Into a 1-l. three-necked flask fitted with a stirrer, condenser, and dropping funnel, was placed 23 g (0.2 mole) of sodium phenolate and 300 ml of dry benzene. From the separatory funnel, 37 g (0.2 mole) of freshly prepared trichloroacetyl chloride (prepared by the method of Brown¹⁵) was added with stirring. After the addition was complete, the reaction mixture was stirred for 45 min. The sodium chloride which separated was removed by filtration and the solvent removed on a rotary evaporator. The residue was distilled (1.0 mm) and the fraction boiling at 98–101° was collected and redistilled. The final product was obtained at 100–101° (1.0 mm) [lit.¹³ 122° (14 mm), n_D^{20} 1.5232]. The yield was 13.5 g (28.7%).

Phenyl Chloroacetate. This was prepared in the same manner as phenyl trichloroacetate. The solid obtained had mp 40–41° [lit.¹³ bp 140–141° (31 mm)].

Phenyl Methoxyacetate. This was prepared by the same method as phenyl trichloroacetate, except that phenol was used instead of sodium phenolate. The ester, 11.6 g (71%), had bp 127–128° (13 mm), n_D^{25} 1.5000, d_4^{25} 1.11 g/cc. *Anal.* Calcd for C₈H₁₀O₃: C, 65.0. Found: C, 65.3. This compound was not reported in the literature.

Phenyl Formate. This was prepared by the method of Buzas, Engell, and Freon.¹⁴ The final product was obtained in 6.9-g (57%) yield and had bp 62–64° (8 mm), n_D^{25} 1.5055 [lit.¹⁶ bp 178–178.5° (8 mm), n_D^{25} 1.5094].

Phenyl Cyanoacetate. This was prepared by the method of Ziegler and co-workers¹⁶ except that sodium phenolate was used instead of phenol. The white crystalline product was obtained in 5-g (31%) yield and had mp 39–40° (lit.¹⁶ mp 41°).

Phenyl Phenylacetate. This was prepared according to the Schotten–Baumann reaction.¹⁷ The ester, 4.5 g (60% yield), was obtained as white needle-like crystals, mp 39.5–40.5° (lit.¹⁸ 39–40°).

Phenyl Acetate. This was prepared by the method of Chattaway¹⁹ from acetic anhydride and phenol. The product was a colorless liquid, bp 72–74° (11 mm), n_D^{25} 1.5020 [lit.¹⁹ bp 78° (10 mm), n_D^{25} 1.5030].

Phenyl Propionate. Into a 100-ml, round-bottomed flask was placed 0.1 mole of phenol in 35 ml of dry benzene. To this, 0.12

mole of propionyl chloride (prepared by the method of Brown¹⁵) and 1.2 g of magnesium metal were added. A condenser was added and the mixture refluxed on a water bath until evolution of hydrogen chloride ceased. The flask was cooled; 25 ml of ether was added, and the mixture filtered. The filtrate was extracted once with 5% aqueous sodium hydroxide and three times with 50-ml portions of cold water. After drying over sodium sulfate, and removal of solvent with a rotary evaporator, the residue was distilled under reduced pressure. The fraction boiling at 82–85° (2 mm) was collected and redistilled. The final product was obtained in 9-g (60%) yield and had bp 82–83°, n_D^{25} 1.4952 [lit.²⁰ bp 98–99° (8 mm), n_D^{25} 1.5003].

Phenyl Pivalate. This was prepared by the same method as phenyl propionate. The clear liquid product was obtained in 20-g (70%) yield and had bp 109–111° (21 mm), n_D^{25} 1.4761 [lit.²⁰ bp 118–119° (35 mm)].

Kinetics. A Bausch and Lomb Spectronic 505 ultraviolet spectrophotometer with jacketed cell compartment was used for the kinetic measurements. Water at 25.5 ± 0.1° was circulated through the cell compartment by means of a constant-temperature bath unit, Haake Circulator Series F. The reactions were carried out in 1-cm, ground-glass-stoppered, fused silica absorption cells.

The reactions were followed by rate of appearance of the phenol peak at 274 mμ. The corresponding amides and esters showed no absorption in the 230–290-mμ region. Complete spectra taken for several mixtures of amide and phenol in *p*-dioxane corresponded to the spectra of pure phenol solutions having the same concentration of phenol. Also, complete spectra taken at the end of each kinetic run corresponded to the spectra of phenol solutions of the same concentration. Beer's law was found to be obeyed within the concentration and wavelength range employed.

Stock solutions of esters, usually about 10⁻³ M, were prepared and the concentrations checked by comparing the optical density with that calculated from the Beer's law relationship at 274 mμ. Stock amine solutions were prepared and the concentration determined by acid–base titration. Appropriate concentrations of amine and ester were prepared by dilution of the stock solutions with *p*-dioxane. All ester concentrations were 5.00 × 10⁻⁴ M.

Reactions were followed to 90–99% completion, with at least 15 readings taken. For kinetic runs which could be completed in a day or less, the reactions were carried out in the absorption cells. For slower runs, the reactions were begun in 25-ml volumetric flasks. A sample was removed and placed in the cell in the instrument, and the cell was returned to the constant-temperature bath. The cell was allowed to remain in the instrument for the first day, frequent readings being taken. The solution in the cell was discarded and aliquots were removed from the flask for all subsequent readings.

The reference solution was that of dioxane containing an equal amine concentration to that being used in the particular run.

Comparison of the spectra of a completed reaction and a mock solution consisting of the phenol, amine, and amide in *p*-dioxane in the expected concentrations showed a consistency within 1–2% transmittance units. In all runs, at least a tenfold excess of amine over ester was used in order to obtain pseudo-first-order kinetics. Duplicate or triplicate runs were performed for each concentration, and readings taken in any single kinetic run covered a rate of 85% transmittance units.

Stoichiometry and Isolation of Products. Authentic samples of *N*-*n*-butyldichloroacetamide and of 1-difluoroacetyl piperidine were prepared by independent methods. Laboratory quantities of two reactions were carried out: (1) phenyl dichloroacetate with *n*-butylamine, (2) phenyl difluoroacetate with piperidine. The expected amides were obtained in about 70% yield and were identical in physical properties with the authentic samples.

Results. Pseudo-first-order kinetics were obtained for all runs. Reactions were followed to 90–99% completion with at least 15 points being taken, and good first-order plots of log ($D - D_1$) against time were obtained as shown in Figure 1. In all kinetic runs the ester concentration was 5.0 × 10⁻⁴ M. The average deviation from the mean value of the rate constant in duplicate or triplicate experiments was ± 5% or less.

For the reactions of primary amines with all esters except phenyl methoxyacetate, the following rate equation was obtained

$$k_1/(\text{amine}) = k_2 + k_3(\text{amine})$$

This is illustrated in Figure 2, where a plot of $k_1/(\text{amine})$ against amine concentration gives a straight line.

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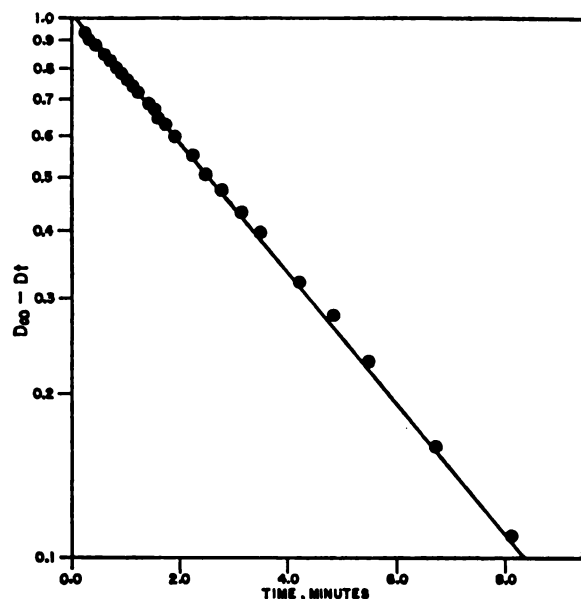


Figure 1. Typical first-order plot for aminolysis of phenyl esters. Reaction of 0.180 *M* *N*-methyl-*n*-butylamine with phenyl dichloroacetate.

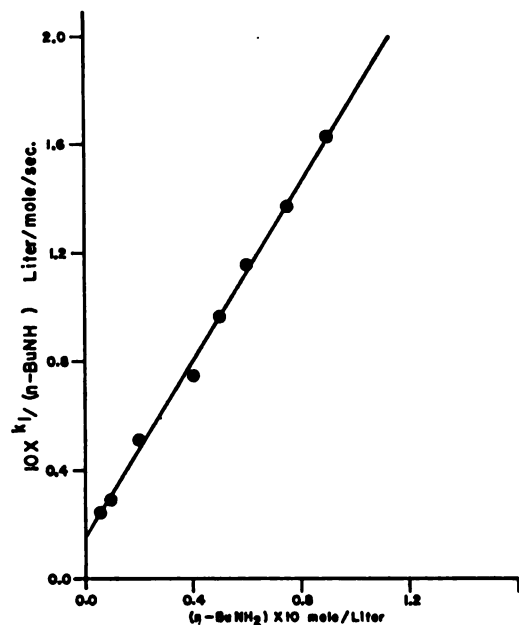


Figure 2. Plot of $k_1/(\text{amine})$ against amine concentration for the reaction of phenyl dichloroacetate with *n*-butylamine in *p*-dioxane at 25.5°.

Simple second-order kinetics were found for the reactions of secondary amines and diamines with all esters, and for the reaction of phenyl methoxyacetate with *n*-butylamine, as shown in Figure 3, where a plot of k_1 against amine concentration gives a linear relationship. That is

$$k_1 = k_2(\text{amine})$$

For the reaction between *n*-butylamine and phenyl dichloroacetate, with triethylamine added as a catalyst, the following relationship was found

$$k_1 = k_2(\text{amine}) + k_3(\text{amine})^2 + k_3(\text{Et}_3\text{N})(\text{amine})$$

Since in this series both the ester and *n*-butylamine concentrations were held constant and the triethylamine concentration varied, plots of k_1 against triethylamine concentration were linear as shown in Figure 4. The calculated intercept of this plot, equal to k_2 .

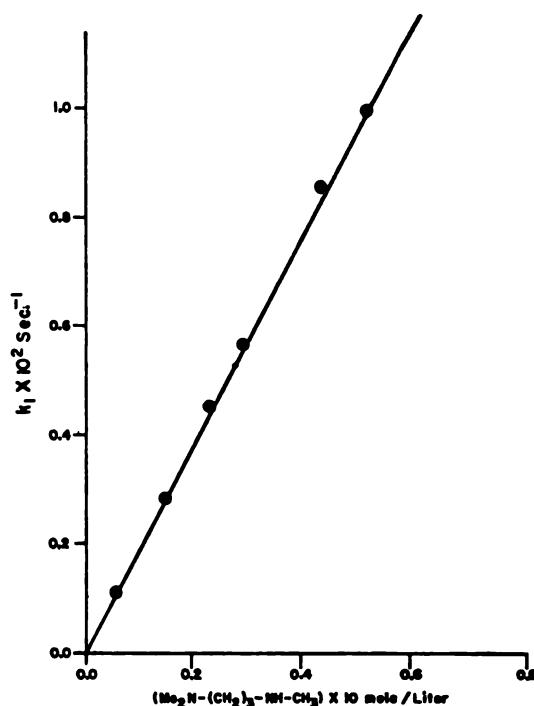


Figure 3. Simple second-order plot for the reaction of phenyl dichloroacetate with *N,N,N'*-trimethyl-1,3-propanediamine in *p*-dioxane at 25.5°.

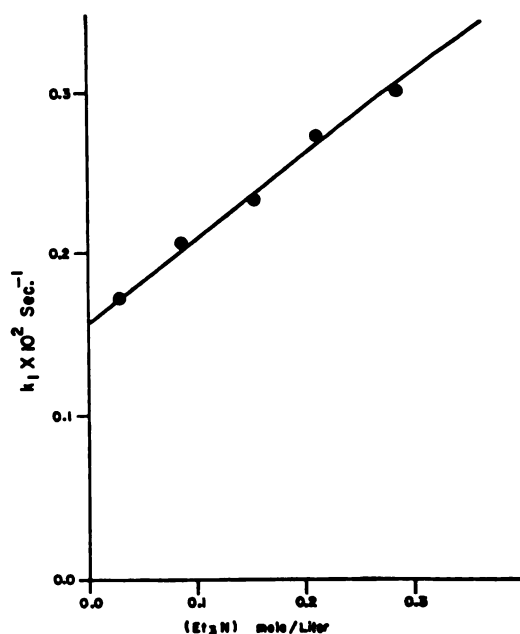


Figure 4. Plot of k_1 against triethylamine concentration for *n*-butylaminolysis of phenyl dichloroacetate in *p*-dioxane at 28.0°; *n*-BuNH₂ concentration is held constant (0.021 *M*).

(amine) + $k_3(\text{amine})^2$ agrees within experimental precision with the experimentally determined pseudo-first-order rate constant for aminolysis of phenyl dichloroacetate by *n*-butylamine in the absence of triethylamine under the same conditions of temperature and *n*-butylamine concentration.

Values of k_2 , k_3 , and k_3' were calculated by the method of least squares and are summarized in Tables I, II, and III.

In a series of experiments carried out in cyclohexane on the reaction of *n*-butylamine with phenyl dichloroacetate, only third-order kinetics were obtained, as shown in Figure 5, where no intercept was obtained from a plot of $k_1/(\text{amine})$ against (amine).

Table I. Kinetic Expressions and Associated Rate Constants Determined with a Series of Nitrogen Bases in *p*-Dioxane, at 25.5°

Amine (<i>M</i>)	Reaction kinetics	No. of <i>k</i> detns	<i>k</i> ₁	<i>k</i> ₂	<i>k</i> ₃ '
Phenyl Dichloroacetate					
<i>n</i> -Butylamine (0.006–9.00)	<i>k</i> ₂ (E)(A) + <i>k</i> ₃ (E)(A) ²	17	0.0143	1.65	
Piperidine (0.121–1.21)	<i>k</i> ₂ (E)(A)	10	0.0478		
<i>N</i> -Methyl- <i>n</i> -butylamine (0.0240–33.3)	<i>k</i> ₂ (E)(A)	13	0.0245		
3-Methoxy- <i>n</i> -propylamine (1.70–8.51)	<i>k</i> ₂ (E)(A) + <i>k</i> ₃ (E)(A) ²	12	0.0347	1.15	
<i>N,N</i> -Dimethyl-1,3-propanediamine (0.281–0.702)	<i>k</i> ₂ (E)(A)	15	2.70		
<i>N,N,N'</i> -Trimethyl-1,3-propanediamine (0.576–5.18)	<i>k</i> ₂ (E)(A)	12	0.199		
<i>n</i> -Butylamine (0.01); triethylamine (2.78–28.5)	<i>k</i> ₂ (E)(A) + <i>k</i> ₃ (E)(A) ² + <i>k</i> ₃ (E)(A)(Et ₃ N)	12			0.264
Phenyl Difluoroacetate					
<i>n</i> -Butylamine (0.70–2.16)	<i>k</i> ₂ (E)(A) + <i>k</i> ₃ (E)(A) ²	22	0.01	22.8	
Piperidine (0.288–7.71)	<i>k</i> ₂ (E)(A)	14	0.246		
<i>N</i> -Methyl- <i>n</i> -butylamine (0.954–8.59)	<i>k</i> ₂ (E)(A)	21	0.124		

Table II. Kinetic Expressions and Associated Rate Constants for the Reactions of a Series of Phenyl Esters, RCOOPh, with *n*-Butylamine in *p*-Dioxane, at 25.5°

R	<i>k</i> ₂ , M ⁻¹ sec ⁻¹	<i>k</i> ₃ , M ⁻² sec ⁻¹	No. of <i>k</i> detns	<i>k</i> ₂ / <i>k</i> ₃	Amine concn range, <i>M</i>
Cl ₂ C	0.107	41.2	20	286	0.007–0.025
F ₂ CH	0.100	22.8	22	228	0.70–2.16
Cl ₂ CH	0.0143	1.65	17	115	0.006–9.00
NCCH ₃	6.59 × 10 ⁻³	4.16 × 10 ⁻³	13	6.42	0.044–0.486
ClCH ₂	1.73 × 10 ⁻³	2.12 × 10 ⁻³	13	12.2	0.121–0.883
CH ₂ OCH ₃	8.31 × 10 ⁻⁴	...	18	...	0.101–0.901
H	7.86 × 10 ⁻³	5.44 × 10 ⁻³	14	6.90	0.070–0.490
PhCH ₂	9.83 × 10 ⁻³	4.01 × 10 ⁻³	12	4.08	0.221–2.40
CH ₃	8.09 × 10 ⁻⁴	5.95 × 10 ⁻⁴	17	0.74	0.080–2.63
CH ₃ CH ₂	4.85 × 10 ⁻⁴	1.82 × 10 ⁻⁴	12	3.76	1.64–4.38
(CH ₃) ₂ C	1.17 × 10 ⁻⁷	1.06 × 10 ⁻⁷	8	0.91	1.02–4.76

Table III. Phenyl Methoxyacetate

Amine (<i>M</i>)	Reaction kinetics	No. of <i>k</i> detns	<i>k</i> ₂
<i>n</i> -Butylamine (0.10–0.901)	<i>k</i> ₂ (E)(A)	18	8.31 × 10 ⁻⁴
<i>N</i> -Methyl- <i>n</i> -butylamine	<i>k</i> ₂ (E)(A)	8	6.30 × 10 ⁻⁴

The polar and steric susceptibility parameters for this series were as follows

	ρ^*	δ
<i>k</i> ₂	+3.03	+1.08
<i>k</i> ₃	+2.14	+1.03

Discussion

Mechanism of Base Catalysis. The disappearance of the second-order rate constant when cyclohexane is used as solvent seems to indicate that the second-order term obtained in the reaction of phenyl esters with *n*-butylamine represents a solvent-catalyzed term, rather than an uncatalyzed term. This suggests that the reaction of phenyl esters with secondary amines may proceed *via* a different mechanism than that with primary amines. In this paper, only the mechanism involving general base catalysis will be discussed.

Consistent with the observations are eq 1 and 2. In the first step, the intermediate II is pictured as forming by nucleophilic attack of nitrogen with simultaneous protonation of the carbonyl, in order to avoid the use of ionic intermediates, which are considered here

The kinetic data for the series of esters excluding phenyl methoxyacetate was found to be correlated by the Taft equation of the type

$$\log (k/k_0) = \sigma^* \rho^* + \delta E_s^{21}$$

Both second- and third-order constants were correlated by this equation, as shown in Figures 6 and 7. Figure 8 shows the scatter obtained when a correlation of the type $\log (k/k_0) = \sigma^* \rho^*$ was attempted; similar scatter was obtained from plots of $\log (k/k_0)$ against E_s , log relative rate constants for alkaline specification of esters, and acid dissociation constants (Hammett-type plot).

(21) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

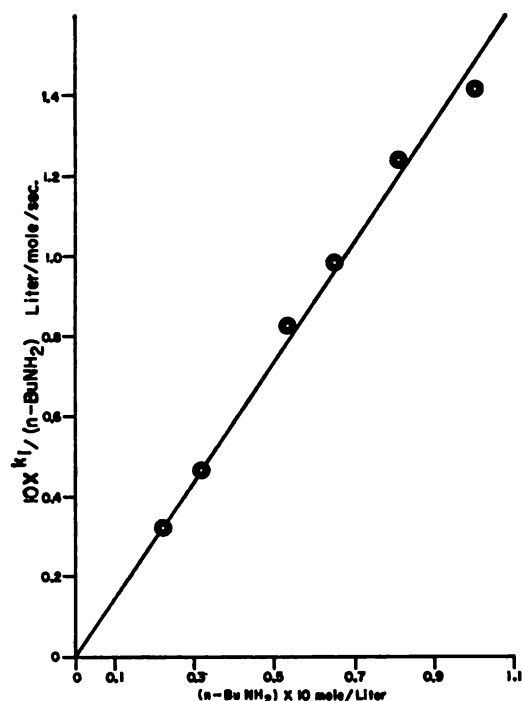
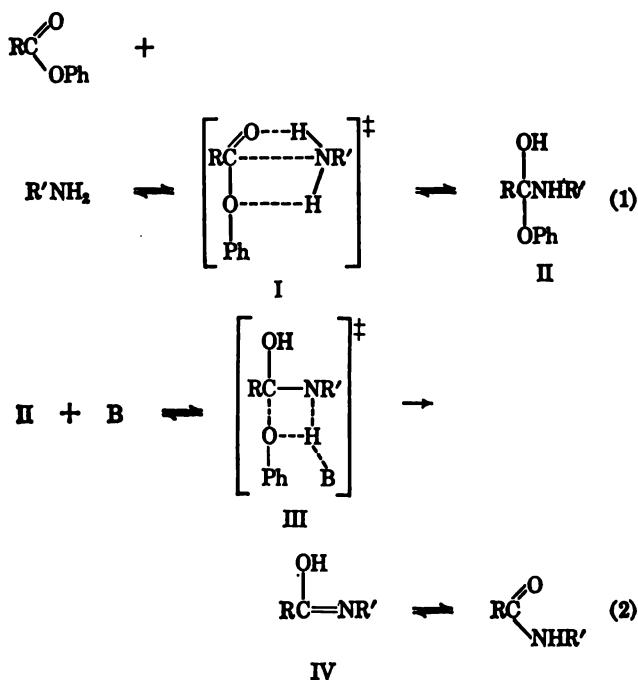


Figure 5. Plot of $k_1/(\text{amine})$ against amine concentration for the reaction of phenyl dichloroacetate with *n*-butylamine in cyclohexane at 25.5°.

as having little importance since the reaction takes place in a solvent of low dielectric constant. Construction of Godfrey models has shown that this simultaneous bond formation is sterically and geometrically feasible.



In the second step, the intermediate is shown as losing phenol by protonation of phenoxy group by amine nitrogen, assisted by the base catalyst B. In this study, B could be another molecule of attacking amine, triethylamine, or the solvent, dioxane.

This stepwise scheme is, of course, kinetically indistinguishable from a concerted mechanism, as follows

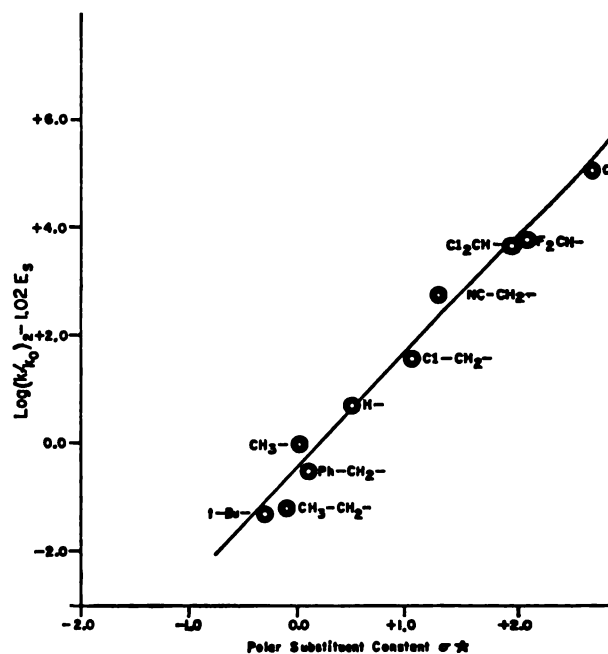


Figure 6.

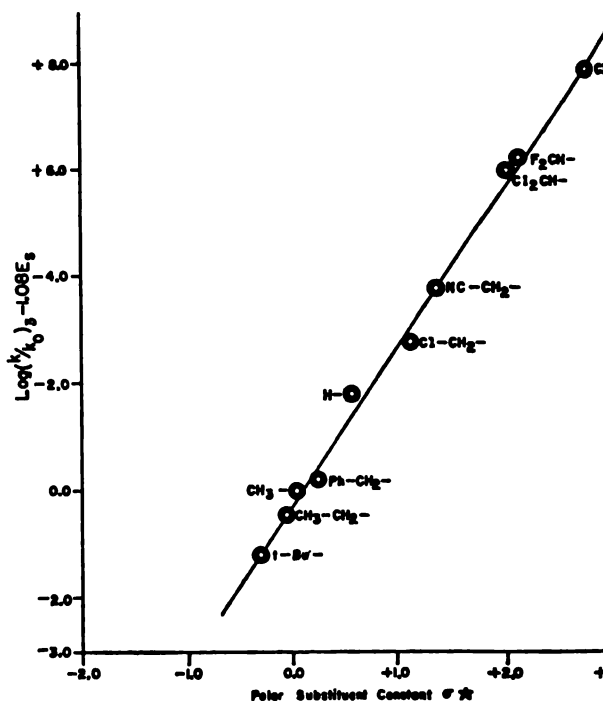
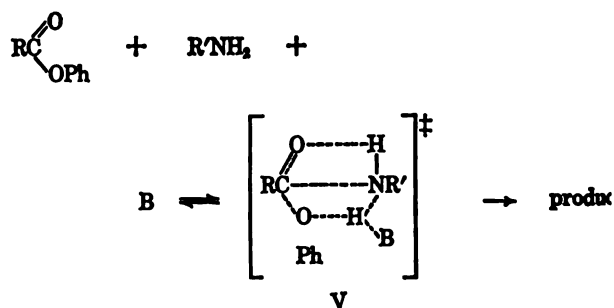


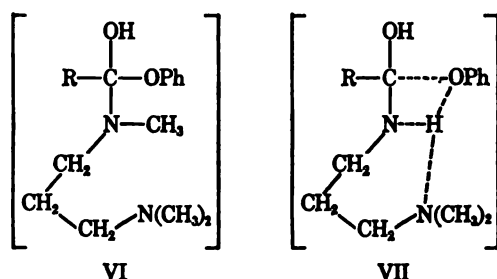
Figure 7.



Our data do not permit a distinction between the two alternatives at the present time; however, our

servations are consistent with the protonation of the phenoxy group by the amine hydrogen, rather than by the base catalyst. Catalysis by triethylamine, a tertiary amine, and the observation that base catalysis does not occur with secondary attacking amines, seem to substantiate this. Although the mechanism in aqueous solution may not be the same as that in dioxane, it is interesting that much of the literature data for aqueous solutions is consistent with this explanation. For example, in aminolysis of phenyl acetate, Jencks and co-workers found general base catalysis for the primary amines *n*-butylamine, hydroxylamine, glycine, and glycyglycine,²² methylamine, ethylamine, and *n*-propylamine,²³ but not for the secondary amines piperidine and morpholine.²³ Bruice and co-workers²⁴ obtained no general base catalysis for three cyclic secondary amines. One notable exception is the observation of Jencks and Carriuolo²² that general base catalysis does occur for the reaction of dimethylamine with phenyl acetate. This amine will be investigated in dioxane solution in this laboratory.

Intramolecular Catalysis. The observation of second-order kinetics without general base catalysis in the reactions of two diamines with phenyl esters in dioxane is in agreement with the results of Bruice and Willis²⁴ who found no general base catalysis for a series of diamines in aqueous solution. One may suggest an explanation in terms of intramolecular catalysis, as shown below



A reaction involving the intermediate VI might be expected to proceed more slowly than that involving VII since the pictured catalytic effect cannot operate in VI. In fact, the observation was made that the reaction of *N,N*-dimethyl-1,3-propanediamine with phenyl dichloroacetate had a rate constant 13 times as large as that for the reaction of *N,N,N'*-trimethyl-1,3-propanediamine with the same ester, as can be seen from the data in Table I.

An analogous explanation may be given to explain the lack of external base catalysis for phenyl methoxyacetate, where the methoxy group might act as the base, B, in the proposed mechanism. If one accepts the idea that dioxane may act as a base catalyst in this reaction, extrapolation to include the methoxy group is not too difficult. Again, a difference in rate constants by a factor of 13 (Table III) between the two amines, *n*-butylamine (the faster) and *N*-methyl-*n*-butylamine, is consistent with this, since in the latter the catalytic effect is not expected to operate.

The Effect of Structure. The probability of a coincidental fit to the Taft equation $\log k/k_0 = \rho^*\sigma^* + \delta E_s$

(22) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960).

(23) L. R. Fedor, T. C. Bruice, K. L. Kirk, and J. Meinwald, *ibid.*, **88**, 108 (1966).

(24) T. C. Bruice and R. G. Willis, *ibid.*, **87**, 531 (1965).

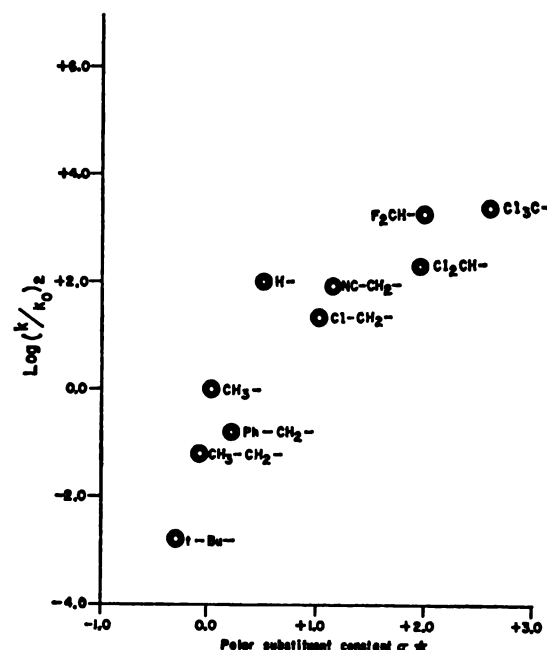


Figure 8.

is very small, since the lack of generality of this equation is well established; indeed, only two other reaction series have been found to be correlated by this equation, *viz.*, the methanolysis of 1-menthyl esters²⁵ and the alkylation of amino acids by acetonitrile.²⁶ In the present study, a range of eight powers of 10 in the rate constants was covered, increasing the unlikelihood of a coincidental fit to the equation.

Comparison of the reaction parameters of the solvent-catalyzed reaction and the amine-catalyzed reaction shows that the reaction with the stronger base is much more susceptible to polar requirements than is the solvent-catalyzed reaction. On the other hand, the steric requirements appear to be independent of the nature of the catalyzing base. This can also be seen by examination of the rate constant ratios, k_3/k_2 , shown in Table I. The ratios are large for those substituents having large electron-withdrawing properties, and decrease to around one for the alkyl substituents.

These observations may be reconciled with the proposed mechanism as follows. If the decomposition of the intermediate is considered to be rate determining, then this will be made more difficult with increased polar requirements of the acyl substituent. The base-catalyzed decomposition of the intermediate, then, could be considered to require a much stronger base to remove the phenol than would be needed for compounds having substituents of lesser polarity. The first step, on the other hand, would be facilitated by electron-withdrawing substituents, and the larger over-all rate for these compounds may be considered to be due to a greater "piling up" of the intermediate than occurs with compounds having substituents of lesser polarity.

Work is now in progress to investigate the effect of different donor groups in the acyl portion of the ester, both to seek a Brønsted relationship if this be base catalysis, and to determine the effect of proximity to the reaction center by addition of methylene groups between

(25) W. A. Pavelich and R. W. Taft, Jr., *ibid.*, **79**, 4935 (1957).

(26) M. Friedman and J. S. Wall, *ibid.*, **86**, 3735 (1964).

the carbonyl and the donor group. Entropies of activation will also be obtained, and the mechanism of the uncatalyzed reaction will be investigated more fully.

Acknowledgments. The authors are grateful to the Lowell Technological Institute Research Foundation for a grant supporting this work and for assistance in

preparing the manuscript. Gratitude is also extended to the United Arab Republic for financial support of Mr. Shawali during the course of his doctoral work. The many helpful suggestions of Dr. James B. Pierce and the referees who read the manuscript in its original form are also gratefully acknowledged.

A New Approach to the Synthesis of α -Hydroxy- β -diketones and γ -Bromo- α -hydroxy- β -diketones and Their Phosphate Esters

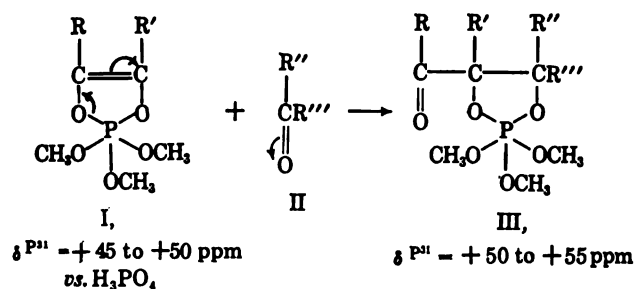
Fausto Ramirez,¹ S. B. Bhatia, and C. P. Smith

Contribution from the Department of Chemistry of the State University of New York at Stony Brook, Stony Brook, New York 11790.

Received February 10, 1967

Abstract: 2,2,2-Trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene, made from trimethyl phosphite and biacetyl, reacted with ketene, $\text{CH}_2=\text{C}=\text{O}$, and gave 2,2,2-trimethoxy-4-methylene-5-acetyl-5-methyl-1,3,2-dioxaphospholane in over 90% yield. This phospholane was quantitatively converted by hydrogen chloride into the dimethyl phosphate ester of 3-methylpentan-3-ol-2,4-dione (diacetylmethylcarbinol). The phosphorus-free hydroxydiketone was made from the phospholane or the phosphate in boiling aqueous benzene. Bromination of the phospholane gave the dimethyl phosphate ester of 1-bromo-3-methylpentan-3-ol-2,4-dione.

The formation of a carbon-carbon single bond by the nucleophilic addition of a 2,2,2-trialkoxo-1,3,2-dioxaphospholene² (I) to a carbonyl function II was first reported in 1961.³ This condensation reaction made available the new 2,2,2-trialkoxo-1,3,2-dioxaphospholanes⁴ (III).



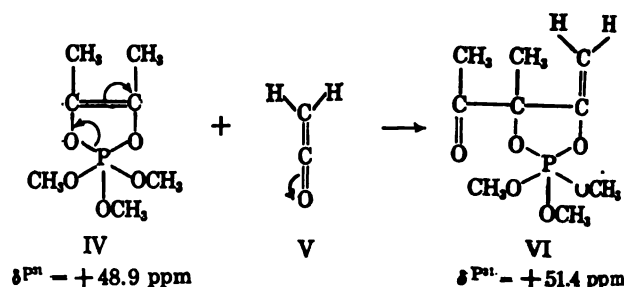
The phospholanes III could be transformed into cyclic and open-chain phosphate esters, and into phosphorus-free polyoxygenated functions.⁵ Some of the phospholanes were also capable of undergoing molecular rearrangements when heated in methanol solution.^{4,6}

This paper describes the condensation of a phospholene I with ketene,⁷ and discloses a new approach to the

synthesis of α -hydroxy- β -diketones and γ -bromo- α -hydroxy- β -diketones and their phosphate esters.

Results

Reaction of Ketene with the Trimethyl Biacetylphosphite 1:1 Adduct IV. The reaction of ketene V with 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene (IV) took place at 0° in methylene chloride solution. The product was 2,2,2-trimethoxy-4-methylene-5-acetyl-5-methyl-1,3,2-dioxaphospholane (VI) isolated in 90% yield.



The phospholane VI probably arose in a concerted nucleophilic addition of the phospholene IV to the ketene V without the formation of an intermediate dipolar ion like VII.⁸ However, the transient formation of undetectably small amounts of VII cannot be excluded.

The pentaoxyphosphorane VI was distinguished from the isomeric tetraoxyalkylphosphorane VIII on the basis of the following spectral data.

(7) While this work was in progress, A. J. Kirby [*Tetrahedron*, 22, 3001 (1966)] published experiments involving the phospholene IV and carbon disulfide. Our studies of the reactions of IV, and of related phospholenes, with a number of systems having cumulated double bonds will be published in a separate communication.

(8) (a) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, 30, 2575 (1965); (b) *ibid.*, 31, 474 (1966).

(1) This investigation was supported by Public Health Service Grant No. CA-04769-08 from the National Cancer Institute, and by the National Science Foundation, Grant GP-6690-Y.

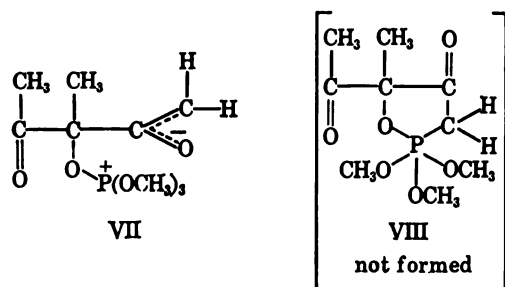
(2) For a review, see F. Ramirez, *Pure Appl. Chem.*, 9, 337 (1964).

(3) (a) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, 26, 3041 (1961); (b) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Am. Chem. Soc.*, 84, 1317 (1962); (c) F. Ramirez, N. B. Desai, and N. Ramanathan, *Tetrahedron Letters*, 323 (1963).

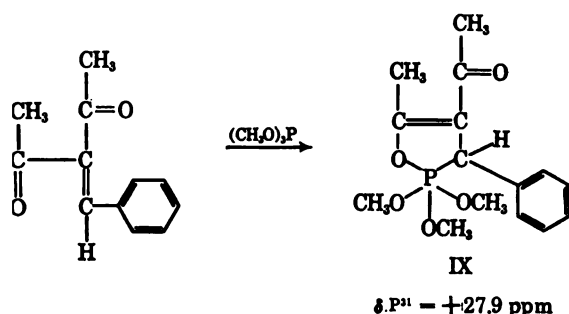
(4) For a review, see F. Ramirez, *Bull. Soc. Chim. France*, 2443 (1966).

(5) (a) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *J. Am. Chem. Soc.*, 87, 549 (1965); (b) F. Ramirez, N. Ramanathan, and N. B. Desai, *ibid.*, 85, 3465 (1963); (c) F. Ramirez, S. B. Bhatia, and C. P. Smith, *Tetrahedron*, in press.

(6) F. Ramirez, H. J. Kugler, and C. P. Smith, *Tetrahedron Letters*, 261 (1965).



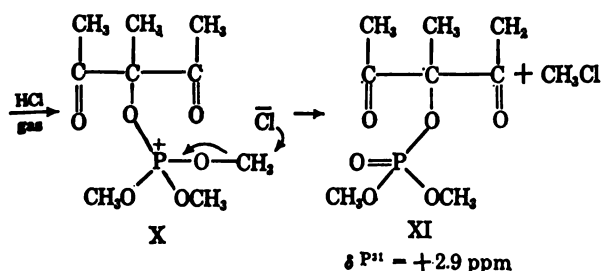
1) The P^{31} nmr shift, δP^{31} , of VI was very close to that found for other related pentaoxyphosphoranes^{4,9} of type III. On the other hand, the tetraalkoxyalkylphosphorane IX gave a signal at a much lower magnetic field.¹⁰



2) The H^1 nmr spectrum of VI, examined at 60 and 100 Mc/sec, had one-proton signals at τ 5.80 and 6.21. These signals consisted of doublets of doublets. The coupling between the two vinyl protons was $J_{HH} = 1.9$ cps. One of the hydrogen-phosphorus couplings was ~ 1.9 cps and, therefore, the signal looked like a distorted triplet. The other J_{HP} value was approximately 1.4 cps. These values were in agreement with structure VI but not VIII. The three indistinguishable methoxy groups gave one doublet at τ 6.40, $J_{HP} = 13$ cps. The acetyl and the methyl protons were at τ 7.82 and 7.95, respectively.

3) The infrared spectrum of VI had the expected bands at 5.80 and 6.00 μ due to the acetyl and the enol phosphorane, respectively.¹¹

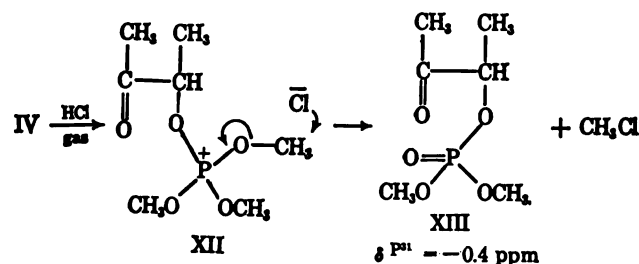
Reaction of the Phospholane VI with Hydrogen Chloride. This reaction afforded the dimethyl phosphate ester of 3-methylpentan-3-ol-2,4-dione (XI) in quantitative yield. Probably, a tetraalkoxyphosphonium chloride X was an intermediate.



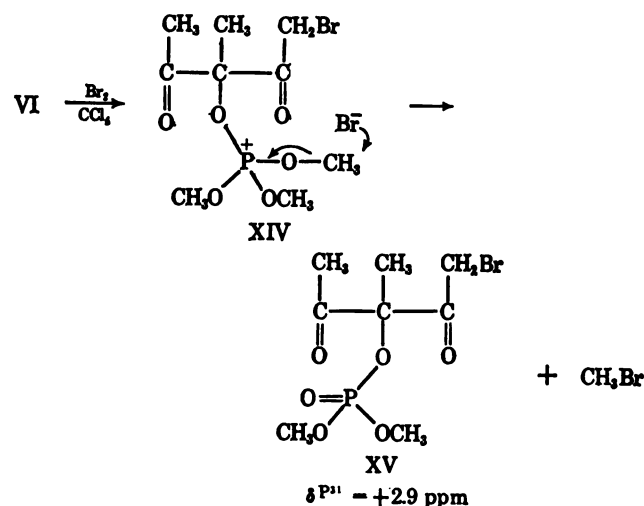
The reaction can be considered as an alkylation of hydrogen chloride by the unsaturated phospholane

- 1) For open-chain pentaoxyphosphoranes, see D. B. Denney and S. J. Gough, *J. Am. Chem. Soc.*, **87**, 138 (1965), and references therein.
 2) F. Ramirez, O. P. Madan, and S. R. Heller, *ibid.*, **87**, 731 (1965).
 3) The spectrum of VI had a strong band at 12.0 μ , which could be due to the hydrogen out-of-plane deformations of the vinyl group; see J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 51.

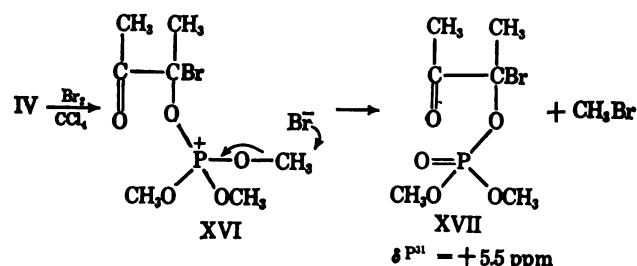
VI. A similar alkylation by the phospholene IV was previously reported¹² and is shown in formulas XII \rightarrow XIII.



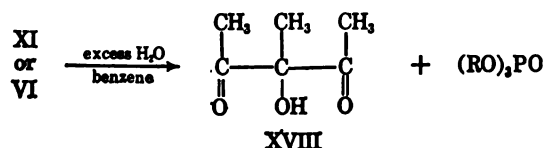
Reaction of the Phospholane VI with Bromine. This reaction was carried out in CCl_4 solution at 0° and gave α -bromo- α -hydroxy- β -diketone XV in quantitative yield.



A possible mechanism is shown in formula XIV. It should be noted that the bromination of the phospholene IV gave α -bromo- α -ketol phosphate¹³ XVII, probably by a similar path.

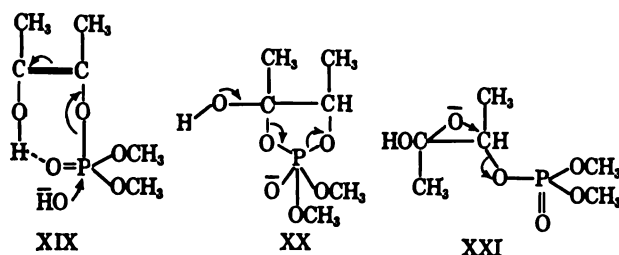


Hydrolysis of the α -Hydroxy- β -diketone Phosphotriester XI. The phosphotriester XI was converted into 3-methylpentan-3-ol-2,4-dione or diacetylmethylcarbinol^{13,14} (XVIII) by aqueous benzene at 80°.

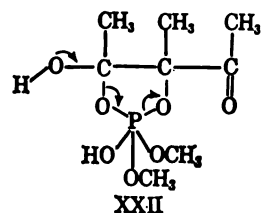


- (12) F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.*, **82**, 2652 (1960).
 (13) "Water solutions" of diacetylmethylcarbinol have been described (cf. ref 14). The pure alcohol was not isolated, and, consequently, analytical data were not provided. The bis(2,4-dinitrophenylhydrazones) was said to melt at 234–238°. The water solutions of the alcohol were made by acid hydrolysis of its acetate, which was prepared from α -methyl- α -acetylacetone and lead tetraacetate.
 (14) (a) E. Juni and G. Heym, *Arch. Biochem. Biophys.*, **67**, 410 (1957); (b) E. Juni and G. Heym, *J. Biol. Chem.*, **218**, 365 (1956).

This is a remarkably facile hydrolysis; trimethyl phosphate, or even dimethylphosphoacetoin (XIII), was not affected by water in boiling benzene, under comparable conditions. We have shown¹⁶ that the second-order rate constant for the *hydroxide ion catalyzed* conversion of dimethylphosphoacetoin (XIII) into acetoin and dimethyl hydrogen phosphate was $k_2 = 360 \text{ l. mole}^{-1} \text{ sec}^{-1}$, at 25° , in water at pH 7.7–8.3. This was at least 2×10^6 times faster than the corresponding value for trimethyl phosphate. Two possible explanations were proposed for this rate difference. (1) The acceleration could be due to the unsaturated nature of the leaving group and to hydrogen-bonding assistance (formula XIX). (2) The effect might result from carbonyl participation and oxyphosphorane formation during the hydrolysis (formula XX). Subsequently, a third explanation involving a hydroxyepoxide intermediate was proposed¹⁶ (formula XXI).



Rate data for the hydroxide ion catalyzed hydrolysis of the hydroxydiketone phosphate XI are not available yet. However, it seems at least possible, that the extraordinarily rapid hydrolysis in aqueous benzene might involve the oxyphosphorane intermediate XXII.



Hydrolysis of the Phospholane VI. The phospholane VI was readily converted into diacetylmethylcarbinol (XVIII) by an excess of water in benzene solution at 80° .

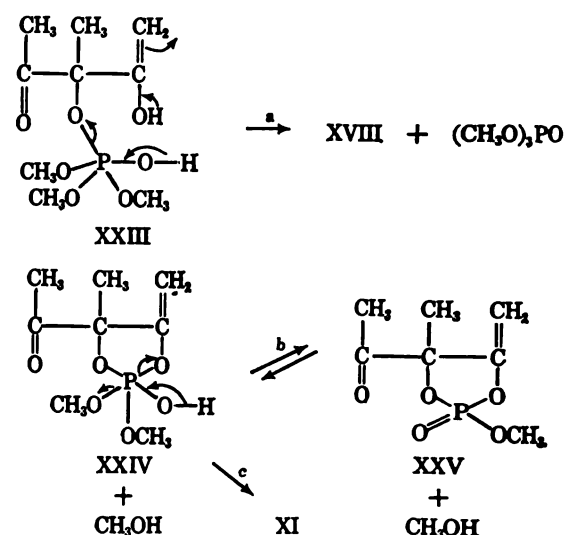
When 1 molar equiv of water, or of D_2O , was added to a solution of the phospholane VI in benzene, or in deuteriochloroform, four substances were produced almost instantaneously at 20° , or even at 0° . These were trimethyl phosphate, the hydroxydiketone XVIII, the dimethyl phosphate ester XI derived from this alcohol, and methanol. There was no evidence for the formation of the cyclic phosphotriester XXV. These conclusions were reached by an examination of the P^{31} and the H^1 nmr data of the solutions at various times. These results are explained in terms of the intermediates XXIII and XXIV.

Support for the formation of intermediates like XXIII and XXIV has been adduced previously.^{17–19}

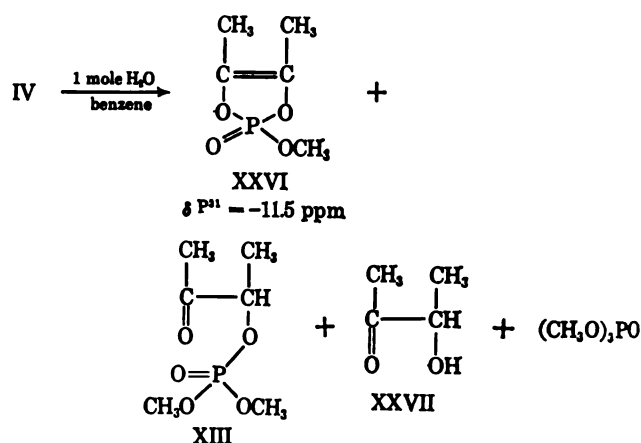
(15) F. Ramirez, B. Hansen, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 4588 (1962).

(16) (a) H. Witzel, A. Botta, and K. Dimroth, *Ber.*, **98**, 1465 (1965); (b) T. C. Bruice and S. J. Benkovic, "Biorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, p 104, have recently discussed this problem.

(17) F. Ramirez, O. P. Madan, and C. P. Smith, *J. Am. Chem. Soc.*, **87**, 670 (1965).



In particular, it should be noted that the hydrolysis of the phospholene IV gave trimethyl phosphate, acetoin, dimethylphosphoacetoin (XIII), *acetoinenediol cyclophosphate* (XXVI), and methanol. The relative proportion of these products could be greatly altered by changes in temperature and other experimental conditions.¹⁷



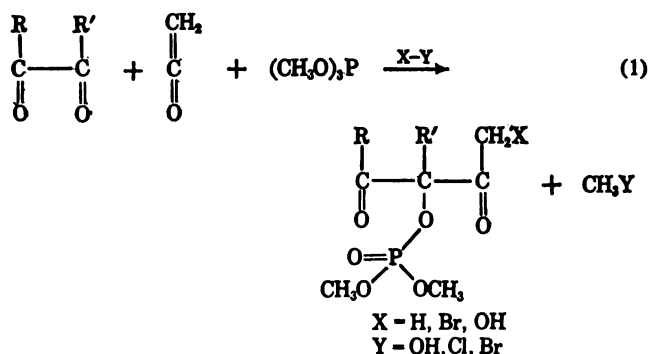
Discussion

The condensation of α -dicarbonyl compounds with ketenes by means of trialkyl phosphites opens a new route to a variety of polyoxygenated functions related to the carbohydrates. The phosphate esters of these sugar-like materials can also be obtained in this manner (eq 1).

The various steps in these transformations can be carried out rapidly and under exceptionally mild conditions. The final products can be isolated easily and in high yields. Experiments are now under way to delimit the scope of these reactions in terms of (1) variations in the structure of the carbonyl compounds and the ketenes; (2) further transformations of the

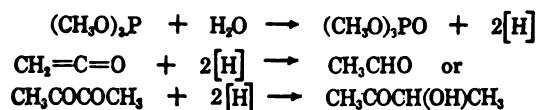
(18) (a) F. Ramirez, N. B. Desai, and N. Ramanathan, *ibid.*, **85**, 1874 (1963); (b) F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson, and E. M. Banas, *ibid.*, **85**, 2681 (1963).

(19) The formation of an intermediate (rather than a transition state) with quintuply connected phosphorus, which we have advocated to explain our observations on the hydrolysis of pentaoxyphosphoranes and of five-membered cyclic phosphotriesters (see ref 17 and 18), has been recently proposed also by Westheimer and co-workers to account for their observations during a comprehensive study of the hydrolysis of cyclic phosphates, phosphonates, and phosphinates; see E. A. Dennis and F. H. Westheimer, *ibid.*, **88**, 3431, 3432 (1966), and previous references given there.

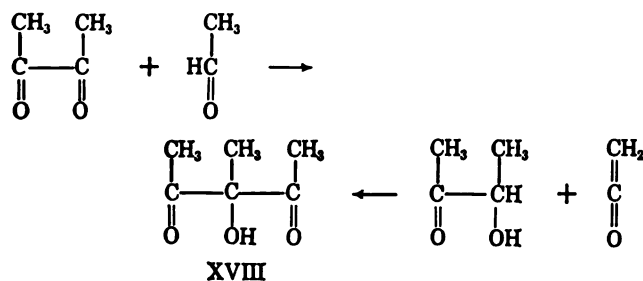


carbonylketene phosphite adducts to polyfunctional phosphorus-free materials; (3) synthesis of new types of polyfunctional phosphate esters and further transformations of them.

It should be noted that the combination of the oxyphosphorane condensation with a hydrolytic step accomplishes the following objective²⁰



Formally, the reductive phosphorylation of the α -dicarbonyl compound by a phosphite ester in the presence of ketene amounts to a condensation between biacetyl and acetaldehyde, or its equivalent, acetoin and ketene.



Diacetylmethylcarbinol (XVIII) and acetoin were reported to be formed simultaneously when biacetyl was used as the substrate for the enzyme pyruvic oxidase.^{14,21}

Experimental Section

The analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The instrumentation was described previously.⁴ All P^{31} nmr shifts are given in parts per million from 85% H_3PO_4 as zero; they were determined at 40.5 Mc/sec. All H^1 nmr shifts are given in parts per million from TMS as 10 (τ values); they were determined at 60 or at 100 Mc/sec, as indicated.

Reaction of Ketene with 2,2,2-Trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene (IV). Ketene was bubbled through a stirred solution of the phospholene IV (95 g) in methylene chloride (75 ml) kept in an ice bath. H^1 nmr analysis showed the complete disappearance of IV within 1.5 hr. The solvent and some of the acetone introduced with the ketene were removed at 20°, first at 20 mm, then at 1 mm. The residue was distilled through a 6-in. Vigreux column. Fraction 1 (19 g) was collected below 55° (0.3 mm) and consisted of the adduct VI contaminated with some trimethyl phosphate. Fraction 2 (85 g) was 2,2,2-trimethoxy-4-methylene-5-acetyl-5-methyl-1,3,2-dioxaphospholane (VI), bp 56–57° (0.1 mm). The spectral characteristics of this material did not change after redistillation. A sample fractionated through a 24-in. spinning-

band column had bp 62° (0.2 mm); prolonged heating may lead to partial decomposition.

Anal. Calcd for $\text{C}_8\text{H}_{17}\text{O}_6\text{P}$: C, 42.9; H, 6.7; P, 12.3; mol wt, 252. Found: C, 42.5; H, 6.8; P, 12.1; mol wt, 247.

The P^{31} nmr spectrum (neat liquid) had a multiplet at +51.4 ppm vs. H_3PO_4 . The H^1 nmr spectrum in CDCl_3 had a 1 H^1 doublet of doublets at τ 5.80, $J_{\text{HH}} = 1.9$ cps, $J_{\text{HP}} = 1.9$ cps, and a second 1 H^1 doublet of doublets at τ 6.21, $J_{\text{HH}} = 1.9$ cps, $J_{\text{HP}} = 1.4$ cps; the separation between the centers of these two multiplets was 23 cps at 60 Mc/sec and 39 cps at 100 Mc/sec. The spectrum had also a 9 H^1 doublet at τ 6.40, $J_{\text{HP}} = 13$ cps, and 3 H^1 singlets at τ 7.82 and 8.50, respectively. Better resolution was achieved in benzene, where the signals were at τ 5.80, 6.20, 6.45, 7.88, and 8.52, respectively. The low-field vinyl phosphorane protons had the appearance of a distorted triplet in all solvents.

The infrared spectrum (CH_2Cl_2) had bands (μ) at 3.43 (w), 3.55 (w), 5.80 (s) ($\text{C}=\text{O}$), 6.00 (m) ($\text{C}=\text{CO}$), 6.90 (w), 7.30 (w), 7.40 (w), 7.75 (m), 8.50 (m), 8.60 (m), 9.20 (vs) (POCH_3), 10.00 (vs), 10.45 (w), 11.42 (m), 12.00 (s) (probably H out-of-plane deformation of $\text{OC}=\text{CH}_2$, with shoulder at 11.85), and 12.90 (ms).

Redistillation of fraction 1 using a 12-in. spinning-band column gave an additional amount of adduct VI, which was formed in about 90% yield. The H^1 nmr of the original distillation residue showed the presence in it of more adduct VI.

Reaction of the Phospholane VI with Hydrogen Chloride. Anhydrous hydrogen chloride was passed through a solution of the dioxaphospholane VI (19 g) in methylene chloride (50 ml) at 0° until saturation was achieved. The solvent was removed at 20° (20 mm); the H^1 nmr spectrum of the crude residue showed the presence of nearly pure diketo phosphate XI. Short-path distillation gave pure 3-methylpentan-3-ol-2,4-dione dimethyl phosphate (XI), bp 87° (0.1 mm), yield 17 g (90%), n_D^{20} 1.4358; δP^{31} (in CDCl_3) = +2.9 ppm, a septet.

Anal. Calcd for $\text{C}_8\text{H}_{15}\text{O}_6\text{P}$: C, 40.3; H, 6.30; P, 13.0. Found: C, 40.8; H, 6.5; P, 12.6.

The H^1 nmr spectrum in CDCl_3 had a 6 H^1 doublet at τ 6.18, $J_{\text{HP}} = 11$ cps (CH_2O), a 6 H^1 singlet at τ 7.75 (acetyl), and a 3 H^1 singlet at τ 8.25 (methyl). No major differences were observed in benzene solution. The infrared spectrum (CH_2Cl_2) had bands at 3.45 (w), 5.80 (s), 5.85 (s) ($2\text{C}=\text{O}$), 6.95 (w), 7.42 (m), 7.85 (s), (PO), 8.45 (w), 9.58 (vs) (POCH_3), 9.85 (s), 11.70 (s) μ .

Reaction of the Phospholane VI with Bromine. A solution of bromine (11.4 g, 71 mmoles) in CCl_4 (25 ml) was added over a period of 1 hr to a stirred solution of the phospholane VI (18 g, 71 mmoles) in CCl_4 (50 ml) at 0°. The colorless solution was evaporated at 20° (20 mm). The residue gave only one P^{31} nmr signal at ± 2.6 ppm (in CH_2Cl_2); the H^1 nmr spectrum was very similar to that of the distilled bromoketo phosphate XV. The analytical sample of 1-bromo-3-methylpentan-3-ol-2,4-dione dimethyl phosphate (XV) was obtained as a pale yellow oil, n_D^{20} 1.4697, after short-path distillation; the approximate boiling point was 106–108°. XV was obtained in nearly quantitative yield. The material slowly turns pink and then reddish brown on prolonged standing at 20°, δP^{31} (CDCl_3) = +2.9 ppm, septet.

Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_6\text{BrP}$: C, 30.3; H, 4.4; Br, 25.3; P, 9.7. Found: C, 29.9; H, 4.5; Br, 24.6; P, 9.3.

The H^1 nmr spectrum in CDCl_3 had a 2 H^1 singlet at τ 5.58 (CH_2Br); a 3 H^1 doublet at τ 6.16, $J_{\text{HP}} = 11.5$ cps (CH_2OP), and a second 3 H^1 doublet with about the same coupling constant displaced 0.6 cps to higher field (CH_2OP); a 3 H^1 singlet at τ 7.67 (acetyl); and a 3 H^1 singlet at τ 8.15 (methyl). The infrared spectrum (CH_2Cl_2) had bands at 5.70 (s), 5.80 (s) ($2\text{C}=\text{O}$), 6.90 (m), 7.30 (m), 7.40 (m), 7.80 (s) (PO), 8.40 (m), 8.80 (m), 9.4–9.6 (vs) (POCH_3), and 11.65 (s).

Hydrolysis of 3-Methylpentan-3-ol-2,4-dione Dimethyl Phosphate (XI). Water (20 ml, 15 molar equiv) was added to a solution of the phosphate ester XI (19 g) in benzene (70 ml). The mixture was kept 6 hr at reflux. The water layer was separated and extracted with two 40-ml portions of benzene. The benzene extracts and the original benzene layer were combined, dried over MgSO_4 , and distilled through a 6-in. Vigreux column to remove benzene (care should be exercised to avoid loss of product XVIII). The spectral analysis of the crude oil showed only one component, the hydroxydiketone XVIII. The analytical sample of 3-methylpentan-3-ol-2,4-dione or diacetylmethylcarbinol¹⁸ (XVIII) had bp 43° (4.5 mm), n_D^{20} 1.4272. XVIII was obtained in 67% yield.

Anal. Calcd for $\text{C}_8\text{H}_{16}\text{O}_5$: C, 55.3; H, 7.8. Found: C, 55.7; H, 7.9.

The H^1 nmr spectrum in CDCl_3 had a 1 H^1 singlet at τ 5.14 (OH), a 6 H^1 singlet at τ 7.76 (acetyl), and a 3 H^1 singlet at τ 8.48 (methyl).

- (20) (a) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **23**, 778 (1958);
 (b) F. Ramirez and S. Dershowitz, *J. Am. Chem. Soc.*, **81**, 587 (1959);
 (c) F. Ramirez, E. H. Chen, and S. Dershowitz, *ibid.*, **81**, 4338 (1959).
 (21) R. P. Hullin and H. Hassall, *Biochem. J.*, **83**, 298 (1962).

The infrared spectrum in CH_2Cl_2 had bands at (μ) 2.92 (OH), 5.85 (CO), 7.40, 8.35, and 8.70.

Reaction of the Phospholane VI with an Excess of Water. Water (8 ml, 462 mmoles) was added to a solution of the phospholane VI (15 g, 58 mmoles) in benzene (50 ml). The mixture was kept 4 hr at reflux. The water layer was extracted with benzene. The combined benzene extracts and original solution were fractionated as before. Diacetylmethylcarbinol (XVIII) was isolated in 75% yield.

Reaction of the Phospholane VI with 1 Molar Equiv of Water.
a. In CDCl_3 Solution. Water (1 molar equiv) was added to a solution of the phospholane VI in CDCl_3 at 20° . After the vigorous exothermic reaction had subsided, the solution was analyzed by P^{31} nmr spectroscopy at 40.5 Mc/sec. Only the signals due to trimethyl

phosphate and to diacetylmethylcarbinol dimethyl phosphate (XI) were observed. The experiment was repeated using D_2O and a 6 M solution of the phospholane VI in CDCl_3 ; the H^1 nmr after 5 min had the signals due to trimethyl phosphate, the deuteriodiacetylmethylcarbinol (XVIII), the open phosphotriester XI, and deuteriomethanol.

b. In Benzene Solutions. Water (1 molar equiv) was added to a 2 M solution of phospholane VI in benzene at 0° . The solvent was removed after ca. 1 min at 0° (3 min). The residue was dissolved in CDCl_3 . The P^{31} and H^1 nmr spectra showed the signals of the species mentioned above plus those of some unreacted phospholane VI. There was no evidence for the formation of the cyclic phosphate ester XXV.

A New Synthesis of 5-Acylhydantoins, Precursors of β -Keto- α -amino Acids

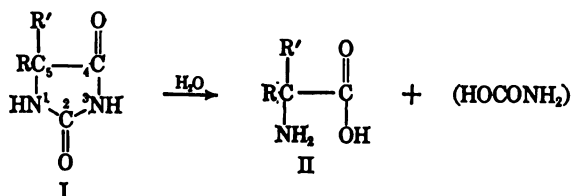
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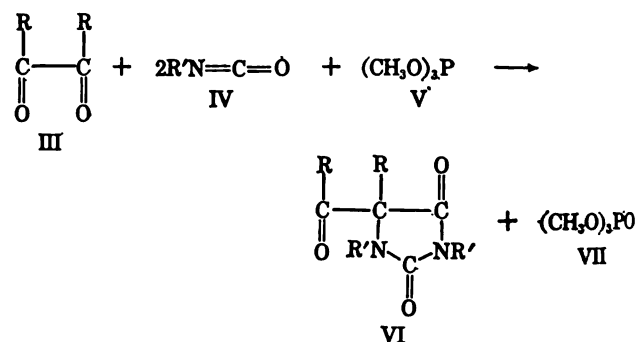
Abstract: A new reaction leading to 5-acylhydantoins, the precursors of β -keto- α -amino acids, is described. In this reaction, a trialkyl phosphite induces the condensation of one molecule of an α -diketone with two molecules of an aryl isocyanate with formation of the 5-acylhydantoin and a trialkyl phosphate. Three steps are involved, and the intermediates can, but need not, be isolated. The intermediates are organic compounds with pentacovalent phosphorus as shown by P^{31} nmr spectroscopy.

The hydantoins I are one of the classical synthetic precursors of the α -amino acids² II.



This type of heterocycle is associated with powerful anticonvulsant action; for example, 5,5-diphenylhydantoin (Dilantin) is widely used in the control of epilepsy.² Consequently, many alkyl- and arylhydantoins have been prepared.² On the other hand, the 5-acylhydantoins, which are the precursors of β -keto- α -amino acids, have not received much attention.^{2c} Modifications of the carbonyl function of the 5-acetylhydantoins prior to hydrolysis would make available a variety of β -substituted α -amino acids.

This paper describes a new approach to 5-acylhydantoins VI based on the condensation of an α -dicarbonyl compound III with an isocyanate³ IV under the influence of a trialkyl phosphite^{4,5} V.



Results

The 2,2,2-trialkoxo-1,3,2-dioxaphospholene⁶ (VIII), prepared from biacetyl and trimethyl phosphite, reacted with phenyl isocyanate (IX) at 30° . The course of the reaction was followed by means of infrared and H^1 and P^{31} nmr spectroscopy. Two distinct steps were observed. The first step was the nucleophilic addition of a carbon atom of the phospholene VIII to the carbonyl carbon of the isocyanate. The product was 2,2,2-trimethoxy-4-phenylimino-5-acetyl-5-methyl-1,3,2-dioxaphospholane (X).

(1) This investigation was supported by Public Health Service Grant No. CA-04769-08 from the National Cancer Institute, and by the National Science Foundation, Grant CP-6690-Y.

(2) For reviews of hydantoin chemistry see: (a) E. Ware, *Chem. Rev.*, **46**, 403 (1950); (b) E. S. Schipper and A. R. Day in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957; (c) H. Finkbeiner, *J. Org. Chem.*, **30**, 3414 (1965).

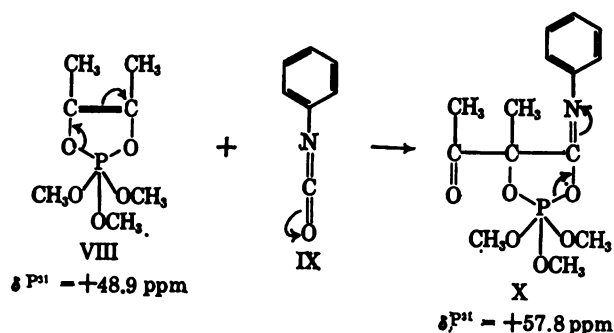
(3) For reviews on isocyanates see: (a) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **57**, 47 (1957); (b) C. V. Wilson, *Org. Chem. Bull.*, **35**, 1 (1963); (c) P. A. S. Smith, "The Chemistry of

Open-Chain Organic Nitrogen Compounds," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 6.

(4) The deoxygenation of alkyl isocyanates by trialkyl phosphites at elevated temperatures (180 – 190°) has been reported: cf. T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, **27**, 3651 (1962).

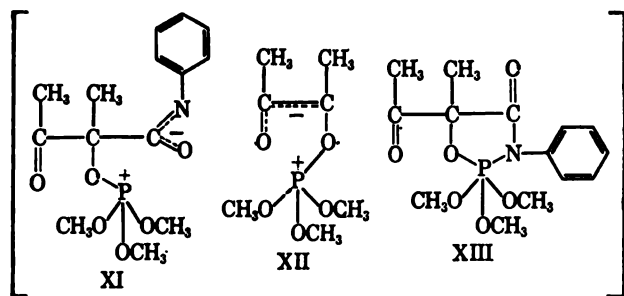
(5) The formation of certain 2-iminoxazolidines and 2-imidazolidones from the reaction of aryl isocyanates with ethyl bis(β -aminoethyl)phosphite has been described: cf. O. Mitsunobo, T. Ohashi, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, **39**, 708 (1966).

(6) The literature has been reviewed by F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964).

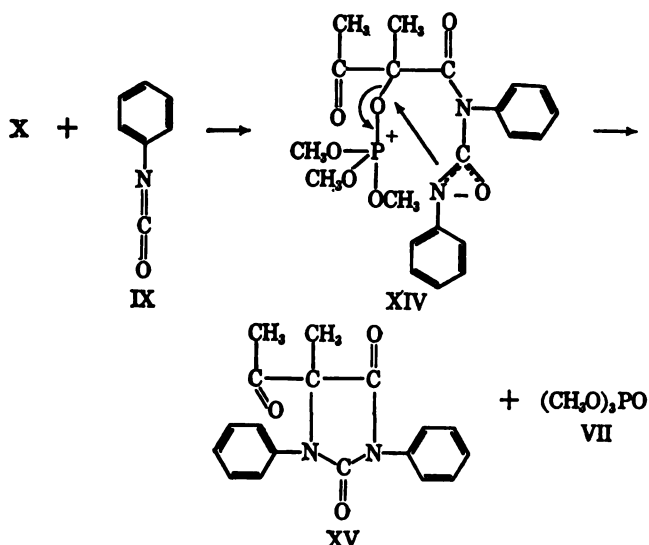


The phospholane X may arise in one concerted step which requires little or no charge separation.⁷ There was no experimental indication of the presence of open dipolar structures⁸ such as XI and XII.

Furthermore, a structural isomer of the pentaoxyphosphorane X, namely, the aminotetraoxyphosphorane XIII, could not be detected. This is consistent with our previous observations on the relative stabilities of these ring systems.^{8,9}



The phospholane X reacted with a second molecule of phenyl isocyanate. The products were trimethyl phosphate (VII) and 1,3-diphenyl-5-acetyl-5-methylhydantoin (XV).



No intermediate could be detected in this reaction, but we assume that the nitrogen of the phospholane X first performed a nucleophilic addition to the carbon of the isocyanate to form a dipolar intermediate XIV.

(7) (a) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **30**, 2575 (1965); (b) *ibid.*, **31**, 474 (1966); (c) *ibid.*, **31**, 3159 (1966).

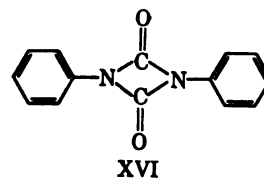
(8) (a) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Am. Chem. Soc.*, **87**, 4973 (1965); (b) F. Ramirez, A. V. Patwardhan, H. J. Kugler, and C. P. Smith, *Tetrahedron Letters*, 3053 (1966).

(9) F. Ramirez, *Bull. Soc. Chim. France*, 2443 (1966).

The latter then cyclized to a five-membered hydantoin ring with ejection of phosphate ester, instead of forming a seven-membered cyclic phosphorane.

A structural isomer of the hydantoin, which would be derived from an attack by oxygen on carbon in the intermediate XIV, could not be isolated.

It was shown that the isocyanate dimer XVI, prepared by addition of traces of tri-*n*-butylphosphine to the isocyanate,¹⁰ did not react with the phospholene VIII.



The rates of the reactions of phenyl isocyanate with the phospholene VIII and with the phospholane X were very similar. Therefore, the best procedure to make phospholane X involved a slow addition of isocyanate to an excess of phospholene VIII.

The preparation of hydantoin XV was very simple. Isocyanate (2 moles) and phospholene VIII (1 mole) were allowed to react in boiling methylene chloride solution. Compound XV was isolated in 75% yield. Small amounts of a second substance, not investigated further, were found in the residues.

It was possible to condense biacetyl with 2 moles of phenyl isocyanate and 1 mole of trimethyl phosphite *in situ*, without isolation of intermediates, as shown in the scheme III + IV + V \rightarrow VI + VII.

The following data established the structure of the phospholane X. (1) The P^{31} nmr shift, $\delta P^{31} = +57.8$ ppm *vs.* H_3PO_4 , showed that five oxygen atoms were bound to the phosphorus.^{6,9,11} The shift of the aminotetraoxyphosphorane XIII should fall in the range 30–40 ppm.⁸

(2) The H^1 nmr spectrum of X had a 3 H^1 singlet at τ 7.71 and another at τ 8.36, which correspond to the acetyl and the methyl groups, respectively.^{6,9} The 9 H^1 of the three methoxy groups gave rise to one doublet, $J_{HP} = 13$ cps, at τ 6.41. As was the case with a number of related compounds, the three methoxy groups were magnetically indistinguishable at 20°, probably due to rapid positional exchange in the trigonal bipyramid.^{6,9}

(3) The infrared spectrum of X had strong bands at 5.98 and 5.78 μ , which are attributed to the C=N and the C=O groups, respectively.

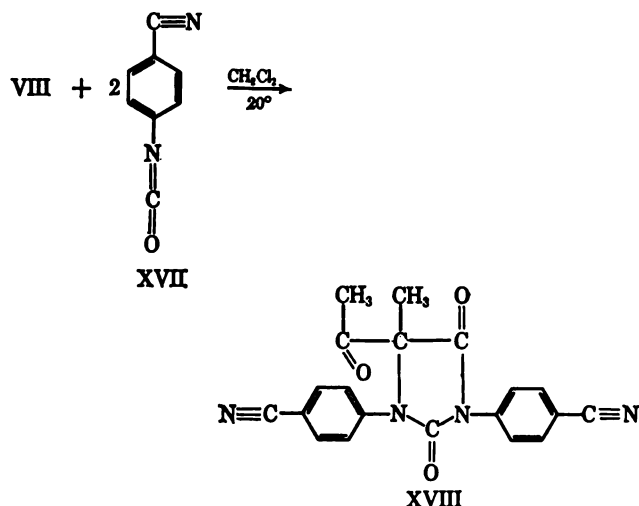
The hydantoin XV had infrared bands at 5.62 and 5.83 μ attributed to the carbonyl groups at the 4 and 2 positions, respectively.¹² The band due to the acetyl carbonyl was at 5.78 μ . The H^1 nmr spectrum of XV had the expected 10 H^1 aromatic multiplet and the 3 H^1 singlets at τ 7.68 and 8.28 due to the acetyl and the methyl groups, respectively.

p-Cyanophenyl isocyanate (XVII) reacted faster than the unsubstituted isocyanate IX with the phospholene VIII. The N-(*p*-cyanophenyl)hydantoin (XVIII) was isolated in 75% yield.

(10) R. B. Buckles and L. A. McGrew, *J. Am. Chem. Soc.*, **88**, 3582 (1966).

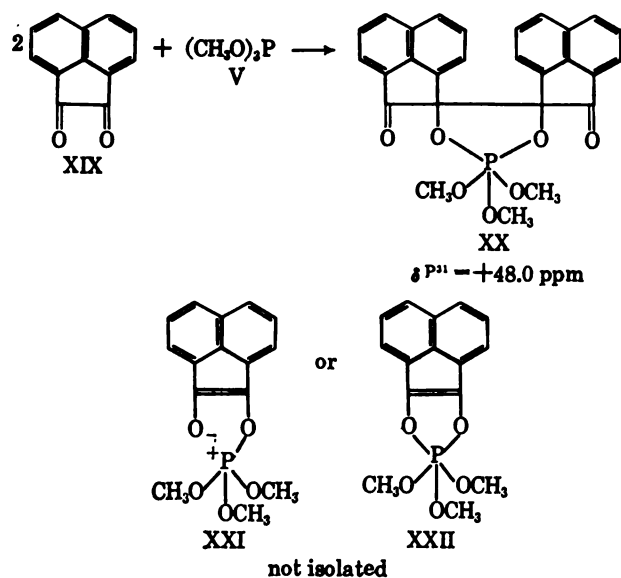
(11) W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *ibid.*, **87**, 127 (1965).

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p 221.

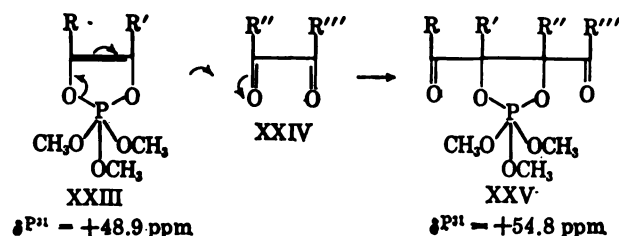


Discussion

The formation of a 2,2,2-trialkoxo-1,3,2-dioxaphospholane (XX) from the reaction of the α -dicarbonyl compound XIX with the trialkyl phosphite V was first reported in 1961.¹³ The exact nature of the precursor, XXI or XXII, of the phospholane XX could not be established, since this precursor reacted very rapidly with a second molecule of the carbonyl compound.



Shortly thereafter, it was demonstrated that isolable 2,2,2-trialkoxo-1,3,2-dioxaphospholenes (XXIII) underwent nucleophilic additions to carbonyl functions XXIV with formation of analogous phospholanes XXV.

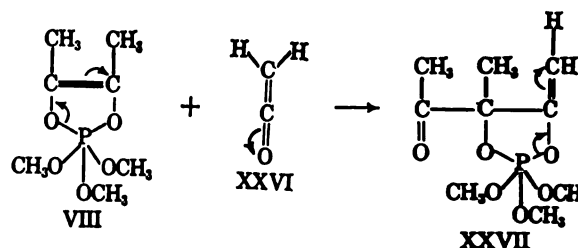


(13) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961).

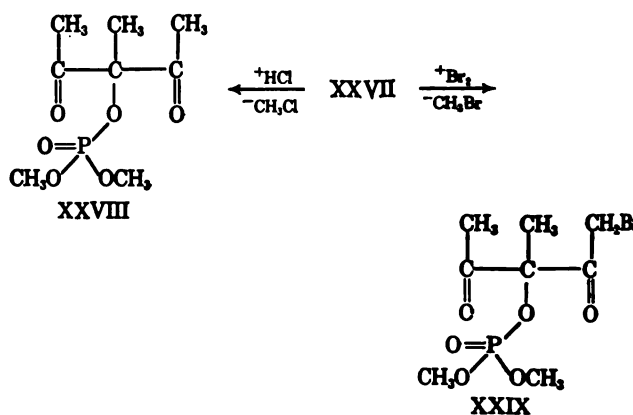
(14) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 1317 (1962).

Subsequently, the mechanism and the synthetic scope of this new reaction were investigated in detail.^{6,7,9}

More recently, it was found that the phospholene VIII condensed very readily with ketone XXVI to give 4-methylene-2,2,2-trialkoxo-1,3,2-dioxaphospholane¹¹ (XXVII).



The *exo*-methylene phospholane XXVII proved to be a valuable reaction intermediate. It was readily converted into the phosphate esters of α -hydroxy- β -diketones and of γ -bromo- α -hydroxy- β -diketones¹¹ XXVIII and XXIX.



The present paper emphasizes the generality of this new method of making carbon-carbon single bonds by means of triply and quintuply connected phosphorus compounds.¹⁶ Evidently, the method seems adaptable to the syntheses of α -amino acids and of carbohydrates. These studies are now in progress.

Experimental Section

The analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The instrumentation was described previously.^{6,7} All P^{31} nmr shifts are given in parts per million from 85% H_3PO_4 as zero; they were measured at 40.5 Mc/sec.

Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene (VIII) with 1 Molar Equiv of Phenyl Isocyanate. The phospholene^{6,7} VIII (11.8 g, 56 mmoles) and the isocyanate IX (5.9 g, 50 mmoles) were mixed at 20° in the absence of solvent and with protection against moisture. There was no visible reaction, but the infrared and H^1 nmr spectra showed evidence of reaction within 1 hr. After 20 hr at 20° under stirring, all the isocyanate had been consumed and there were new infrared bands at 5.62, 5.78, 5.82, and 5.93 μ . The H^1 nmr spectrum in CDCl_3 showed some unreacted dioxaphospholene VIII, some trimethyl phosphate (doublet at τ 6.32, $J_{PH} = 11$ cps), the dioxaphospholane X, and the hydantoin XV. Better resolution was achieved in CH_2Cl_2 . The P^{31} nmr spectrum in CH_2Cl_2 confirmed the presence of the phospholene ($\delta P^{31} = +48.9$ ppm), the phospholane ($\delta P^{31} = +57.8$ ppm), and trimethyl phosphate ($\delta P^{31} = -2.2$ ppm).

(15) F. Ramirez, S. B. Bhatia, and C. P. Smith, *ibid.*, **89**, 3026 (1967).

(16) While this work was in progress, A. J. Kirby [*Tetrahedron*, **22**, 3001 (1966)] described the reaction of the dioxaphospholene VIII with carbon disulfide. Our studies of the reaction of VIII with a number of systems having cumulated double bonds will be published soon.

mixture was freed from the phospholene VIII and trimethyl phosphate by short-path distillation at 0.3 mm. The residue dissolved in ether (40 ml) and kept at -20° to effect crystallization of the hydantoin XV. The latter (2.0 g, 28% yield) was collected and was recrystallized from benzene-hexane. 1,3-Diphenyl-5-methylhydantoin (XV) had mp $134-135^{\circ}$.

Anal. Calcd for $C_{18}H_{16}O_2N_2$: C, 70.1; H, 5.2; N, 9.1; mol wt, 280. Found: C, 70.2; H, 5.3; N, 9.3; mol wt, 300 (cryo- in benzene).

1H nmr spectrum (τ values in parts per million from TMS in $CDCl_3$) had signals at 2.58 (four aromatic protons), 2.71 (aromatic protons), 7.68 (three acetyl protons), and 8.28 (three β protons). The infrared spectrum (in CH_2Cl_2) had bands at 5.78 (s), 5.82 (s), 6.23 (w), 6.67 (m), 7.13 (ms), 7.42 (m), 45 (m) μ .

The ether filtrate was evaporated. The residue was shown to contain more hydantoin and small amounts of trimethyl phosphate; main component was the dioxaphospholane X. The latter is prepared as described below.

Reaction of the Dioxaphospholene VIII with 2 Molar Equiv of Phenyl Isocyanate. Optimum Conditions for the Synthesis of Hydantoin XV. The phospholene VIII (9.8 g, 46.7 mmoles) and phenyl isocyanate (11.1 g, 93.5 mmoles) were dissolved in 25 ml methylene chloride. The solution was kept 24 hr at reflux temperature, and then the solvent was removed at 20° (20 mm). The residue was kept several hours at -20° under ether, and the crop (8 g) of nearly pure hydantoin XV was filtered. The ether was evaporated to remove first ether and then trimethyl phosphate (0.1 mm, bath at 80°). The residue was kept several hours at 20° under ethanol giving a second crop (2.1 g) of hydantoin XV; combined yield 70%. The material balance consisted of hydantoin (estimated 10-15%) and a second substance whose structure was not investigated further.

Direct Synthesis of 5-Acetyl-5-alkylhydantoin (XV) from α -Diketene, Isocyanate, and Phosphite without Isolation of Intermediates. Phenyl isocyanate (8.6 g, 100 mmoles) and phenyl isocyanate (24 g, 200 mmoles) were dissolved in 20 ml of methylene chloride. The solution was cooled to 0° and was treated with trimethyl phosphite (100 mmoles). The solution was stirred 1 hr at 0° and 0.5 20° . It was then kept at reflux for 7 hr; the infrared spectrum showed little unreacted isocyanate. The reaction mixture was set up as described above, after an additional 8-10-hr reflux period. The hydantoin was isolated in 70% yield.

Reaction of 2,2,2-Trimethoxy-4-phenylimino-5-acetyl-5-methyl-dioxaphospholane (X). Phenyl isocyanate (9.7 g, 82 mmoles) was introduced into the stirred dioxaphospholene VIII (34.3 g, 82 mmoles) over a 12-hr period, at 20° . The mixture was stirred for an additional 12-hr period. The excess of phospholene and a small amount of trimethyl phosphate were removed at 0.1 mm and a temperature of 80° . The residue (22 g) was the viscous, non-crystalline dioxaphospholane X. The latter had the following spectral characteristics: $\delta P^{31} = +57.8$ ppm (CH_2Cl_2); τ ($CDCl_3$) (doublet), $J_{HP} = 13$ cps, 7.72 (singlet), 8.35 (singlet); τ (Cl_2) 6.50, $J_{HP} = 13$ cps, 7.75 and 8.40; τ (benzene) 6.60, $J_{HP} = 13$ cps, 7.80 and 8.40; infrared bands (CH_2Cl_2) at 5.78 (s), 5.82 (s), 6.27 (m), 6.70 (ms), 6.92 (m), 7.20 (ms), 7.40 (m), 8.50 (m),

8.70 (m), 9.30-9.40 (vs and broad), 9.86 (m), 11.72 (ms), and 12.15 (ms) μ .

Reaction of the Trimethyl Biacetyl(phenyl isocyanate)phosphite Adduct X with Phenyl Isocyanate. The phospholane X obtained above was converted into the hydantoin XV by 1 molar equiv of phenyl isocyanate in methylene chloride at reflux temperature.

Effect of Temperature and of Solvent on the Yield of Hydantoin XV. (a) In 1,2-Dichloroethane. The phospholene VIII and 2 molar equiv of phenyl isocyanate were dissolved in 1,2-dichloroethane, and the solution was kept at various temperatures for various periods of time. The hydantoin XV was isolated in the following yields: 65% after 10 hr at 55° , 59% after 8 hr at 65° , 63% after 17 hr at 65° . A second substance was also isolated from these experiments in about 10% yield.

(b) In Ether. Significant amounts of phenyl isocyanate remained after 24 hr at reflux temperature.

(c) In the Absence of Solvent. The hydantoin XV was isolated in ca. 40% yield after 24 hr at 20° . At higher temperatures the reaction was erratic and, at times, violent. In one case, 48% of hydantoin was isolated after 4 hr at 60° .

Reaction of 5-Acylhydantoin XV with 2,4-Dinitrophenylhydrazine. The hydantoin XV (800 mg) in ethanol (30 ml) was treated with a solution made from 2,4-dinitrophenylhydrazine (1.2 g), H_2SO_4 (1.5 ml, concentrated), and methanol (30 ml). The red solution was kept 2 hr at reflux, cooled, and filtered yielding the yellow 2,4-dinitrophenylhydrazone, mp $195-196^{\circ}$ (benzene).

Anal. Calcd for $C_{14}H_{10}O_6N_4$: N, 17.2. Found: N, 17.1. The infrared spectrum (CH_2Cl_2) had bands at 3.15 (w), 5.62 (m), 5.80 (s), 6.18 (s), 6.27 (s), 6.67 (s), 7.15 (s), 7.46 (s), and 7.62 (m) μ , among others.

Reaction of the Dioxaphospholene VIII with 2 Molar Equiv of *p*-Cyanophenyl Isocyanate (XVII). The phospholene VIII (9.1 g, 43.1 mmoles) was added to a suspension of *p*-cyanophenyl isocyanate (12.5 g, 86.4 mmoles) in 1,2-dichloroethane at 20° . The mixture was stirred at 20° for 12 hr. The first crop of the cyanohydantoin XVIII (8.8 g) was filtered. The filtrate was evaporated, and the residue was kept several hours at 20° under ether to give a second crop of hydantoin (1.1 g), combined yield 70%. The analytical sample of 1,3-di-(*p*-cyanophenyl)-5-acetyl-5-methylhydantoin (XVIII) had mp $234-235^{\circ}$ (from $CH_2Cl_2 \cdot CH_2Cl_2$).

Anal. Calcd for $C_{20}H_{14}O_2N_4$: C, 67.1; H, 3.9; N, 15.6. Found: C, 67.2; H, 4.1; N, 15.7.

The 1H nmr in $AsCl_3$ had the following signals (in τ): aromatic multiplet at 2.1-2.6, acetyl protons at 7.53, and methyl protons at 8.09. The infrared spectrum (in CH_2Cl_2) had bands at 4.50 (m) (CN), 5.62 (ms) (CO), 5.78 (s) (CO), 5.82 (s) (CO), 6.23 (ms), 6.65 (ms), 7.20 (s), and 7.48 (ms) μ .

Attempted Reaction of the Dioxaphospholene VIII with the Phenyl Isocyanate Dimer¹⁰ XIV. The phenyl isocyanate dimer XIV was formed immediately when a few drops of tri-*n*-butylphosphine was added to the isocyanate.¹⁰ The dimer was filtered, washed with ethanol, and recrystallized from boiling toluene; it had mp $174-175^{\circ}$ and showed infrared bands at 5.60 (s), 6.23 (w), 6.67 (s), and 7.23 (s) μ in CH_2Cl_2 , in which it was slightly soluble.

The dimer failed to react with the dioxaphospholene VIII, with or without solvents, at 20° for several days.

Pyracylenes. III.¹ Radical Anions in the Pyracylene System

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Abstract: The pyracylosemiquinone anion was generated from the quinone under a variety of conditions and compared to the related semiquinones from acenaphthaquinone and 1,2-diketopyracene. The hyperfine splitting constants were found to be dependent upon the method of generation, one set of values obtained by chemical reduction in the presence of base and the other by electrochemical generation. The differences are attributed to the presence of the "free" ion under the base conditions and chelates or tight ion pairs under the electrochemical conditions. The correlation of these spectra with molecular orbital theory is discussed. Stone's theory of g factors is modified to allow one to calculate spin density at a heteroatom, oxygen, from two experimental quantities, g factors, and half-wave potentials. Thus, pyracylosemiquinone is found to have approximately one-fifth the spin density at oxygen compared to other semiquinones. This fact plus the large hyperfine splitting constants suggest that this semiquinone anion is more akin to hydrocarbon radical anions than normal semiquinone anions, in excellent agreement with theory. Protonation of the dianion of pyracycloquinone, generated electrochemically, under thermodynamic conditions occurred at carbon to produce diketopyracene. Strain energy and not resonance energy appears to be the determining factor in the equilibrium¹ between diketopyracene and dihydroxypyracylene.

The question of aromaticity is of fundamental theoretical and practical concern and has occupied the attention of many investigators. A particularly interesting compound having $4n + 2$ π electrons and fulfilling Craig's rules of aromaticity is pyracylene (I).² Calculations predict a resonance energy of 5.42β ,^{3,4} whereas the strain of bridging both *peri* positions with sp^2 carbons is estimated to destabilize I by 48 kcal/mole.⁵ The unique feature of the electronic structure of this molecule is the prediction that it will have an empty nonbonding molecular orbital, the simplest aromatic hydrocarbon predicted to have this electronic configuration. In order to investigate the properties of the pyracylene system, we synthesized the quinone II related to the parent hydrocarbon.^{1b,6} Reduction of this quinone would produce a substituted pyracylene. Since no identifiable products could be isolated by standard reduction procedures,⁷ we explored the one electron reduction product (II, pyracylosemiquinone) by the esr technique. This study and some comments

regarding correlations between esr spectra and MO calculations form the subject of this paper.

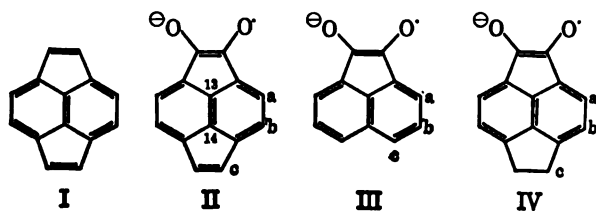
Esr Spectra

To see if unusual electronic distribution attributable to the pyracylyl system in pyracylosemiquinone (II) is realized, the esr spectra of II, III, and IV were compared. Esr data for these semiquinones, prepared by reaction of the quinone with potassium *t*-butoxide in DMSO,⁸ appears in Table I.

Table I. Esr Spectral Data (KO-*t*-Bu Reduction in DMSO)

Compd	a_a	a_b	a_c	g
II	1.41 ± 0.02	2.45	2.12	2.0030 ^a
III	1.18	0.27	1.28	2.0044 ^b
IV	1.15	0.21	1.38	2.0043 ^b

^a Error in g is estimated to be ± 0.0002 . ^b Error in g is estimated to be ± 0.0001 .



(1) (a) For part II, see B. M. Trost and S. F. Nelsen, *J. Am. Chem. Soc.*, **88** 2876 (1966). This paper contained a preliminary report of a portion of this work. (b) For part I, see B. M. Trost, *ibid.*, **88**, 853 (1966). (c) For part IV, see B. M. Trost and D. R. Brittelli, *Tetrahedron Letters*, No. 2, 114 (1967).

(2) See A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1962, pp 256-304.

(3) R. D. Brown, *J. Chem. Soc.*, 2391 (1951).

(4) (a) B. M. Trost, unpublished calculations; (b) C. A. Coulson and A. Streitwieser, Jr., "Dictionary of Electron Calculations," W. H. Freeman and Co., San Francisco, Calif., 1965.

(5) H. J. Dauben and A. G. Osborne, Abstracts, 130th National Meeting of the American Chemical Society, Atlantic City, N. J., 1956, p 370; we wish to thank one of the referees for pointing out this revised estimate of strain energy.

(6) Dibenzpyracylene has been reported. See H. W. D. Stubbs and S. H. Tucker, *J. Chem. Soc.*, 2936 (1951).

(7) B. M. Trost, to be published.

The splitting constants of acenaphthasemiquinone (III) are close to those reported⁹ for the same species generated electrochemically. Placing a saturated two-carbon bridge across the *peri* positions of III to give IV slightly reduces the ring hydrogen splittings (and hence the ring spin density), which is expected. Because of the slightly electron-releasing character of alkyl compared to hydrogen, electronic density is shifted away from the alkyl group. Unsaturating the *peri* two-carbon bridge (giving II) has a striking effect in that all of the proton splitting constants are raised, which shows that significantly more spin density is on the ring carbons in II than in III or IV. The largest change is at the b position, which has a tenfold increase in spin density, giving it the highest spin density, although the corresponding position of III and IV has the lowest. This is not predictable by simple resonance structure reasoning, for structures with spin at b cannot have the benefit of both benzene resonance and placing the

(8) G. R. Talaty and G. A. Russell, *J. Am. Chem. Soc.*, **87**, 4867 (1965).

(9) R. Dehl and G. K. Fraenkel, *J. Chem. Phys.*, **39**, 1793 (1963), give 1.17, 0.27, and 1.27 g , respectively.

tive charge on oxygen, the most electronegative atom. The g value of II, 2.0030, is quite different from that of I, and indeed from that of all other hydrocarbons, which have g factors which fall in a narrow range of 2.0040–2.0048. Both the splitting constants and g factor of pyraclosemiquinone (II) are to be quite unusual; these facts must be a result of unusual electronic distribution in this system.

In calculations of electronic distribution are for the unperturbed, vapor phase species, it was desirable to generate II under a variety of experimental conditions to see if specific medium effects are important in determining the spin distribution. It was found that II could be formed with the weaker bases NaOH, KOH, and $\text{Ba}(\text{OH})_2 \cdot 2\text{H}_2\text{O}$ if a DMSO solution of the quinone was agitated in the presence of the solid base. II was also formed when a DMSO solution of pyraclosemiquinone was mixed with tetramethylammonium hydroxide. The need for base being present was demonstrated by carrying out the reduction at a mercury electrode using various supporting electrolytes (Figure 1). DMSO solutions 0.1 M in tetraalkylammonium chlorides, sodium perchlorate, lithium chloride, and sodium bromide were all successful. Using DMF as solvent was 0.1 M in tetrabutylammonium perchlorate gave no difference in splitting constants for II from those observed in DMSO. The electrolytic reduction to give workable radical concentrations in DME and THF with alkali metal supporting electrolytes. Surprisingly, large amounts of II are not formed if a DME solution of pyraclosemiquinone is stirred with sodium hydroxide (in contrast to the results in DMSO), but violet irradiation (λ 366 $m\mu$) of such a mixture¹¹ leads to formation of II. Although sodium hydroxide is not visibly soluble in DME, the presence of base is necessary, for solutions in pure DME or 0.1 M sodium chloride in DME fail to give radical upon irradiation.

Splitting constants observed under these conditions are summarized in Table II. For the alkali hy-

II. Pyraclosemiquinone (II) ESR Splitting Constants, a_{H}

Irradiation/ Electrolysis ^b / ion	Method of generation/solvent				
	0.1 M KO- <i>t</i> -Bu/ DMSO	NaOH- sat. DME	0.1 M M ⁺ - DMSO	0.1 M R ₄ N ⁺ - DMSO ^c	MOH ^a / DMSO
	1.41	1.14	0.93	0.90	1.37
	2.45	2.69	2.83	2.88	~2.37
	2.12	2.31	2.55	2.57	~2.37

^a KOH = NaOH, KOH, $\text{Ba}(\text{OH})_2 \cdot 2\text{H}_2\text{O}$. ^b Supporting electrolytes: NaClO₄, LiCl, CsBr. ^c With Et₄NClO₄, Bu₄NClO₄, and without electrolysis, just using Me₄NOH in DMSO.

droxide/DMSO spectrum (last column of Table II) a difference in splitting constant between the b and c positions could not be resolved. Observed line widths were \sim 300 $m\mu$ in these spectra, compared to 120 $m\mu$ for the electrolysis and irradiation spectra, and

(a) M. Adams, M. S. Blois, and R. H. Sands, *J. Chem. Phys.*, **28**, 958; (b) M. S. Blois, H. W. Brown, J. S. Hyde, and J. E. Maling, *Sci. (Geneva)*, **13**, Spec. No. 243-ss (1960); *Chem. Abstr.*, **57**, (1961); (c) B. G. Segal, M. Kaplan, and G. K. Fraenkel, *J. Chem. Phys.*, **43**, 4191 (1965).

Irradiation of basic quinone solutions to give the semiquinones in *vacuo* process: E. C. Lucken, *J. Chem. Soc.*, 4234 (1964).

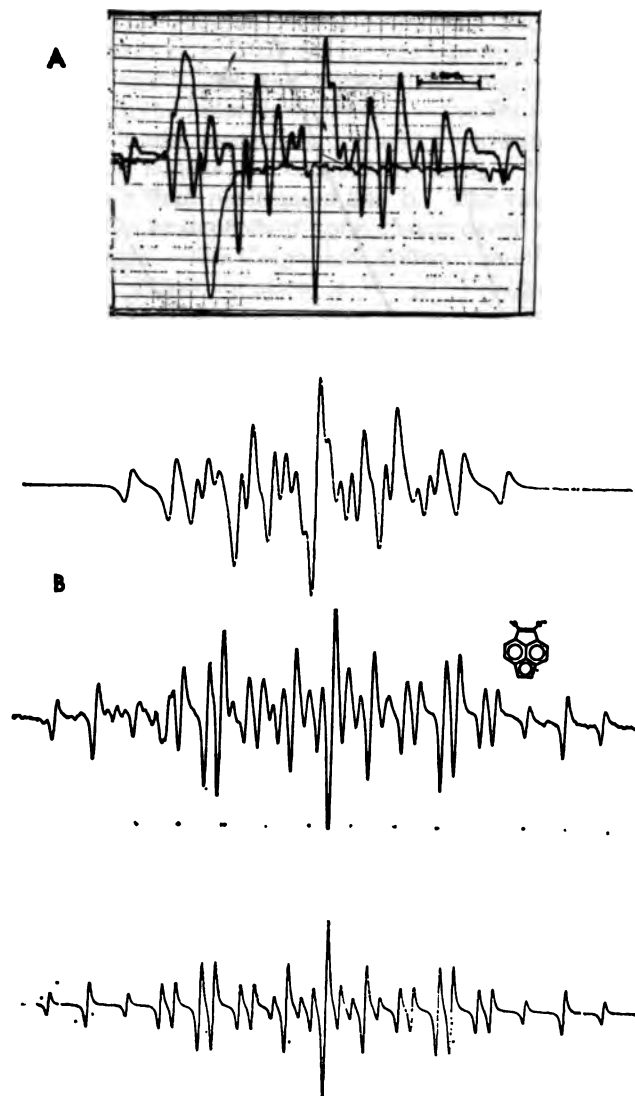


Figure 1. (A) The observed (top) and the calculated (bottom) spectrum of pyraclosemiquinone anion generated by treatment of the quinone with potassium *t*-butoxide in DMSO. (B) The observed (top) and the calculated (bottom) spectrum of pyraclosemiquinone anion generated by electrolysis in DMSO employing tetra-*n*-butylammonium perchlorate as supporting electrolyte.

240 $m\mu$ for the potassium *t*-butoxide spectrum. Position assignments for the splitting constants which agree with MO predictions (*vide infra*) were proved by deuteration, the middle-sized splitting being changed as predicted [observed splitting constants 2.93 (2 H), 0.93 (2 H), and 0.44 (2 D)] when pyraclosemiquinone-*c,c*- d_2 was electrolyzed.

There is a large "base effect" on the spectrum of II. Significantly higher spin density at the b and c positions of II is observed in the electrolytic spectra than in the *t*-butoxide spectrum. Since the "electrolytic" spectrum was observed with tetramethylammonium hydroxide, a stronger base than this is necessary to change the splittings. The irradiation spectrum is truly intermediate, the splitting constant observed being exactly (within experimental error) the average of the two extreme spectra. Changing cations does not affect the electrolytic spectrum much; there is a significant difference between tetraalkylammonium and alkali metal, but differences between alkali metals were not measurable.

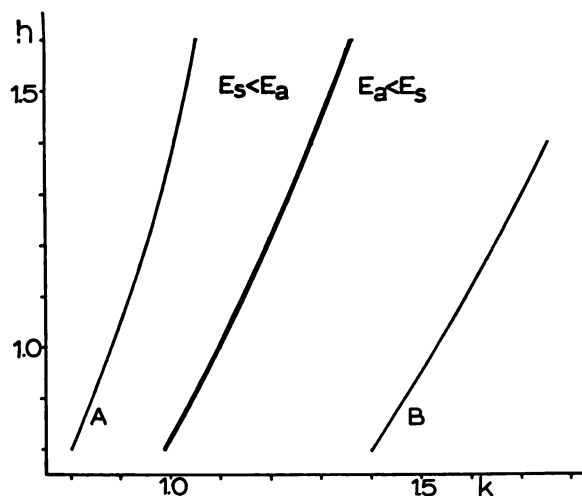
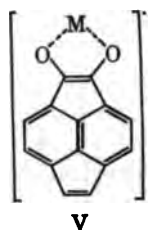


Figure 2. Variation of h and k in Hückel calculations for pyracloquinone. The heavy line passes through h and k values for which $E_A = E_B$. To the right $E_A < E_B$ (experiment shows this is fact), while to the left $E_B < E_A$ ("crossed" region). Lines A and B give h and k values for best fit to the *t*-butoxide and electrolytic spectra, respectively. For the former, it was assumed the odd electron is in ψ_A in spite of the energy crossing.

We assign the differences in splitting constants observed to having "free" ions (II plus cation) and chelated ion pairs (V). We attribute the base effect to



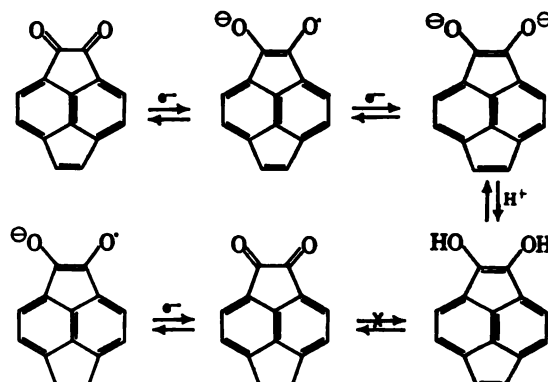
preferential coordination of the alkoxide with the cation thus liberating the free radical anion II. Thus the electrolytic spectrum represents that of the chelate V. Metal splittings might be expected for V¹² in ether solvents; however, we have been unable to obtain high enough radical concentration for esr spectra by electrolytic reduction in ethers. In agreement with this interpretation is the observed spectrum when the radical was generated by irradiation of a solution of quinone in DME saturated with sodium hydroxide. Rapid equilibrium of chelate and free forms (lifetime less than *ca.* 10^{-7} sec) would lead to the averaged splitting constants observed. Since the hydroxide concentration is extremely low, the semiquinone anion is an effective competitor for chelation (or tight ion-pair formation).

When pyracloquinone is electrolytically reduced at potentials on the second polarographic wave (*vide infra*), II disappears and the dianion VI is presumably formed. If the applied potential is dropped to zero, a negative current is observed and II appears; the reduction is reversed.¹³ In unpurified spectro grade DMF, however, III, not II, appears after high-potential

(12) Although the very stable tetracyanoethylene radical anion does not give metal splittings (M.C.R. Symmons, Michigan State University, ESR Symposium, Aug 1-3, 1966) II is considerably stabler than other semiquinones, which do show metal splittings, even in the presence of base.¹⁰

(13) Breaking the circuit causes appearance of II at a slower rate; presumably quinone diffuses into the region where the dianion is and disproportionation occurs.

reduction is ceased. A reasonable interpretation involves protonation (from solvent impurities?) of the dianion. Although kinetic protonation should occur at oxygen, if the large strain energy⁸ overrides the resonance energy^{3,4} associated with the pyraclyene system, tautomerization would occur to the more stable 1,2-diketopyracene. Further reduction of diketopyracene generates its radical anion, which is observed. This sequence is summarized below.



The formal reverse process, enolization of III to form VI, could have occurred in potassium *t*-butoxide-DMSO, but does not; VI would have oxidized to form II under our conditions and no II was observed. We have been unable to demonstrate that diketopyracene can tautomerize to dihydroxypyraclyene.

Molecular Orbital Calculations

HMO calculations of the spin densities of II were performed to examine the agreement of predictions with experiment. Although simple HMO theory does not work particularly well for nonalternant systems (such as IV),⁹ II is a special case, in this as in so many other respects. The odd-electron MO, the only one which normally is considered for esr spectra, has zero electron density at carbons 13 and 14. Thus, for the purposes of esr, this molecule can be considered an alternant system.

Values for the Coulomb integral at oxygen and the C-O resonance integral are required. By convention,¹⁴ these are expressed as $\alpha_O = \alpha_C + h\beta_{CO}$, $\beta_{CO} = k\beta_{CC}$, respectively. Various h and k parameters have been used; values of $h = 1.2$, $k = 1.6$ gave the best fit in McLachlan calculations on *p*-quinones,⁹ while $h = 0.8$, $k = 1.0$ fit several properties of unsaturated ketones best.¹⁵ For II there is another criterion for choosing h and k besides best fit to coupling constants. As h and k are varied, the energy levels of the first two empty molecular orbitals cross. With $h = 0.8$, $k = 1.0$, the ninth MO (antisymmetric with respect to the $C_{13}-C_{14}$ axis, ψ_A) is 0.005β lower in energy than the tenth (symmetric, ψ_S), but with $h = 1.9$, $k = 1.0$, ψ_S is 0.030β lower than ψ_A . While ψ_A gives reasonable spin densities for any reasonable h and k , ψ_S does not (ψ_S has almost zero spin density at position b and much higher spin density at oxygen). At constant k , increasing h lowers ψ_S much more than ψ_A , causing the crossing). The observed a and g values show the odd electron is in ψ_A . Figure 2 illustrates the energy level crossing.

(14) Reference 2, Chapter 4.

(15) H. E. Zimmerman, private communication.

ues of h and k were varied to find values for best the observed splitting constants. If the electron placed in E_A regardless of the energy crossing, a the h vs. k plot for best fit (which is very good, 13 deviation from experiments for all densities) ntirely in the crossed region (Figure 2). Table III

III. Calculated Spin Densities for Pyraclosemiquinone (II)

Base spectrum					
Exptl ($Q = 24$)	Hückel		McLachlan		SCF
	$h = 0.8, k = 1.0$	$h = 1.2, k = 1.2$	$h = 0.8, k = 0.74^a$	$h = 1.2, k = 0.78^a$	
0.059	0.048	0.049	0.048	0.059	0.053
0.102	0.106	0.108	0.113	0.103	0.110
0.088	0.086	0.088	0.088	0.091	0.089

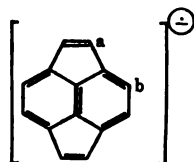
Electrolytic spectrum					
Exptl ($Q = 24$)	Hückel		McLachlan		SCF
	$h = 0.8, k = 1.4$	$h = 1.2, k = 1.7$	$h = 0.8, k = 0.85^a$	$h = 1.2, k = 1.0$	
0.038	0.038	0.038	0.035	0.040	
0.120	0.120	0.120	0.121	0.126	
0.107	0.091	0.093	0.090	0.090	

hückel energies crossed. Calculation at crossing of Hückel levels gives ρ_A far too low, ρ_B far too high; ρ_B is quite insensitive to h and k .

ins values near the crossing points, the best "uncrossed" values. A similar line may be calculated for electrolytic spectrum. Here the best fit line lies in the "uncrossed region." McLachlan calculations¹⁶ allow for electron correlation do not improve the experiment. All of the energy levels, not just the ones involved in these calculations, so this could have been expected. Best fit lines can be drawn for the McLachlan calculations as well; both lie in the crossed region of the h, k plot.

Finally, a closed shell SCF calculation¹⁷ (which gives remarkable agreement with the ultraviolet spectrum⁷) gives spin densities slightly closer to experiment than the best "uncrossed" Hückel calculations for the base spectrum, which we assign to the "free" anion.

The above discussion assumes constant Q 's at all positions to get the "experimental" spin densities. Fraenkel^{18a} and Higuchi^{18b} have calculated that Q_H increases if the C-CH-C angle is decreased. Recent work¹⁹ has shown that for pyracene anion (VIII), $Q_b = 22.6$, $Q_a = 30.0$ ²⁰ are required to fit the spectrum using Hückel spin densities. Since bond angles at position a of VIII and c of II should be similar,



VIII

A. D. McLachlan, *Mol. Phys.* 3, 233 (1960). We thank Professor Holme for the use of his computer program for McLachlan calculations.

We are deeply indebted to Dr. Howard E. Simmons for this calculation. This calculation shows that ψ_A is of lower energy than ψ_B .

(a) I. Berual, D. H. Rieger, and G. K. Fraenkel, *J. Chem. Phys.*, 39 (1962); (b) J. Higuchi, *ibid.*, 39, 3455 (1963).

B. M. Trost, S. F. Nelsen, and D. Brittelli, to be published.

This angle is estimated to be approximately 106°. Fraenkel's calculation gives a Q of about 38 for this angle.

$Q = 30$ for position c of II might be expected. This would make $\rho_c = 0.071$ for the base spectrum and 0.086 for the electrolytic spectrum, which improves agreement with the latter, but makes it worse for the former. Since ρ_r is very insensitive to h and k variations, changing h and k does not account for using a larger Q at position c than positions a and b. The value of Q is claimed to be dependent upon charge density as well as bond angle. The Colpa and Bolton²¹ modification of the McConnell equation, $a_i = (Q' + k_i)\rho_i$, where e_i is the excess charge at position i, does not improve the fit, nor justify use of a larger Q' at position c than positions a or b. The Giacometti modification,²² $a_H = Q_1\rho_1 - Q_2 \sum_j c_i c_j$ where j are atoms bonded to i, does not produce significant changes from the regular McConnell equation; to obtain as good a fit, Q_1 must be about 24 instead of the 31.5 which fits best.

Thus the excellent agreement of simple Hückel theory with experiment using constant Q 's seems to be fortuitous, since Q_c ought to be larger than Q_a and Q_b .

The esr spectrum of III was calculated using the method of Levy²³ to predict the methylene splitting constants. Table IV gives results for the extreme h_0 and k_{CO} values used for II; agreement is considerably less favorable for the ring protons of III than II, as is expected.⁹ The methylene splitting constants agree about as well as other examples.

Table IV. Calculated Spectrum for Diketopyracene Anion (III)

	Exptl	HMO, $Q = 24$ $h = 0.8,$ $k = 1.0$	HMO, $Q = 24$ $h = 1.2,$ $k = 1.6$	McLachlan
a_a	1.15	0.49	0.60	0.60
a_b	0.21	0.00	0.00	0.38
a_c (methylene)	1.38	0.92 ^a	1.22 ^a	1.29 ^a

^a Calculated by the method of Levy.²³

Neither III nor IV shows the "base effect" on the splitting constants which is so prominent in the spectrum of II, although geometry at the carbonyls must be very similar. We suggest that the greater resonance energy and lower oxygen charge density of II could allow free II to be formed in base, but not in III and IV, which would have stronger chelates (or tighter ion pairs) and thus are not as easily broken up.

In addition to the correlation of splitting constants with molecular orbital theory, Stone²⁴ developed a correlation of hyperfine splitting factors (g factors) with molecular orbital theory. For semiquinone anions, he found this relationship could be expressed by eq 1.²⁵

$$\Delta g = b + \lambda c + \rho_o \gamma_o \quad (1)$$

Since the half-wave potential of the quinone also is related to the energy coefficient (λ) of the lowest unoccupied molecular orbital, this equation can be modified so that the g factor shift is expressed as a function of the

(21) J. P. Colpa and J. R. Bolton, *Mol. Phys.*, 6, 273 (1963).

(22) G. Giacometti, P. L. Nurdio, and M. V. Pavan, *Theoret. Chim. Acta*, 1, 404 (1963).

(23) D. H. Levy, *Mol. Phys.*, 10, 233 (1966).

(24) A. J. Stone, *ibid.*, 6, 509 (1962).

(25) In this equation, Δg is the difference between the observed g factor and that for a free electron, 2.00232; λ refers to the energy of the odd electron orbital of the semiquinone; γ_o is a function of λ ; ρ_o is the spin density at oxygen; b , c , and γ_o are experimental constants.

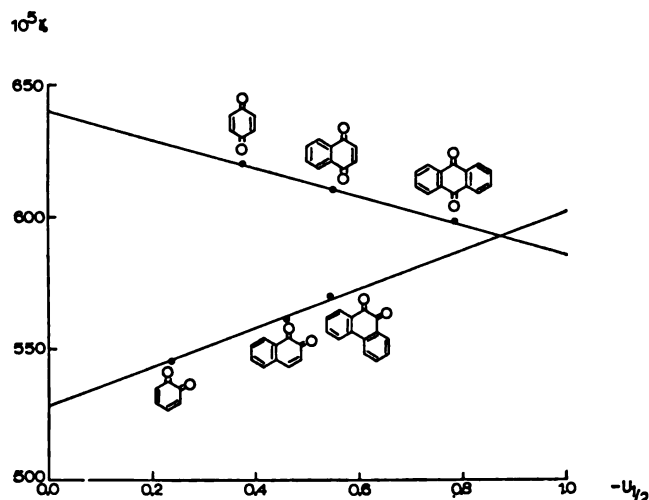


Figure 3. A plot of γ_0 , which is a function of the energy of the first unoccupied molecular orbital (λ), vs. the half-wave potentials of the same quinones employed by Stone.²⁴

half-wave potential and the oxygen spin density. Such a modification allows one to calculate the spin density at a heteroatom, oxygen, from two experimental quantities, g factors and half-wave potentials.

To examine this possibility, we undertook a study of the half-wave potentials of the same quinones chosen by Stone for his correlations.²⁶ For our polarographic studies, we employed DMSO as solvent since we had employed this solvent for our esr studies and since it gave the best polarographic results. The half-wave potentials ($U_{1/2}$) are summarized in Table V. For the molecular orbital calculations, we chose the oxygen parameters suggested by Fraenkel as those giving best fit for esr spectra, $h = 1.2$ and $k = 1.6$. Plotting λ vs. $U_{1/2}$ for the first wave gives two straight lines, one for *o*-quinones (eq 2) and one for *p*-quinones (eq 3).²⁷

$$\lambda = 0.626U_{1/2} + 0.115 \quad (2)$$

$$\lambda = 0.580U_{1/2} + 0.187 \quad (3)$$

Table V. Half-Wave Potentials of Selected Quinones*

Quinone	Wave 1, v	Wave 2, v
1,4-Benzoquinone	-0.376	-1.174
1,4-Naphthoquinone	-0.550	-1.289
9,10-Anthraquinone	-0.784	-1.454
1,2-Benzoquinone ^b	-0.220	...
1,2-Naphthoquinone	-0.463	-0.772
9,10-Phenanthroquinone	-0.545	-1.277

* Values reported are vs. a standard calomel electrode. ^b Assuming $\Delta U_{1/2}$ on changing from DMF to DMSO is similar to that for the other quinones.

Since Stone's constant γ_0 is a function of λ , we re-plotted γ_0 in terms of half-wave potentials to obtain the two lines in Figure 3. Substituting these values into Stone's equations leads to eq 4 for *o*-quinones and eq 5

$$\Delta g = 22.5 \times 10^{-5} - 12.1 \times 10^{-5}U_{1/2} + \rho_0\gamma_0 \quad (4)$$

$$\Delta g = 21.1 \times 10^{-5} - 11.2 \times 10^{-5}U_{1/2} + \rho_0\gamma_0 \quad (5)$$

(26) For a similar correlation under a different set of conditions and employing different parameters of h and k for oxygen for molecular orbital calculations, see M. E. Peover, *J. Chem. Soc.*, 4540 (1962).

(27) Equations are for the best least-squares lines.

for *p*-quinones. The success of the method can be illustrated by the striking agreement between the spin densities obtained from eq 5 and Hückel spin densities for a series of *p*-quinones in Table VI. For the latter, best fit was not attempted; the oxygen parameters are those used in developing the equations (Fraenkel's best fit values) and the methyl group parameters are those suggested by Coulson and Crawford.²⁸

Table VI. Spin Densities at Oxygen

Quinone	Eq 5*	Hückel
2-Methylbenzoquinone	0.33 ± 0.03	0.346
2-Methyl-1,4-naphthoquinone	0.28 ± 0.03	0.228
Duroquinone	0.38 ± 0.03	0.332

* Obtained employing the literature values for g factors and half-wave potentials,²⁹ the latter adjusted for change in solvent. The error is principally due to the uncertainty in the g factor.

Table VII summarizes the polarographic data and spin density calculations for the quinones of interest in this study. These data confirm the previous conclusion that the oxygens of pyraclosemiquinone anion bear extremely low spin density, approximately one-fifth that for normal semiquinone anions. Since presently we are unable to measure g factors more accurately, a large error exists in the spin densities calculated from eq 4.²⁹ Nevertheless, the quantitative agreement within our experimental error is excellent. These results in conjunction with the abnormally large hyperfine splitting constants of II indicate the unique nature of the pyracylene system and suggest its semiquinone anion is more akin to a hydrocarbon radical anion rather than a quinone radical anion. Theory and experiment and the excellent correlation between them attest to this conclusion.

Experimental Section

Materials. The quinones, pyracloquinone and 1,2-diketopyracene, were prepared as previously described.^{4,7} Acenaphthaquinone, *p*-benzoquinone, 9,10-phenanthraquinone, and 9,10-anthraquinone were obtained from Aldrich Chemical Co. 1,2-Naphthaquinone and 1,4-naphthaquinone were obtained from Eastman Kodak Co. Pyracloquinone-5,6-*d*₂ was prepared as described for the undeuterated compound^{4,7} except acenaphthene-*d*₄ was employed in the initial step. Mass spectral analysis³⁰ indicated the deuterated compound was 97% *d*₂ and 3% *d*₁. Dimethyl sulfoxide and dimethoxyethane were dried by distillation from calcium hydride. Tetra-*n*-butylammonium perchlorate was dried *in vacuo* at 68°. Tetra-*n*-butylammonium iodide was dried *in vacuo* at room temperature.

Esr Determinations. Esr spectra were recorded using a Varian V4502 instrument with a 9-in. magnet. Fremy's salt in saturated sodium carbonate was used as a calibration standard ($g = 2.0055$, $a_N = 13.0$ gauss) with dual cavity. The Varian electrolytic cell was used for *in situ* reductions. Solutions were deoxygenated by bubbling nitrogen through them and sample tubes were either 1-mm Pyrex capillaries or the Varian electrolytic cell. Ultraviolet irradiation was carried out using a Bausch and Lomb "high intensity" monochromator with Osram HBO-200W superpressure source.

(28) C. A. Coulson and V. A. Crawford, *J. Chem. Soc.*, 2052 (1953).

(29) It is important to point out that methods for more accurate g factor determinations are becoming available. The main source of error to the spin densities calculated by eq 4 and 5 is the uncertainty in this value.

(30) Mass spectral determinations were performed by Morgan-Schaeffer Corp., Montreal, Quebec, and by Professors Larry A. Singer and Joseph Ciabattini. We are deeply indebted to them for these determinations.

Table I. Rotations of Serine Derivatives^a

Compd	Mol wt	Solvent ^b	No. of samples ^c	$\alpha \times 10^{-3}$ ^d	λ_0 , m μ ^d	589 m μ ^e	546 m μ ^e	Error ^f
Z-Asp(OBt)-OH	357.3	7-10 HOAc	3,3	<i>g</i>	<i>g</i>	42.8	50.0	2.5
Z-Ser(H)-OH	239.2	0.3-1 EtOAc	8,8	15.873 \pm 0.6	219.76 \pm 9	53.2	63.5	1.0
Z-Ser(H)-OH	239.2	4-6 HOAc	3,3	3.9005 \pm 0.2	224.30 \pm 13	13.2	15.7	2.5
Z-Ser(H)-OH	239.2	2 DMF	4,4	<i>h, i</i>		-8.7	-10.1	10.0
Z-Ser(H)-OH	239.2	0.6 H ₂ O	3,3	-3.5398 \pm 1.0 ^k	152.95 \pm 130 ^k	-10.9	-12.9	10.0
H-Ser(H)-OH	105.1	2-5 5 N HCl	5,5	3.7429 \pm 0.2 ^j	267.71 \pm 9	13.6 ^j	16.5 ^j	1.8
Z-Ser(H)-Gly-ONP ^l	417.4	2-4 1% HOAc 99% DMF	3,3	-5.4642 \pm 0.3 ^m	181.53 \pm 30	-17.4	-20.6	1.8
HBr-H-Ser(H)-Gly-ONP	364.1	2 CH ₂ OH	6,7	13.976 \pm 0.4 ⁿ	246.49 \pm 9	48.8	58.9	0.8
HBr-H-Ser(H)-Gly-ONP	364.1	2 H ₂ O	1,1	17.804 \pm 0.2 ⁿ	230.36 \pm 4	60.6	72.7	...
HBr-H-Ser(H)-Gly-ONP	364.1	4 1% HOAc 99% DMF	1,1	20.235 \pm 0.2 ⁿ	229.21 \pm 4	68.7	82.4	...
TosOH-H-Asp(OCH ₃)-Ser(H)-Gly-ONP ^a	584.5	2 H ₂ O	1,1	-15.530 \pm 0.3	255.85 \pm 6	-55.2	-66.7	...
Z-Asp(OCH ₃)-Ser(H)-Gly-ONP ^a	546.5	2 DMSO	1,1	-2.1555 \pm 0.4 ⁿ	335.45 \pm 24	-9.2	-11.6	...
Z-Asp(OBt)-Ser(H)-Gly-ONP ^a	622.6	4 10% HOAc 90% DMF	5,5	-4.9746 \pm 0.3 ⁿ	298.84 \pm 14	-19.3	-23.8	1.1
HBr-H-Asp(OH)-Ser(Ac)-Gly-ONP	521.3	2 H ₂ O	1,1	-9.9813 \pm 0.5 ⁿ	259.34 \pm 10	-36	-43	...
HBr-H-Gly-Ser(H)-Gly-ONP	421.2	2 DCA	1,1	-40.571	254.86	-144.0	-174.0	...
Z-Gly-Ser(H)-Gly-ONP	474.4	2 DCA	1,1	-33.267	258.12	-119.0	-144.0	...
Poly Asp(OCH ₃)-Ser(H)-Gly ^a	273.2	2 DCA	1,1	-21.974	272.60	-81.0	-98.0	...
Poly Asp(OH)-Ser(Ac)-Gly ^a	301.2	2 DCA	1,1	-13.115	301.37	-51.0	-63.0	...
Poly Gly-Ser(H)-Gly ^a	201.2	2 DCA	1,1	-12.308	269.07	-45.0	-54.0	...

^a See ref 4 for description of procedures and for definition of terms. All amino acids are of the L configuration. Within the limits of the technique all compounds shown in this table are optically pure. The molecular weight of the polymer is the residue weight. ^b The first number is the concentration in weight per cent. DMF is dimethylformamide. DMSO is dimethyl sulfoxide. DCA is dichloroacetic acid. ^c The first number is the number of independent samples; the second is the total number of rotations run. ^d Drude parameters. With these parameters it is a simple matter to run off the rotations at any wavelength within 589-365 m μ by use of a desk calculator. The results so obtained may be considered to be averages of our measurements and have precisions of the order of 0.1% and accuracies as specified in the last column. Also note that this is the per cent error, not the absolute error. The molecular weight is given to facilitate calculation of specific rotations. The large error limits of α and λ_0 are the result of their correlation. ^e Molar rotations. ^f Estimated per cent standard deviation of the calculated molar rotations = $100s/Mn$; s is the standard deviation of the observed values; n , number of rotations run. Rotations run from 589 to 365 m μ unless noted. ^g Does not fit Drude; Moffitt (the Moffitt equation is used here merely as an empirical three-term Drude expression) parameters: $a_0 = 354.49$, $b_0 = -227.77$, $\lambda_0 = 200.00$ (chosen arbitrarily). Any value of λ_0 from 100 to 240 m μ is almost as good providing the correct corresponding values of a_0 and b_0 are used. ^h Does not follow Drude. Moffitt (the Moffitt equation is used here merely as an empirical three-term Drude expression) $\pm a_0 = -47.748$ 105, $b_0 = 32.491 \pm 159$, $\lambda_0 = 246.51 \pm 200$. ⁱ The large standard deviations indicate that a wide selection of parameters work equally well. The cited values reproduce the calculated values to within about 0.1%, and these calculated values taken as averages of the observed values have a standard deviation of 10%. The large error is due to the fact that the observed α values were small. ^j 105% of the values obtained on hydrolysis of Z-Ser(H)-OH. See text. ^k Optical purity by hydrolysis with 5 N HCl, 100°, 15 hr; rotation in 5 N HCl (c 2). ^l 100.9% (av of 2). ^m 589-435 m μ . ⁿ For optical purity see Table II.

The use of the *p*-nitrophenyl group as a carboxyl-blocking group required an extensive study of factors which affect the yield of product.^{2,8} One preparative detail that should be mentioned is an unconventional order of mixing reagents: a solution of the acid and triethylamine is added to a suspension of the hydrobromide in a solution of the carbodiimide. Required rates of addition depend on the choice of solvent and are related to the rate of solution of the salt. It may also be noted that diisopropylcarbodiimide can often be used to advantage where the peptide product is difficult to separate from the very insoluble dicyclohexylurea.

The removal of the benzyloxycarbonyl group was carried out with hydrogen bromide in nitromethane or in dioxane solution since with acetic acid the serine was partly esterified. The tripeptide hydrobromide is difficult to purify but is readily converted to the *p*-toluenesulfonate 7 by mixing it with triethylammonium *p*-toluenesulfonate in methanolic solution.

(8) D. F. DeTar, R. Silverstein, and F. F. Rogers, Jr., *J. Am. Chem. Soc.*, **88**, 1024 (1966).

Polymerization was carried out in dimethyl sulfoxide or in dimethylformamide using the equivalent amount of triethylamine or of sodium *p*-nitrophenoxide as the base. The polymer was precipitated with chloroform or with methanol and was extracted with chloroform and with methanol. Some samples were dialyzed against water.

The optical purity of the intermediates and of the polymers was subjected to a careful study. For the peptides two criteria were used, the repeatability of the observed rotations for samples prepared by different techniques (summarized in Table I) and the rotations obtained after complete acid hydrolysis under carefully defined conditions. The hydrolysis technique has a repeatability of about 2%, and there is a further uncertainty of 2% in the rotation values assigned to L-serine. L-Z-Ser-OH provided a definitive serine standard subject to the assumption that loss of optical activity upon hydrolysis was the same as for serine itself (5%). It was possible to show that small amounts of DL-Z-Ser-OH can be removed from L-Z-Ser-OH by recrystallization from ethyl acetate.

The use of hydrolysis to estimate the optical purity of

lides containing both serine and aspartic acid is necessarily less accurate, but the results were still excellent. In Table II are given the expected molar rotations of aspartic acid and of serine appropriate to the hydrolysis conditions along with the rotations found for the tripeptides. Agreement is within the 3–4% specified.

Table II. Optical Purity of Peptides and of Polymers

	Molar rotation in 5 N HCl (c 2) at λ , m μ			
	589	578	546	435
-Asp(OH)-OH ^a	31.8	33.2	37.9	66.7
-Ser(H)-OH ^a	13.0	13.6	15.7	30.3
um: for comparison with peptides	44.8	46.8	53.6	97.0
TosOH-H-Asp(OCH ₃)-Ser(H)- Gly-ONP	45.2 ^c	47.2	54.0	97.0
-Asp(OCH ₃)-Ser(H)-Gly-ONP	45.3 ^f	47.5	54.6	97.1
-Asp(OBt)-Ser(H)-Gly-ONP	46.1 ^e	48.2	55.3	97
poly Asp(OCH ₃)-Ser(H)-Gly ^b	46.8 ^e	48.8	55.7	100.8
poly Asp(OCH ₃)-Ser(H)-Gly ^c	46.3	48.4	55.6	100.4
poly Asp(Im)-Ser(H)-Gly ^d	24.8	26.2	29.9	52.6
poly Asp(OH)-Ser(Ac)-Gly ^e	47.1	50.3	56.6	101.2
poly Asp(OH)-Ser(H)-Gly ^b	45.3	48.0	55.0	99.8

These values are lower than the respective values reported for aspartic acid and for pure serine since they refer to hydrolysis obtained after heating at 100° for 15 hr in 5 N hydrochloric acid. This treatment leads to about 3% loss of activity in the aspartic acid and 5% in the serine. ^b Based on polymer purity of 92.8% estimated from elemental analysis. ^c Based on polymer purity of 92.8% estimated from elemental analysis. ^d Based on polymer purity of 89% estimated from elemental analysis. Assume that the serine is 100% L, the aspartic acid has been racemized by triethylamine treatment and is 35% L and 65% DL. ^e Averages of two independent samples. ^f Average of five independent samples. ^a Purity 90.6%. ^b Purity 92.0.

evaluation of the optical purity of the polymers is more difficult for they absorb such solvents as water and chloroform tenaciously, and do not lose solvent completely even on prolonged drying at 100° and 0.1 mm. The reported molar rotations (Table I) are based on the peptide content as estimated from elemental analysis. The error limits are estimated to be about 0% for the polymers. Conversion of Tos-OH-H-Asp(OCH₃)-Ser(H)-Gly-ONP to polymeric imide by use of excess triethylamine (third from last line in Table I) led to a low rotation; racemization is presumably attributed to the aspartyl residue.

The fact that the polymer is only partly racemic suggests that imide formation is faster than racemization. This in turn permits the absence of racemization in the other polymer samples to be taken as a demonstration of the absence of such a process as reversible conversion of ester to imide. Such conversion, if it occurred, would lead to a mixture of α - and β -aspartyl linkages. Hydrolysis of the methyl ester of poly Asp(OCH₃)-Ser(H)-Gly by hydrolysis leads to imide formation, and the imide hydrolyzes to a mixture of α - and β -aspartyl linkages.^{4,9} An attempt was therefore made to remove the ester group by heating at 85° for 15 hr in lithium iodide in pyridine.¹⁰ The resulting poly-

mer was dark in color and had about half of the ester groups removed.

Proton magnetic resonance of trifluoroacetic acid solutions of peptides and polymers proved most useful in structure verification. Important peak positions are summarized in Table III. Integrated areas agreed well with those expected.

Molecular weights were determined by end-group labeling and by the ultracentrifuge using the Archibald method. The determination of amino end groups by dinitrophenylation using the general procedure of Sanger requires a hydrolysis step and chromatographic isolation of the DNP amino acid. This was carried through on one sample of poly Asp(OCH₃)-Ser(H)-Gly and it was found, as expected, that the only N-terminal residue is aspartic acid. However for estimating molecular weights, this procedure is tedious, involves hydrolytic loss of over half of the DNP-Asp(OH)-OH, and requires relatively large samples. A shorter procedure was therefore developed which involves spectrophotometric measurements directly on the DNP polymer. Details are given in the Experimental Section. Properties of the polymers are summarized in Table IV. The observed relationship between \bar{M}_w and intrinsic viscosity $[\eta]$ is given by the expression $\log [\eta] = 0.367 \log \bar{M}_w - 2.061$ with a variation in $[\eta]$ from 0.15 to 0.28 and of \bar{M}_w from 2500 to 12,000. For condensation polymerization of the type used here the \bar{M}_w/\bar{M}_n is expected to be about 2.¹¹ Low values are believed to reflect in part the presence of cyclic material, a known by-product in these reactions.⁴

The rates of hydrolysis of the methyl ester and of the imide were investigated briefly at constant pH in the pH-Stat. Results were calculated for the rate expression $-d[\text{ester}]/dt = k[\text{ester}][\text{OH}^-]$ and are only approximate since the reaction was somewhat less than pseudo first order in ester. Since the imide gave parallel results, the rate-limiting step is hydrolysis of the imide. At pH 9 in 0.4 M sodium chloride the initial rate constant for both ester and imide is about 200 l. mole⁻¹ sec⁻¹ at 25°. This value is comparable to that reported for Z-Asp(OBt)-Ser(H)-NH₂ (BENCASA),⁹ and the polymeric structure seems to be providing no large special effect. It might be expected that there would be a retarding electrostatic effect of the neighboring carboxylate groups on the rate,¹² but this aspect has not been investigated.

The polymers were titrated quantitatively both before and after a very brief hydrolysis with 0.1 N sodium hydroxide and gave satisfactory agreement with theory. Values were corrected for polymer contents of 80–95% based on elemental analysis. The results are summarized in Table V.

The rate of hydrolysis of the acetate group of poly Asp(OH)-Ser(Ac)-Gly is of interest because of its close relationship to the acetylated form of chymotrypsin, trypsin, and other hydrolytic enzymes.¹³ The second-order rate constant at pH 11.9 was found to be 0.1 l. mole⁻¹ sec⁻¹. This may be compared with 0.07

(11) P. J. Flory, "Principles of Polymer Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 325.

(12) (a) See Table I of ref 9; (b) A. Katchalsky and J. Feitelson, *J. Polymer Sci.*, 13, 385 (1954).

(13) Reviewed by T. Wieland and H. Determan, *Ann. Rev. Biochem.*, 35, 676 (1966).

(9) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, Y. Shalit, *J. Am. Chem. Soc.*, 84, 2421 (1962).

(10) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 43, 113 (1960).

Table III. Proton Magnetic Resonance Absorption in Peptide Intermediates and Polymers*

	Origin of absorption						Other
	NH	Asp	CH ₂ Ser	Gly	Asp	CH Ser	
Poly Ser(H)-Gly	488 ^c		258 ^c	258 ^c		293 ^c	
Poly Asp(Im)-Gly-Gly	478 ^c	196 ^c	(278) ^d	259 ^b	295 ^a		
Poly Asp(Im)-Ser(H)-Gly	490 ^c	200 ^c	264 ^b	264 ^a	318 ^c	318 ^c	^e
Poly Asp(OH)-Ser(Ac)-Gly	488 ^c	194 ^c	280 ^b	261 ^b	310 ^c	310 ^c	136 ^f
Poly Asp(OCH ₃)-Gly-Gly	482 ^c	190 ^c		262 ^a	313 ^c		233 ^g
Poly Asp(OCH ₃)-Ser(H)-Gly	492 ^c	190 ^c	260 ^c	260 ^a	313 ^c	297 ^c	233 ^g
Poly Gly-Ser(H)-Gly	486 ^c		261 ^b	261 ^b		297 ^c	
Z-Ser(H)-OH			259(4) ^a			285 ^a	
Z-Ser(H)-Gly-ONP	488		260(4) ^a	273(5) ^a		290 ^a	
Z-Asp(OCH ₃)-Ser(H)-Gly-ONP	485 ^c	189(6) ^a	258 ^b	273(5) ^a	302 ^c	302 ^c	230 ^c
HBr-H-Asp(OH)-Ser(Ac)-Gly-ONP	486 ^c	209(6) ^a	284(4) ^a	275(5) ^d	308 ^c	308 ^c	136 ^f
TosOH-H-Asp(OCH ₃)-Ser(H)-Gly-ONP	488 ^c	206(6) ^a	262(4) ^a	276(5) ^a	305 ^c	305 ^c	236 ^g
Z-Asp(OBI)-Ser(H)-Gly-ONP	521 ^c						
	485 ^c	193(6) ^a	250 ^c	269(5) ^a	298 ^c	298 ^c	

* Values reported are cycles per second from tetramethylsilane reference. The solvent was trifluoroacetic acid; a Varian A-60 spectrometer was used. ^b Broad simple peak. ^c Complex broad peak; approximate center. ^d CH₂ of the internal glycine. ^e No methoxyl peak detectable. ^f Sharp singlet of CH₃CO. ^g Sharp singlet of OCH₃. ^h Doublet (*J* value in parentheses).

Table IV. Summary of Molecular Weight Data on Polymers

Sample	Polymer	% N ^a	\bar{M}_n^b	\bar{M}_w^c	$[\eta]^d$	\bar{M}_w/\bar{M}_n^e
47	Asp(OCH ₃)-Ser(H)-Gly	13.58	4700 ^f	11,000	0.266	2.3
81	Asp(OCH ₃)-Ser(H)-Gly	14.46	8900 ^{f,g}	10,000	0.251	1.1
70	Asp(OCH ₃)-Ser(H)-Gly	13.50	4400 ^f	6,800	0.225	1.5
50	Asp(OCH ₃)-Ser(H)-Gly	13.46	4000 ^f	7,500	0.234	1.9
137	Asp(OCH ₃)-Ser(H)-Gly	13.00	4000 ^f	7,600	0.218	1.9
92	Asp(OCH ₃)-Ser(H)-Gly	12.79	1800 ^f	3,700	0.165	2.1
102A	Asp(OCH ₃)-Ser(H)-Gly	12.45	5800 ^a	7,600	0.244	1.3
102B	Asp(OCH ₃)-Ser(H)-Gly	11.70	3400 ^a	2,500	0.154	0.7
61	Asp(OCH ₃)-Ser(H)-Gly	13.38	5700 ^a	4,900	0.208	0.9
112	Asp(Im)-Ser(H)-Gly	15.31 ^h	3200 ^a	5,000	0.163	
124	Asp(OH)-Ser(Ac)-Gly	12.15 ⁱ	3800	6,300	0.168	
181	Asp(OH)-Ser(Ac)-Gly	12.52 ⁱ	...	5,300
185	Asp(OH)-Ser(H)-Gly	15.67 ^a	...	3,900
147	Asp(0.5Im)-Ser(H)-Gly ^m	14.82 ^a	8100	4,900	0.184	
95	Gly-Ser(H)-Gly	18.22 ^p	4700 ^r	...	0.286	
115	Gly-Ser(H)-Gly	18.95 ^p	3200 ^r	...	0.183	
141	Ser(H)-Gly	16.76 ^q	1800 ^r	...	0.145	

^a Theoretical 15.38. Lower values are believed due to presence of solvent, and this has been demonstrated in some cases. ^b By dinitrophenylation, corrected for amount of polymer present in a given sample as based on % N. ^c By Archibald technique, ultracentrifuge. ^d In dichloroacetic acid at 30°. ^e Based on 20% standard deviation of \bar{M}_w and 20% for \bar{M}_n , expected error is 0.55. Average of first seven is 1.73 with standard deviation of 0.54 per value or 0.2 for the average. Average of all nine is 1.52 with standard deviation of 0.57 per value or 0.2 for the average. ^f Using sodium *p*-nitrophenoxide. ^g Dialyzed. ^h Using triethylamine. ⁱ Using triethylamine plus 6.7 *M* urea. ^j Collected from miscellaneous preparations. ^k Theory 17.42. ^l Theory 13.95. ^m From attempted pyridine-LiI hydrolysis. ⁿ Theory 16.21. ^o Theory 16.81. ^p Theory 20.89. ^q Theory 19.44. ^r Small insoluble residue present in DNP run.

Table V. Titration of Polymers*

Polymer	Moles of OH ⁻ /mole of residue Before hydrolysis	Moles of OH ⁻ /mole of residue After hydrolysis
Poly Asp(OH)-Ser(Ac)-Gly	0.96, 0.99, 0.95	2.00
Poly Asp(Im)-Ser(H)-Gly	0.061, 0.062	1.01, 0.99
Poly Asp(OCH ₃)-Ser(H)-Gly	0.07, 0.04, 0.05	1.10, 0.99
Poly Asp(OCH ₃)-Gly-Gly	^b	1.07
Poly Asp(OH)-Ser(H)-Gly	0.78	...

* Values are based on polymer content based on elemental analysis. Titrations before hydrolysis used as end point pH 7.4. Values after hydrolysis were obtained by treatment with a known excess of 0.1 *N* sodium hydroxide at 50° for 5 min and back titration with 0.2 *N* hydrochloric acid. ^b Insufficiently soluble.

for benzyl acetate and 0.006 for ethyl acetate, in solvents containing some alcohol.¹⁴

(14) "Tables of Chemical Kinetics," National Bureau of Standards Circular 510, U. S. Government Printing Office, Washington, D. C., 1951, p 101.

Experimental Section¹⁵⁻¹⁸

1. Z-Asp(OBI)-OH.¹⁵ The following preparation has been repeated many times. A mixture of 70 g of Z-Asp(OH)-OH, 350 ml of benzene, 10 g of TosOH·H₂O, and 100 ml of benzyl alcohol was refluxed until no more water was collected in a trap. The cooled mixture was shaken with 10 g of magnesium oxide for 10 min and filtered. Benzene and most of the benzyl alcohol were removed *in vacuo*. Trituration of the resulting oil with 200 ml of hexane gave 112 g of crystalline Z-Asp(OBI)-OBI, mp 61-63°.

The dibenzyl ester (112 g) was dissolved in a mixture of 1200 ml of dioxane and 500 ml of water and to this was added a mixture of 120 ml of 2 *N* sodium hydroxide solution, 700 ml of water, and 1200 ml of dioxane. After 24 hr at room temperature the pH was brought to 5.5 by adding a few drops of concentrated hydrochloric acid. Solvents were removed on the rotary evaporator, and the residue was

(15) Nitrogen analyses and rotations by Mrs. Lillian Ross.

(16) We are indebted to Carla Howard for the ultracentrifuge runs.

(17) Peptides are in indexing order, amino acids first, then dipeptides, tripeptides, polymers, alphabetic order from amino acid.

(18) For assays and general procedures see ref 4.

(19) This preparation was carried out by Drs. W. Honsberg and Frank Gilmore.

up in 240 ml of 1 *N* aqueous sodium bicarbonate and extracted ether to remove unreacted diester. Acidification gave an oil, crystallized, 66 g (74%). Recrystallization from benzene 50 g (67%) of product, mp 102–103°. Further recrystallization with 60% recovery gave material with mp 106–108° (lit.^{10,11}). The infrared spectrum (137, oil) showed bands at: 1740, 1705, 1695, 1645, and 1530 cm⁻¹.

Z-Ser(H)-OH.^{12,13} This product has been prepared using methods for maintaining basicity: sodium bicarbonate, addition of sodium hydroxide, and magnesium oxide. Use of magnesium oxide is best for large-scale runs.

A mixture of 125 g of magnesium oxide, 2000 ml of water, and of serine was stirred and cooled to 5°, and 800 ml of ether was added. Then 264 g of benzyl chlorocarbonate was added, one-half immediately, one-half over 10 min, and one-fourth over 20 min. The temperature was maintained at 5° throughout and for an additional 2.5 hr. Filtration required a filter aid (Celite 535, a maceous earth). The ether layer of the filtrate was separated, the aqueous layer extracted with three 600-ml portions of ether, then slowly added to 110 ml of cold concentrated hydrochloric acid.

The product separated as fine white crystals, 191 g, mp 98–100°. Extraction of the filtrate gave another 21 g, mp 103–105°.

The product was further purified by recrystallization from 550 ml of ethyl acetate and then from 500 ml of water to give eventually 115 g of product, mp 114–116°. Ethyl acetate is a convenient solvent for estimating optical purity (see Table I).

Z-Asp(OCH₃)-Ser(Ac)-OH. A mixture of 8.04 g of Z-Asp(OCH₃)-ONP, 3.67 g of HCl-H-Ser(Ac)-OH, and 6.06 g of triethylamine in 50 ml of acetone was allowed to stand for 18 hr at room temperature.

The solvent was evaporated; the residue was taken up in ether, and the solution acidified with hydrochloric acid and extracted with ethyl acetate six times. The ethyl acetate was dried, concentrated in volume to 60 ml, and diluted with 120 ml of hexane to give 7.1 g (87%) of white crystals, mp 132–134°. Recrystallization from the same solvent gave mp 141–142°.

Anal. Calcd for C₁₈H₂₂N₂O₈: C, 52.68; H, 5.40; N, 6.83; wt, 410.4. Found: C, 52.6; H, 5.60; N, 7.00; mol wt by phase osmometer, ethanol, 389, 395.

HBr-H-Ser(H)-Gly-ONP. In 1500 ml of methylene chloride, 84.4 g of phosphorus pentoxide was suspended. Hydrogen bromide was introduced at a slow rate. Within 3 min the suspension thickened and stirring became difficult. After 15 min evolution of carbon dioxide began. Hydrogen bromide was introduced for another 1.5 hr, during which time the thick mixture transformed into an easily stirred suspension. Reaction was judged complete when no material less than methylene chloride was present. Dry air was then added through for 0.5 hr and then the product was filtered and dried with several 200-ml portions of acetonitrile; yield 66.0 g (58%), mp 170.5–171.5°. The product can be recrystallized by dissolution in a minimum quantity of hot DMF followed by a tenfold excess of hot acetonitrile, mp 173–173.5°. Only one spot was found by thin layer chromatography on acidic silica gel using 20% methanol in methylene chloride.

Anal. Calcd for C₁₁H₁₄N₂O₈Br: C, 36.30; H, 3.88; N, 11.55; 5.38; Br, 21.90; ONP, 37.94. Found: C, 36.28; H, 3.87; N, 11.53; O, 26.65; Br, 22.11; ONP, 37.6, 38.0.

Z-Ser(H)-Gly-ONP. A detailed study of this reaction has been reported by Rogers.¹ To a solution of 49.5 g (0.24 mole) of isohexylcarbodiimide in 600 ml of acetonitrile cooled to 5° was added 66.6 g (0.24 mole) of HBr-H-Gly-ONP. The suspension was vigorously stirred and immediate addition begun of a solution of 10.25 g (0.25 mole) of Z-Ser-OH and 31.8 ml (0.23 mole) of triethylamine in 200 ml of acetonitrile. The rate of addition was adjusted to require 8 min. The mixture was stirred at ice-bath temperature for 2 hr with addition of 400 ml of acetonitrile to facilitate stirring. After 2 hr more at room temperature, the mixture was filtered. The solid was stirred with a 250-ml portion of warm (40°) dimethylformamide, and the insoluble portion was extracted with another 250-ml portion. The DMF solutions were allowed to stand for 15 min at room temperature to allow precipitation of excess of DCU. Upon addition of 300 ml of cold 0.01 *N* HCl followed by 200 ml of water, the product precipitated and was filtered after about 30 min, 68 g, mp 161–162°. The acetonitrile filtrate yielded a second crop upon evaporation to dryness and tri-

thene extraction of the residue with 100 ml of methanol, 7.5 g, mp 157–158°. The total crude yield was 75%. Recrystallization from 350 ml of 1:3 DMF-methanol gave 62.3 g (83% recovery) of colorless material, mp 170–171°.

Thin layer chromatography on acidic silica gel with 4% methanol in methylene chloride gave a single yellow spot when sprayed with dilute alkali.

Anal. Calcd for C₁₉H₂₁N₂O₈: C, 54.67; H, 4.60; N, 10.07; O, 30.65; ONP, 33.09. Found (2 samples): C, 54.30, 54.48; H, 4.67, 4.53; N, 10.12, 10.58; O, 30.65, 30.24; ONP 33.2, 32.7.

6. HBr-H-Asp(OH)-Ser(Ac)-Gly-ONP. A freshly prepared 3.8 *M* solution of hydrogen bromide in acetic acid (50 ml) plus 2.5 ml of acetic anhydride was placed in a pressure-equalized addition funnel and added rapidly with stirring to 6.25 g of Z-Asp(OH)-Ser(H)-Gly-ONP. The material dissolved and during the next 15 min gas evolution (CO₂) was observed. After a total reaction time of 4 hr, 100 ml of ether was added. This caused precipitation of a gum. The solvent was decanted and 100 ml more ether was added. The solvent was decanted from the partly crystalline material. This was dissolved in 30 ml of acetonitrile and ether added to precipitate a sticky product. The residue was again dissolved in 30 ml of warm acetonitrile and then began to crystallize; yield 2.4 g of nonhygroscopic white powder, mp 141–142°. Extraction with 40 ml of hot acetonitrile gave 2.2 g of material, mp 143–144.5°.

Anal. Calcd for C₁₇H₂₁N₂O₁₀Br: C, 39.17; H, 4.06; N, 10.75; O, 30.69; Br, 15.33; ONP, 26.50. Found: C, 38.72; H, 4.11; N, 10.61; O, 30.58; Br, 15.37; ONP, 25.9.

7. TosOH-H-Asp(OCH₃)-Ser(H)-Gly-ONP. Z-Asp(OCH₃)-Ser(H)-Gly-ONP (20 g) was placed in a 1-l. flask fitted for introduction of hydrogen bromide and 400 ml of reagent grade methylene chloride was added. During 1.5 hr, a stream of hydrogen bromide was introduced. A thick suspension formed and this changed to a fine suspension. The product was filtered (hygroscopic) and washed with two portions of methylene chloride and then with two portions of ether. It was then dissolved in 200 ml of methanol and precipitated with 1500 ml of ether. The material solidified upon standing overnight at 0°, 15.9 g of material with an ill-defined melting point. Attempts to get better material were not successful.

It was found practical to form the toluenesulfonate. The above product was dissolved in 75 ml of methanol and 30 g of triethylammonium *p*-toluenesulfonate was added. Removal of solvent on the rotary evaporator gave an oil. This was dissolved in 200 ml of acetonitrile; the solvent was removed and redissolved in 150 ml of acetonitrile. Upon scratching with a glass rod crystals separated; yield 13.8 g, mp 145–147°. The salt was dissolved in a mixture of 10 ml of hot dimethylformamide plus 10 ml of acetonitrile. Addition of 100 ml of hot acetonitrile gave an immediate separation of crystals, 12.4 g (58%), mp 150–151°. Chromatography (thin layer) on acidic silica gel G using 20% methanol in methylene chloride showed a single spot with alkaline spray.

Anal. Calcd for C₂₂H₂₈N₄O₁₂S: C, 47.25; H, 4.83; N, 9.58; O, 32.84; S, 5.49; OCH₃, 5.31; ONP, 23.6. Found: C, 46.91; H, 5.03; N, 9.44; O, 32.69; S, 5.45; OCH₃, 5.64; ONP, 23.3. Three other samples gave N, 9.30, 9.30, 9.36; ONP, 24.0, 23.3, 23.2.

8. Z-Asp(OCH₃)-Ser(H)-Gly-ONP. (This preparation was carried out more than 20 times.)¹ This is a modification of the preparation of Z-Ser(H)-Gly-ONP. To a stirred solution of 22.4 g (0.108 mole) of DCC in 600 ml of acetonitrile, cooled in an ice bath, was added 37.4 g (0.103 mole) of HBr-H-Ser(H)-Gly-ONP and then there was added a solution of 33.3 g (0.118 mole) of Z-Asp(OCH₃)-OH and 14.4 ml (0.103 mole) of triethylamine in 200 ml of acetonitrile at a uniform rate over a period of 1 hr. The proportions of reagents, their purity, and the rate of addition all affect the yield of product.

The resulting thick suspension was filtered, and the solid was extracted with two 100-ml portions of dimethylformamide containing 1 ml of 0.2 *N* HCl. The combined filtrates were concentrated to 300 ml in the rotary evaporator (flask temperature 40°). This was stirred while 300 ml of a slurry of ice in 0.01 *N* HCl was added slowly. This gave a moderately rapid precipitation of a white product. Then 500 ml of ice water was added and the material collected, 33.4 g, mp 176–179°.

The urea was extracted with an additional 100 ml of dimethylformamide and the product precipitated with 200 ml of ice water. The product was converted to a manageable solid by addition of 100 ml of methanol, yield 16.3 g, mp 183–185°, total yield 88%. The combined crops were stirred with 250 ml of hot methanol for 30 min and filtered, 46.5 g (78%), mp 186–188°. For analysis the material was recrystallized from ethyl acetate to give a product, mp 187–188°. This gave a single spot (alkaline spray) upon thin layer

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-) A. Berger and E. Katchalski, *J. Am. Chem. Soc.*, **73**, 4084 (1951).
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-) S. S. Brown and R. Wade, *J. Chem. Soc.*, 3280 (1962).

chromatography on acid silica gel G with 5% methanol in methylene chloride.

Anal. Calcd for $C_{24}H_{32}N_4O_{11}$: C, 52.75; H, 4.80, N, 10.26; O, 32.22; OCH_3 , 5.68; ONP, 25.3. Found (2 samples): 52.77, 52.69; H, 4.86; 4.96; N, 10.24, 10.23; O, 32.45, 34.20; OCH_3 , 6.00, 5.90; ONP, 24.8, 25.2.

9. **Z-Asp(OCH_3)-Ser(Ac)-Gly-OBl.** A mixture of 3.7 g of Z-Asp(OCH_3)-Ser(Ac)-OH, 3.04 g of TosOH-H-Gly-OBl, 3.81 g of CMC, 1.25 ml of triethylamine, and 50 ml of chloroform was stirred for 3 hr at 20°. The solvent was evaporated; the residue was extracted with acetone and the insoluble urea removed by filtration. The acetone was removed, and the residue was taken up in ethyl acetate, washed with water, 1 N sodium bicarbonate, 3% hydrochloric acid, and water, and dried over magnesium sulfate. Addition of hexane caused precipitation of 2.5 g (50%) of product, mp 122–125°. Recrystallization from ethyl acetate–hexane gave mp 135–136°.

Anal. Calcd for $C_{27}H_{31}N_5O_{10}$: C, 58.16; H, 5.60; N, 7.54; mol wt, 557.5. Found: C, 58.1; H, 5.41; N, 7.08, 7.50, 7.60; mol wt (osmometer, ethanol), 530, 561.

10. **Z-Gly-Ser(H)-Gly-ONP.** This preparation was similar to that of Z-Asp(OCH_3)-Ser(H)-Gly-ONP: to 7.15 g of DCC in 150 ml of acetonitrile was added 12.2 g of HBr-H-Ser(H)-Gly-ONP, cooled to ice temperature, then a solution of 7.83 g of Z-Gly-OH and 4.62 ml of triethylamine in 60 ml of acetonitrile was added over 1 hr. The infrared curve indicated 8% remaining DCC and anhydride peaks at 1830 cm^{-1} . After another 30 min only 2% of DCC remained, and the anhydride peaks remained. One milliliter of 1 N HCl was added; the urea was removed by filtration and washed with 25 ml, and twice the volume of iced methanol (pH 1) was added to give 4.25 g of product, mp 178–180°. Another 7.4 g was obtained from the urea by extraction with 25 ml of DMF and precipitation by addition of 50 ml of iced methanol, total yield 67%. The former fraction was taken up in 8 ml of hot DMF and precipitated with 40 ml of hot acetonitrile to give 3.1 g of material, mp 195°. The latter had mp 195–196° as isolated.

Anal. Calcd for $C_{21}H_{22}N_4O_9$: C, 53.16; H, 4.68; N, 11.81; O, 30.35; ONP, 29.1. Found: C, 53.33; H, 4.80; N, 11.92; O, 30.91; ONP, 29.1.

11. **Z-Asp(OBl)-Ser(H)-Gly-ONP.** This preparation was carried out similarly to the preparation of Z-Asp(OCH_3)-Ser(H)-Gly-ONP. To 13.6 g of DCC (0.065 mole assuming 98.5% purity) in 200 ml of acetonitrile was added 23.6 g (0.065 mole) of HBr-H-Ser(H)-Gly-ONP and then a solution of 26.6 g (0.074 mole) of Z-Asp(OBl)-OH and 9.8 ml (0.065 mole) of triethylamine in 50 ml of acetonitrile over 75 min. Addition of 150 ml of acetonitrile was necessary to permit stirring. The reaction was allowed to proceed for 1 hr with removal of the ice bath after the addition was complete. An infrared curve of the supernatant liquid showed that 98% of the DCC had disappeared, and there was still a small absorption at 1830 cm^{-1} . The work-up was also similar to that for the methyl ester: 100 ml and then 30 ml of DMF containing 1 ml of 0.1 N HCl per 100 ml was used to extract the filter cake. The crude product was dissolved in 80 ml of hot 50:50 dimethylformamide–methanol, filtered to remove a small amount of solid, 300 ml of hot methanol added, and the suspension allowed to cool, yielding 25.2 g of soft needles, mp 161–162°. Recrystallization from a DMF–acetonitrile mixture gave a product which melted at 148° and then resolidified and melted again at 162°. Both forms have the same rotation in DMF. The product gave a single spot (alkaline spray) when chromatographed (tlc) on acidic silica gel G with 5% methanol–methylene chloride.

Anal. Calcd for $C_{30}H_{30}N_4O_{11}$ (two samples for N and ONP): C, 57.87; H, 4.86; N, 9.00; O, 28.27; ONP, 22.2. Found: C, 58.27; H, 4.95; N, 9.18, 9.10; O, 27.83; ONP, 22.2, 21.5.

Polymerization of H-Asp(OCH_3)-Ser(Ac)-Gly-OH. To a solution of 0.2–0.3 g of the tripeptide acid in 5 ml of dimethylformamide, DCC (1–2 equiv) was added. Evaporation of the solvent and extraction with water gave low molecular weight material (about 750, equivalent to 2.5 tripeptide units). This line was not pursued for reasons indicated in the discussion.

Poly Asp(OCH_3)-Ser(H)-Gly. a. **Use of Triethylamine and Dimethyl Sulfoxide.** A solution of 7.8 g of TosOH-H-Asp(OCH_3)-Ser(H)-Gly-ONP was prepared in 10 ml of dimethyl sulfoxide (DMSO) by slight warming. This was cooled to room temperature and stirred while 1.87 ml of triethylamine was added over a period of 2 min. During the next 10 min an unstirrable gel formed. This was stored for 4 hr, and addition of 10 ml of DMSO redissolved the gel. The mixture was stored in the dark for 4 days and the polymer precipitated by slow addition of 100 ml of chloroform.

The polymer was extracted with chloroform, methanol, and ether. It was dried at 50°, then over P_2O_5 at 95° (0.3 μ) for 16 hr to give 3.07 g of polymer (84%).

This material was subjected to further purification by suspension in DMSO (gel) which was centrifuged at 10,000 rpm; this was repeatedly suspended in chloroform and centrifuged. After drying, it was extracted with chloroform in a Soxhlet extractor and dried for 24 hr at 100° and 0.1 mm against P_2O_5 .

Anal. Calcd for $C_{10}H_{15}N_2O_4$: C, 43.95; H, 5.53; N, 15.38, O, 35.13; OCH_3 , 11.36. Calcd for $C_{10}H_{15}N_2O_4$ plus 8.2% of $CHCl_3$ and 1.8% of inorganic residue: C, 40.3; H, 5.04; N, 13.83, O, 31.6, OCH_3 , 10.22; Cl, 7.3; residue, 1.8. Found: C, 39.9; H, 5.07; N, 13.7; O, 32.4; OCH_3 , 10.2; Cl, 7.3; residue, 1.8.

b. **Use of Sodium *p*-Nitrophenoxide.** To a solution of 0.346 g of dried sodium *p*-nitrophenoxide (in oven at 110°) in 2 ml of DMSO was added 1.26 g of TosOH-H-Asp(OCH_3)-Ser(H)-Gly-ONP. Within 30 min the mixture gelled. After 50 hr at room temperature, the polymer was precipitated by addition of 25 ml of methanol. It was washed with methanol and acetonitrile and dried at 70° over P_2O_5 to give 0.44 g of polymer. Several samples were combined and dialyzed against water. After drying, the analysis was: C, 43.7; H, 6.14; N, 14.13; O, 35.99; OCH_3 , 9.4.

Rotation of L-Serine. Literature values of the rotation of serine are insufficiently precise to permit a definitive assay of optical purity. Different lots of commercial serine (Nutritional Biochemicals) showed rotations of 80–97% of the values of pure L-serine as determined below and even lower purities were suggested by comparison with certain literature values. Since nitrogen assays were theoretical (13.32 found vs. 13.33 theory), the presence of considerable DL-serine was indicated.

Fortunately it was discovered that fairly pure L-Z-Ser(H)-OH can be recrystallized from ethyl acetate to give optically pure material. Among several samples which gave rotations close to those summarized in Table I, one had mp 118–119° when the capillary was placed in the bath at 100° and with the temperature rising 3°/min. A DL sample under these conditions showed mp 124–125°. A series of mixtures was made up containing 5, 10, and 20% of DL-Z-Ser(H)-OH, the remainder being the purest sample of L isomer available. The first crops obtained upon recrystallization from ethyl acetate showed melting points of 116–117, 115–117, and 113–116° and rotations, 100, 98, and 89% of the best values.

Other reference compounds containing serine were available for comparison; HBr-H-Ser(H)-Gly-ONP, e.g., prepared by three different workers in our laboratories had rotations within 1% of the average value. The concordance of rotations of such samples prepared at different times is good evidence that all are optically pure.

The rotation of pure L-serine was estimated by controlled hydrolysis of various serine derivatives with 5 N HCl (15 hr at 100°). This procedure gives values with some scatter, about 5% from the average, but with a common average. Similar treatment of serine itself gave a 2% scatter and a 5% loss of activity. The reported values for pure serine in Table I are based on the averages of several different types of samples and on the assumption that the average of the hydrolyzed samples is to be increased by 5% to compensate for loss. These resulting rotation values are appreciably lower than those tabulated by Greenstein and Winitz.¹⁴ We believe the reported values to be too high; they correspond fairly well with our measurements in 1 N HCl.

Identification of End Groups by Dinitrophenylation. The modification by Porter of Sanger's method of identifying end groups was used as a basis for examining one polymer (RC-50-A) both for molecular weight and for identity of the end group. Poly Asp(OCH_3)-Ser(H)-Gly (29.2 mg) and 50 mg of sodium bicarbonate were dissolved in 2 ml of distilled water by warming to 50°. The solution was cooled to room temperature, and a solution of 6.5 mg of dinitrofluorobenzene in 2 ml of ethanol was added. After 3 hr, 0.1 ml of concentrated aqueous ammonia was added and 15 min later the solvent removed. The residue was refluxed for 12 hr with 10 ml of 6 N hydrochloric acid, diluted to 25 ml with distilled water, and a 10-ml aliquot taken for assay.

The DNP-aspartic acid and other products were extracted with ethyl acetate, and the residue from the ethyl acetate was taken up in chloroform and chromatographed on a 2 × 0.5 in. column of silica gel which had been treated with a 15% by weight acetic acid–sodium acetate buffer. The first yellow band consisted of dinitro-

(24) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961, p 116.

aniline as determined by thin layer chromatography on silica gel G, buffered with acetic acid-sodium acetate, and with ethanol-0.22 M ammonia (89:11) as eluent, R_f 0.77. The second yellow band was eluted from the column with ether-methanol-acetic acid (49:49:2.5), and on thin layer chromatography as above had R_f 0.12. This is the value found for DNP-aspartic acid. There were no traces of DNP-serine (R_f 0.36), nor of DNP-glycine (R_f 0.55) in any fraction.

The DNP-aspartic acid was taken up in 25 ml of a sodium borate buffer and absorbance read at 361 $m\mu$. When the above procedure starting with the hydrochloric acid hydrolysis was carried out on pure DNP-aspartic acid, it was found that recovery was only 48%. Losses have been noted before during the hydrolysis steps.

The calculated number-average molecular weight, correcting for the loss, was 7200.

Number-Average Molecular Weights by Dinitrophenylation. An appropriate weight of sample (1-6 mg) was dissolved in 2 ml of 2% sodium bicarbonate, warming if necessary to effect solution. To this was added 2 ml of a freshly prepared 1-3% solution of 2,4-dinitrofluorobenzene in ethanol. After 2 hr at room temperature the solution was transferred quantitatively to a separatory funnel using 6 ml of 3 N hydrochloric acid for rinsing. The solution was extracted with two 10-ml portions of carbon tetrachloride and the aqueous layer filtered through wet filter paper into a 25-ml volumetric flask and diluted to volume with 3 N hydrochloric acid. Absorbance was read at 353 $m\mu$. A blank run was used to correct for absorbance owing to dissolved carbon tetrachloride or other substances. Sample size was chosen to give an absorbance of about 0.8, and an extinction coefficient of 1.59×10^4 l. mole⁻¹ cm⁻¹ was used. The rationale is that the extinction coefficient of the DNP derivatives may be expected to be relatively insensitive to the amino acid or the peptide to which the DNP is attached. In support of this it was found that five samples of DNP-Asp(OH)-OH in 2% sodium bicarbonate and in hydrochloric acid ranging from 1.2 to 6 N all had an extinction coefficient at 353 $m\mu$ of 1.59×10^4 with a standard deviation of 0.022 per run or 0.01 for the average. The value for DNP-Gly-Gly-Gly-OH was 1.60. Values reported at 350 $m\mu$ for DNP-Gly-OH (1.55), DNP-Phe-OH (1.57), DNP-Gly-Gly-OH (1.58), DNP-Phe-Val-OH (1.55), and for H-Lys-(DNP)-OH (1.49) are close.²⁵ (All values are to be multiplied by 10^4 .) Properties of the polymers are summarized in Table IV.

(25) F. Sanger, *Biochem. J.*, **39**, 507 (1945); R. R. Porter, *Methods Enzymol.*, **4**, 221 (1957).

$$\bar{M}_n = \text{mg of sample} \times$$

$$1.59 \times 10^4 / (A_{\text{sample}} - A_{\text{blank}}) (\text{volume in milliliters})$$

Weight-Average Molecular Weights from Ultracentrifuge Measurements. The data in this paper are based on the Archibald method using the Beckman-Spinco Model E ultracentrifuge.²⁶ Runs were made in aqueous solution (mostly in 0.01 M KCl, but sometimes in water alone with comparable results) and at a concentration of 0.5-1%, usually using a Schlieren angle of 70° (50-85°) and a speed of 12,590, 20,410, or 24,630 rpm with photographs at intervals ranging from 10 to 100 min. In most cases only the meniscus values were used.

The principal source of error is the estimation of the intercept at the meniscus, and the error arises both from the problem of accurately identifying the meniscus and from the fading of the pattern. In the present series the meniscus was taken as the boundary as it appeared on the photographic plate, and extrapolation procedures were used to get the $(dc/dx)_0$ value at this point. Plots of several sets of data showed that the arbitrary function $\log (dc/dx)$ gave good agreement with the visual estimated of $(dc/dx)_0$ and that parabolic extrapolation was less satisfactory. Errors arising from $(dc/dx)_0$ estimates are the major source of the roughly 10% standard deviation per exposure. Data were processed by the computer program ARCHBD.

The calculated molecular weight is sensitive to the assumed density of the polymer, or of its reciprocal, the partial specific volume \bar{V} . Estimates of solution densities at concentrations of 1% with a precision of 1 part in 5000 lead to a 25% error in \bar{V} . We therefore used a calculated value for \bar{V} of 0.61 for poly Asp(OCH₃)-Ser(H)-Gly.²⁷ The weight-average molecular weights in this paper have an estimated accuracy of about 20%. All data have been processed in a uniform fashion so that comparisons between samples involve only the standard deviation of the scatter which is 10%. Control runs on ribonuclease gave much sharper curves and satisfactory agreement with published results.

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Halide Ions as Probes for Nuclear Magnetic Resonance Studies of Proteins. The Sulfhydryl Groups of Hemoglobin

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Abstract: Chlorine nmr spectroscopy is used to verify that the unreactive sulfhydryl groups of hemoglobin are incapable of forming structures of the type protein-S-HgCl even when the protein is dissociated in media of high ionic strength or low pH. However, dissociation of hemoglobin into fragments appears to be accompanied by conformational changes that restrict the motion of chlorine ions bound to mercury atoms complexed at the sites of the reactive sulfhydryl groups. The changes in structure and chemical reactivity of hemoglobin in urea solution are complex.

In recent years there has been a great deal of interest in the application of nmr techniques to systems of biological importance.² Since the direct application of nmr to proteins in solution is seldom fruitful, several indirect methods involving relaxation effects have been

developed.^{3,4} Recently Stengle and Baldeschwieler⁵ reported a novel technique which involves the use of a halide ion (usually chloride) as a probe for the study of mercury complexes of proteins. In this paper, this

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(2) (a) A. Kowalsky and M. Cohn, *Ann. Rev. Biochem.*, **33**, 481 (1964); (b) O. Jardetzky, *Advan. Chem. Phys.*, **7**, 499 (1964).

(3) A. S. Mildvan and M. Cohn, *Biochemistry*, **2**, 910 (1963).

(4) O. Jardetzky, N. G. Wade, and J. J. Fisher, *Nature*, **197**, 183 (1963).

(5) T. R. Stengle and J. D. Baldeschwieler, *Proc. Natl. Acad. Sci. U. S. A.*, **55**, 1020 (1966).

method is applied to a specific protein, hemoglobin, with the aim of developing some information on the behavior of the sulfhydryl groups.

An interesting property of the hemoglobin molecule is its ability to dissociate into halves when dissolved in certain media. This phenomenon has been extensively investigated since it serves as a model for a variety of protein reactions.⁶ From the nature of the media capable of causing dissociation it seems that the forces holding the halves together are primarily electrostatic, whereas further dissociation or unfolding, often leading to denaturation, must also involve the rupture of hydrophobic bonds.^{7,8} The problem of the function of the unreactive sulfhydryl groups has been intimately connected with this aspect of the tertiary structure. There is some evidence to indicate that the unreactive sulfhydryl groups are directly involved in the interchain linkage,⁹ although other work has not substantiated this contention.⁸ This question can be resolved by a study of the SH groups of the dissociated molecule. If dissociation exposes originally unreactive SH groups to the solvent, hence activating them, the inference is that they are involved in the interchain binding. However, if the unreactive SH groups remain unreactive when the protein is cleaved, they must not be involved in interchain binding. Cecil and Thomas⁸ studied the unreactive SH groups in a mixed water-alcohol solvent which was designed to rupture hydrophobic bonds without causing dissociation of the hemoglobin molecule. They found that the addition of alcohol to the solvent did cause an enhancement of the SH reactivity, indicating that the SH groups were involved in hydrophobic bonding and, hence, in intrachain structure.

Since the halide ion nmr technique can be specific for SH groups, it can be used to verify and extend the earlier results. The nmr method is particularly appropriate since it examines reactive SH groups, whereas Cecil and Thomas⁸ worked with the unreactive ones.

Theory

For a nucleus of spin greater than $1/2$ (e.g., ^{35}Cl , ^{79}Br , ^{127}I) the interaction of the nuclear electric quadrupole moment, Q , with the fluctuating field gradient, q , at the nucleus can provide a simple and dominant relaxation mechanism. In the extreme narrowing approximation, the contribution to the nuclear resonance line width from quadrupole relaxation is

$$\Delta\nu = K(e^2qQ)^2\tau_c \quad (1)$$

where $\Delta\nu$ is the full line width at half-height in cycles per second, e^2qQ is the quadrupole coupling constant in cycles per second, τ_c is the correlation time for molecular rotation in seconds, and K equals $2\pi/5$ for a nucleus of spin $3/2$ if the asymmetry parameter is neglected. A large range of line widths is possible depending on the values of these quantities. For example, for a chloride ion in dilute aqueous solution, the solvation of the ion is essentially symmetric, and the electric field gradient at the nucleus is nearly zero. This results in a line width of 15–20 cps for the ^{35}Cl

signal in aqueous solutions of NaCl. However, when the chlorine atom is involved in covalent binding, the value of e^2qQ is quite large; the line width for CCl_4 is 14.5 kc/sec. Even greater line widths are expected for molecules larger than CCl_4 with longer τ_c .

If a quadrupolar nucleus can be located at different kinds of sites in solution, the resulting line shape depends on the relative concentrations of the various sites, the values of e^2qQ and τ_c at each site, and the rate of exchange of chlorine among the various sites. If there are two possible sites, and the exchange of chlorine between them is very rapid, the spectrum will be a single composite signal of line width

$$\Delta\nu = \Delta\nu_a P_a + \Delta\nu_b P_b \quad (2)$$

where $\Delta\nu_a$ and $\Delta\nu_b$ are the line widths at sites a and b, and P_a and P_b are the probabilities that the nucleus is at sites a and b. It is apparent from eq 2 that if $\Delta\nu_b$ is very large, a very small value of P_b may produce an observable effect on the line width $\Delta\nu$. Hence the chloride ion can be used as a probe for interesting sites in low concentrations, and the exchange process functions as a chemical amplifier. For small values of P_b , $P_a \cong 1$ and

$$\Delta\nu - \Delta\nu_a \cong \Delta\nu_b P_b \quad (3)$$

The conditions for the binding and exchange process are reasonably restrictive. The chloride ion must be able to enter the first coordination sphere of the site and form a sufficiently strong bond to give a large value of q , the electric field gradient at the nucleus. Furthermore, the ion must remain bound for a time long compared with τ_c , while exchange with ions in the bulk solvent must occur in a time short compared with $1/\pi\Delta\nu_b$. The binding of chloride to mercuric ion appears to satisfy these requirements.⁵

It is possible to label specific sites in proteins with mercury, and thus use the chloride ion as a probe to examine these sites. Reaction of HgCl_2 directly with SH groups on protein molecules can produce sites of the type P-S-Hg-Cl. In a typical experiment the chlorine nmr line width of a 0.5 M NaCl solution is 16 cps. Addition of 1.4×10^{-5} M hemoglobin causes the line to broaden slightly to 17 cps. When the solution is made 2.8×10^{-5} M in HgCl_2 , the line width changes to 55 cps.

The effect of mercury on the chlorine line width in the presence of hemoglobin is very large. This is due to the long effective correlation time of ^{35}Cl bound to the protein-mercury complex. If it is assumed that the mercuric ions react to completion with the two accessible SH groups, and that q has about the same value in P-S-Hg-Cl as in HgCl_4^{2-} , then the effective τ_c for the Hg-hemoglobin site must be about 100 times as long as that for the small HgCl_4^{2-} complex. The correlation times observed in this work are frequently one or two orders of magnitude shorter than the time of rotation of the protein molecule as a whole.¹⁰ In eq 1, τ_c refers to the correlation time for the change in angle between the electric field gradient at the chlorine nucleus, q , and the external magnetic field, H_0 . This angle is affected by motions within the protein-mercury complex as well as by rotations of the entire molecule. Hence the effective correlation times will be a com-

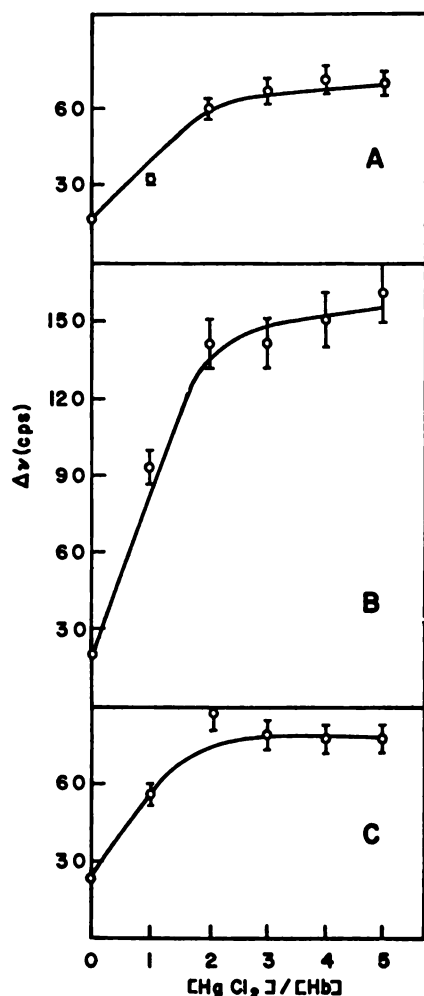
(6) A. Rossi-Fanelli, E. Antonini, and A. Caputo, *Advan. Protein Chem.*, **19**, 73 (1964).

(7) K. Kawahara, A. G. Kirshner, and C. Tanford, *Biochemistry*, **4**, 1203 (1965).

(8) R. Cecil and M. A. W. Thomas, *Nature*, **206**, 1317 (1965).

(9) Y. Enoki and S. Tomita, *J. Mol. Biol.*, **11**, 144 (1965).

(10) R. F. Steiner and H. Edelhoch, *Chem. Rev.*, **62**, 457 (1962).



1. Titration of equine methemoglobin vs. HgCl_2 at various concentrations. All solutions were adjusted to pH 7 with phosphate buffer: A, $\text{NaCl} = 0.5 \text{ M}$, $\text{Hb(E)} = 1.4 \times 10^{-5} \text{ M}$; B, $\text{NaCl} = 2.0 \text{ M}$, $\text{Hb(E)} = 7.0 \times 10^{-5} \text{ M}$; C, $\text{NaCl} = 4.0 \text{ M}$, $\text{Hb(E)} = 7.0 \times 10^{-5} \text{ M}$.

of these two factors. Thus τ_c provides a measure of the rigidity of the structure at the cysteine site, as well as the rotational correlation time of the entire molecule, and should be quite sensitive to any unfolding of the molecule.

Experimental Section

Materials. Twice-recrystallized horse methemoglobin, Hb(E), was obtained from Pentex, Inc. The human hemoglobin, Hb(A), was obtained by the Department of Biochemistry, Stanford Medical School. It was freshly prepared from normal adult human blood and stored in the cold. It was used in the oxy form, and was never kept for more than 1 week. All other chemicals were analytical reagent grade. When hemoglobin was dissolved in dissociating media, NMR measurements were made on the same day. Some of the measurements were quite unstable; in these cases spectra were obtained within a few minutes after the solutions were prepared.

Measurements. The ^{35}Cl spectra were obtained at 4.33 MHz using a Varian V-4311 fixed-frequency radiofrequency spectrometer. Base-line stabilization was achieved by field modulation and phase-sensitive detection using a PAR Model JB-4 lock-in amplifier. Calibration of the spectra was effected by the usual side-chain technique. All spectra were obtained at room temperature. Reported line widths are the average of at least five spectra, and in the case of very unstable samples where only the first few were used.

8

Experimental measurements are most conveniently carried out in the form of a titration. Hemo-

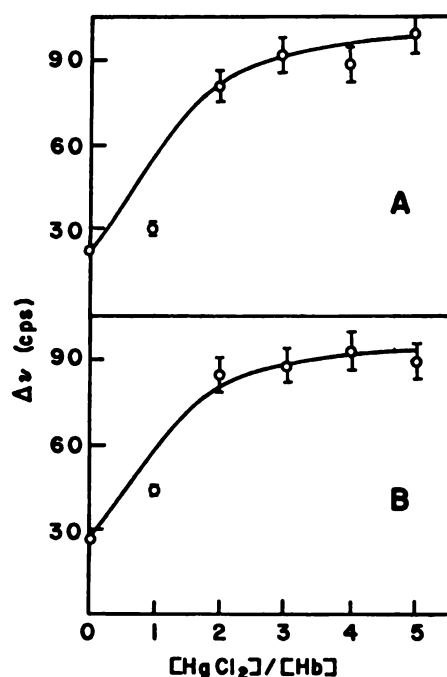


Figure 2. Titration of human oxyhemoglobin vs. HgCl_2 at various NaCl concentrations. All solutions were adjusted to pH 7 with 0.05 M phosphate buffer: A, $\text{NaCl} = 1.0 \text{ M}$, $\text{Hb(A)} = 2.6 \times 10^{-5} \text{ M}$; B, $\text{NaCl} = 4.0 \text{ M}$, $\text{Hb(A)} = 5.1 \times 10^{-5} \text{ M}$.

globin was dissolved in the selected medium containing 0.5 M NaCl , enough NaCl so that the ^{35}Cl resonance is readily observable. The NMR line width was followed as increasing amounts of HgCl_2 were added. In the early stage of the titration, when reactive SH groups are present, each addition of HgCl_2 causes the formation of P-S-Hg-Cl groups which results in a large increase in the ^{35}Cl line width. When all the available SH groups have reacted, further addition of HgCl_2 has little effect on the spectrum. A typical curve for horse methemoglobin is shown in Figure 1A. In this solution the dissociation of the protein is minimized by the low ionic strength and neutral pH. The end point at $[\text{HgCl}_2]/[\text{Hb}] = 2$ is well defined showing that there are only two reactive SH groups per molecule. From eq 2 it is apparent that

$$\Delta\nu - \Delta\nu_a = K(M[\text{Hb}]/[\text{Cl}^-])(e^{1/2}Q)^2\tau_c \quad (4)$$

where M is the number of Cl^- binding sites per labeled hemoglobin molecule, $[\text{Hb}]$ is the concentration of labeled hemoglobin molecules, and $[\text{Cl}^-]$ is the chloride ion concentration. If $e^{1/2}Q$ is assumed to be the same for all these solutions, then for given hemoglobin and chloride ion concentrations the slopes of the titration curves are simply proportional to τ_c . It is known that hemoglobin will dissociate in solutions of high ionic strength.¹¹ At an NaCl concentration of 4 M the dissociation should be essentially complete. The titration curves in 2.0 and 4.0 M NaCl are presented in Figures 1B and C, respectively. These curves clearly show that only two SH groups are reactive. The unreactive SH groups are not exposed to the solvent, even when the molecule is completely dissociated into halves. Similar curves for human oxyhemoglobin in 1.0 and 4.0 M NaCl are shown in Figures 2A and B. The re-

(11) A. Rossi-Fanelli, E. Antonini, and A. Caputo, *J. Biol. Chem.*, **236**, 391 (1961).

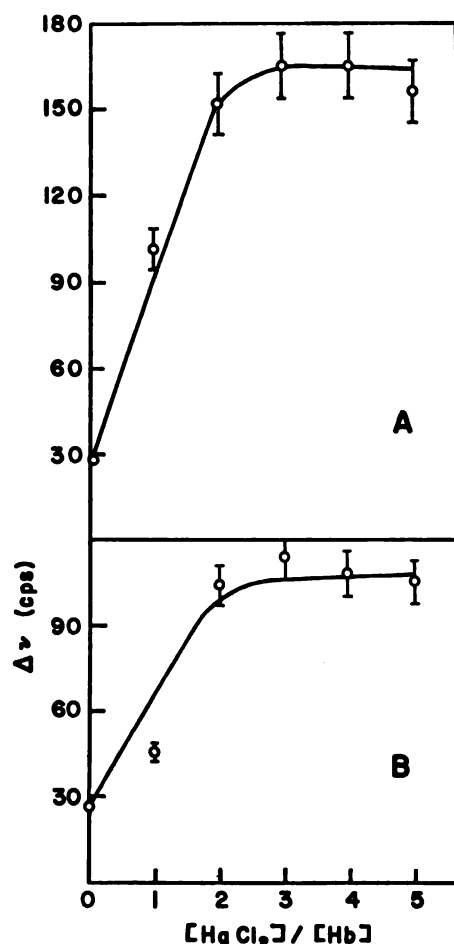


Figure 3. Titration of equine and human hemoglobin vs. HgCl_2 under acid conditions. All solutions were adjusted to pH 5.1 with 0.1 M acetate buffer: A, $\text{NaCl} = 1.0 \text{ M}$, $\text{Hb(E)} = 2.8 \times 10^{-5} \text{ M}$; B, $\text{NaCl} = 2.0 \text{ M}$, $\text{Hb(A)} = 2.6 \times 10^{-5} \text{ M}$.

sults demonstrate that all but two of the SH groups are masked even in 4 M NaCl. Several of the titration curves show an anomaly at the point corresponding to $[\text{HgCl}_2]/[\text{Hb}] = 1$; this solution shows less line broadening than expected. This is probably due to incomplete reaction between the HgCl_2 and the active SH groups; the high chloride ion concentration may tend to hold a small fraction of the metal in the form of HgCl_4^{2-} .

The relative values of the effective correlation times calculated for these solutions are given in Table I. The correlation times measured by this method appear to increase under dissociating conditions. This behavior indicates that in the dissociated protein the motions of the ^{35}Cl nucleus are more restricted than in the whole molecule. For a molecule of the size of hemoglobin, one would expect a rotational correlation time on the order of 100 nsec from the model of a sphere turning in a viscous liquid. Using eq 1 to calculate a value of τ_c from this work we obtain an order of magnitude of 1 nsec, under the assumption that e^2qQ for the protein-Hg-Cl complex is the same as for solid HgCl_2 . Hence τ_c must be determined by motions faster than the rotation of the molecule as a whole, probably motions within the protein chains. Since τ_c increases in dissociating media, it appears that dissociation into fragments may be accompanied by a

Table I. Relative Values of τ_c for Hemoglobin

Figure	$[\text{Cl}^-]$	$[\text{Hb}] \times 10^5$	Type of hemo-globin	$\Delta\nu - \Delta\nu_{\text{Hb}}$, cps at $[\text{HgCl}_2]/[\text{Hb}] = 2.0$	Rel τ_c	Remarks
1A	0.5	1.4	E	43	1.0	
B	2.0	7.0	E	128	2.4	
C	4.0	7.0	E	55	2.0	
2A	1.0	2.6	A	58	1.5	
B	4.0	2.6	A	58	5.8	
3A	1.0	2.8	E	125	3.1	pH 5.1
B	2.0	2.6	A	80	4.0	pH 5.1
4A	1.0	2.8	E	30	0.7	4.0 M urea
B	1.0	2.8	E	20	0.5	6.0 M urea
5A	1.0	2.6	A	50	1.3	4.0 M urea
B	1.0	2.6	A	25	0.6	6.0 M urea

change in conformation of each fragment so as to restrict the motion of the bound chloride ions.

Since hemoglobin is known to dissociate in an acid medium,⁶ a series of measurements was attempted on both the equine and human samples at a pH of 4.5. In this medium, protein denaturation occurred immediately after addition of the HgCl_2 , and no meaningful data could be obtained. It is interesting however that the precipitation of the protein could be followed by a fall in the ^{35}Cl line width with time. At a pH of 5.1 the denaturation was slowed to the point where the solutions were stable for a few minutes. By taking the spectrum immediately after the addition of HgCl_2 , the curves shown in Figures 3A and B were obtained for equine and human hemoglobin at 1 and 2 M NaCl. Here again, only two active SH groups were found. Thus there is no difference in dissociation brought about by high ionic strength and that caused by a low pH insofar as events about the SH groups are concerned. Again the effective values of τ_c appear to increase as shown in Table I.

The effect of urea on hemoglobin has been the subject of some confusion in the past. Steinhardt¹² showed that urea causes dissociation of equine CO-hemoglobin, whereas Gutter, *et al.*,¹³ reported that human CO-hemoglobin is unfolded by urea without appreciable dissociation. Recently Kawahara, *et al.*,⁷ showed that human CO-hemoglobin is indeed dissociated by urea, but they also reported a series of experiments indicating that simultaneous unfolding does not occur. Chlorine nmr titrations on both human and equine hemoglobin in 4 and 6 M urea solutions are shown in Figures 4 and 5. These results are quite different from the other titration curves. Although vestiges of the end points are evident for the titrations in 4 M urea, the results for 6 M urea show no sign of a break at $[\text{HgCl}_2]/[\text{Hb}] = 2$. Furthermore, for a given concentration of hemoglobin and HgCl_2 , the line-broadening effect in the presence of urea and hence the effective τ_c is less than is otherwise produced, as shown in Table I. This behavior cannot be due to an interaction of HgCl_2 with urea; when the experiment is performed in the absence of hemoglobin, such effects are not observed. Urea seems to be unique in other respects as well. For ex-

(12) J. Steinhardt, *J. Biol. Chem.*, **123**, 543 (1938).

(13) F. J. Gutter, H. A. Sober, and E. A. Peterson, *Arch. Biochem. Biophys.*, **62**, 427 (1956).

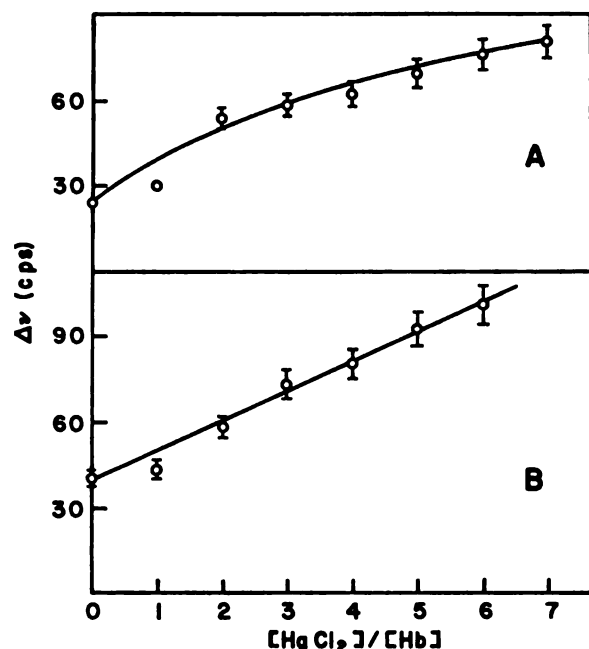


Figure 4. Titration of equine methemoglobin vs. HgCl_2 at various urea concentrations. All solutions were adjusted to pH 7 with 5 M phosphate buffer: A, $\text{NaCl} = 1.0 \text{ M}$, $\text{Hb(E)} = 2.8 \times 10^{-5} \text{ M}$, urea = 4.0 M; B, $\text{NaCl} = 1.0 \text{ M}$, $\text{Hb(E)} = 2.8 \times 10^{-5} \text{ M}$, urea = 6.0 M.

ample, the protein solutions were extremely stable in the presence of urea; no precipitation was ever observed in this medium. Unfortunately it was not possible to study solutions more concentrated in urea than 6 M, since at higher molarity of amide the solubility of NaCl was too low to obtain a good nmr signal.

Discussion

The most interesting result of this work is the lack of activity of the unreactive SH groups even when the hemoglobin molecule is dissociated into halves. This indicates that the unreactive SH groups are incapable of forming structures of the type P-S-Hg-Cl which are exposed to the solvent. Such behavior could be due to any one of several causes. The mercuric chloride could react with the SH groups producing P-S-Hg-S-P linkages. These groups would probably produce no effect on the ^{35}Cl nmr line width as shown by an earlier study of $\text{Hg}(\text{SCH}_2\text{COOH})_2$.⁵ Such a result is unlikely, since the reactive SH groups do not form such bridges, it is improbable that the unreactive ones would. Another process consistent with the experimental data is the formation of P-S-Hg-Cl groups at the expense of the unreactive sulfhydryls, with the subsequent sequestering of these from the solvent by virtue of their location in inaccessible regions of the protein. A third possibility is that there is simply no reaction between HgCl_2 and the unreactive SH groups. In either of the latter two cases, the inference is the same; the behavior of the unreactive SH groups is essentially unaffected by dissociation of the molecule. This result is consistent with the conclusion of Cecil and co-workers^{8,14} that the unreactive SH groups are involved in intrachain binding and would be affected by an unfolding of the individual chains, but not by a simple dissociation of

(14) R. Cecil and N. W. Snow, *Biochem. J.*, **82**, 255 (1962).

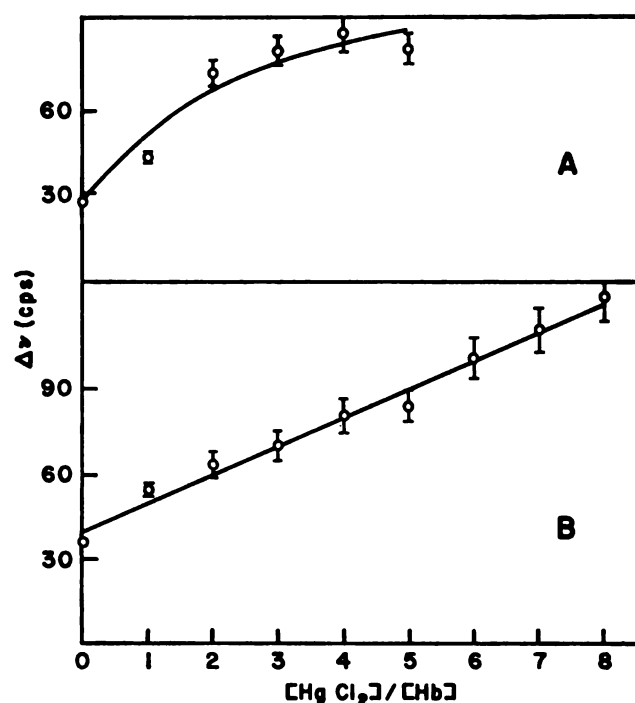


Figure 5. Titration of human oxyhemoglobin vs. HgCl_2 at various urea concentrations. All solutions were adjusted to pH 7 with 0.05 M phosphate buffer: A, $\text{NaCl} = 1.0 \text{ M}$, $\text{Hb(A)} = 2.6 \times 10^{-5} \text{ M}$, urea = 4.0 M; B, $\text{NaCl} = 1.0 \text{ M}$, $\text{Hb(A)} = 2.6 \times 10^{-5} \text{ M}$, urea = 6.0 M.

the hemoglobin molecule. This result is also consistent with the observation that the unreactive SH groups fail to react with iodoacetamide in 2 M NaCl .¹⁶

There appears to be no simple explanation for the behavior of the urea-hemoglobin systems. This is not surprising since these solutions contain two substances capable of affecting the protein. Urea solubilizes amide, peptide, and hydrophobic groups, while sodium chloride decreases the free energy of ionic groups in contact with the solvent. It is not clear what effect a combination of the two will have, but one would expect the mixture to be exceptionally active by analogy with guanidine hydrochloride which also contains an amide-like and an ionic component.

In complex systems it is not always possible to derive an unequivocal explanation of the experimental results from the nmr data alone. The line width depends on the product of two variables, P_b and τ_c ; there is no simple way of separating the effect of each one. It is highly probable that the flexibility of the hemoglobin molecule is enhanced in urea solution, thus lowering τ_c . The absence of an end point in the titrations in 6 M urea shows that P_b has also been affected. The absence of an end point even at mole ratios of $[\text{HgCl}_2]/[\text{Hb}]$ in excess of six indicates that sites in addition to the sulfhydryl group for the formation of mercury complexes with the protein may be available in concentrated urea solutions or the equilibria involving the mercury atom are more complex. Speculation on the changes in gross structure, conformation, and chemical reactivity of hemoglobin in urea solution requires information such as molecular weights in addition to these nmr results.

(15) R. E. Benesch and R. Benesch, *Biochemistry*, **1**, 735 (1962).

Acknowledgments. Helpful discussions with Professors L. Stryer and H. Taube are gratefully acknowledged. This research was supported by the National Science Foundation under Grant GP-4924, and

by the National Institutes of Health under Grant GM-13545-01. T. R. S. was also supported in part by the Center for Materials Research, Stanford University.

Communications to the Editor

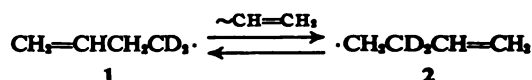
Rearrangement of the Allylcarbinyl Radical¹

Sir:

Extensive carbon skeletal rearrangement accompanies the solvolyses of allylcarbiny l derivatives. These fascinating rearrangements have been the subject of a number of studies.² Vicinal vinyl group migrations occur with facility in allylcarbiny lmagnesium halides and diphenylallylcarbiny l radicals.³ In this communication we wish to report two types of intramolecular structural transformations that allylcarbiny l radicals undergo, as well as several observations which are germane to the detailed mechanism of these changes.

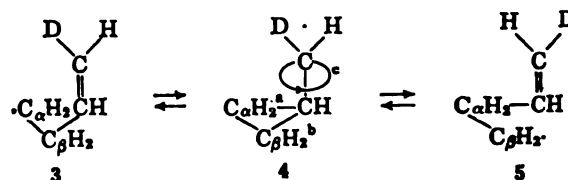
In preliminary experiments it was determined that 4-pentenal decarbonylates by way of a radical chain process (di-*t*-butyl peroxide, chlorobenzene, 130°), yielding 1-butene as the virtually exclusive hydrocarbon product. In order to seek out conceivable carbon skeletal rearrangements that might take place during this reaction, the decarbonylation products of 4-pentenal-2,2- d_2 were examined. A 1.0 *M* solution of 4-pentenal-2,2- d_2 afforded 1-butene-4,4- d_2 and 1-butene-3,3- d_2 in roughly equal quantities (mass spectral analysis). Recovered, unreacted 4-pentenal-2,2- d_2 was not rearranged. Following a procedure developed previously in studies of the decarbonylations of 2- and 3-methyl-4-pentenals and 2- and 3-methyl-*trans*-4-hexenals⁴ which facilitates quantitative interpretation of the rearrangement data, a series of 4-pentenal-2,2- d_2 solutions, varying in concentration from 0.50 to 6.0 *M*, was prepared and allowed to react to only a few per cent conversion. 1-Butene-4,4- d_2 :1-butene-3,3- d_2 ratios were determined for each solution. Ratios for the 0.50–1.5 *M* solutions were all close to 1.0:1.0. There was, however, a small but clearly discernible monotonic increase in the ratios (10–20%) in going from the solutions in the concentration range 0.50–1.5 *M* to the 6.0 *M* solution.⁵ The magnitude of this increase is in reasonable agreement with that which would be pre-

dicted from the decarbonylation studies on 2-methyl- and 3-methyl-4-pentenals.^{4a} The variation in ratios demonstrates that a *minimum* of two radical intermediates gives rise to the observed olefinic products. Classical^{4a,6} radicals 1 and 2, which are interconvertible by vicinal vinyl group migration, suffice nicely as the required intermediates. Homoallylic radicals 1 and



2 must interconvert moderately fast to be compatible with the data. In terms of the proposed mechanistic scheme, the decrease in the extent of rearrangement with increasing aldehyde concentration results from increased trapping of 1, which is formed initially from 4-pentenal-2,2-*d*₂.

If the interconversion of 1 and 2 is intramolecular, a reasonable assumption, a half-migrated entity of cyclopropylcarbinyl structure must be implicated in the very least as a transition state in the rearrangement sequence. The question arises as to whether a cyclopropylcarbinyl intermediate is also involved. In an effort to probe this point, *cis*-4-pentenal-5- d_1 (95% *cis* as inferred by proton nmr analysis) was synthesized and its decarbonylation products were examined. Radical chain decomposition of *cis*-4-pentenal-5- d_1 should generate homoallylic radical 3 initially. If half-migrated structure 4 is merely a transition state for carbon skeletal rearrangement, bond a should be formed



and bond b broken without a loss of geometrical identity about bond c, for transition-state lifetimes are generally considered to be short⁷ relative to internal rotational lifetimes.⁶ Decarbonylation of a 1.0 M solution of *cis*-4-pentenal-5-*d*₁ gave *cis*-1-butene-1-*d*₁ and *trans*-1-butene-1-*d*₁ in a 1.03:1.00 ratio (nmr). Recovered starting material had not rearranged. A straightforward explanation of these results is that a cyclopropylcarbiny radical like **4** is a reaction intermediate and that the double bond geometry of the starting aldehyde is lost in intermediate **4** through rotation

(6) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

(7) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 189.

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work (Grant 2190-A4).

(2) K. L. Servis and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 1331 (1965), and pertinent references cited therein.

(3) (a) M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *ibid.*, **82**, 2646 (1960); (b) D. J. Patel, C. L. Hamilton, and J. D. Roberts, *ibid.*, **87**, 5144 (1965); (c) T. A. Hलगren, M. E. H. Howden, M. E. Medoff, and J. D. Roberts, *ibid.*, **89**, 3051 (1967).

(4) L. K. Montgomery, J. W. Matt, and J. R. Webster, *ibid.*, 89, 923 (1967); (b) L. K. Montgomery and J. W. Matt, *ibid.*, 89, 934 (1967).

(5) The presence of minor contaminants prohibited precise measurement of the 1-butene-4,4- d_2 :1-butene-2,2- d_2 ratios. The ratios are presently being redetermined using chromatographed (glpc) 1-butene- x,x - d_2 samples. Preliminary experiments using this technique support the qualitative trend cited here.

bond c. Finally, neat (6.4 *M*) *cis*-4-pentenal was subjected to decarbonylation. The observed *trans*-1-butene-1-*d*₁:*trans*-1-butene-1-*d*₁ ratio was 1.42:1.00, indicating that 3 can be trapped in a manner analogous to trapping of 1. This lends additional support to the proposed rearrangement scheme, particularly the contention that 4 lies along the rearrangement reaction path.

National Institutes of Health Predoctoral Fellow, 1964–1967.

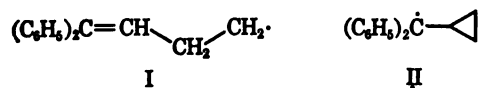
Lawrence K. Montgomery, J. W. Matt^a

Contribution No. 1348, Department of Chemistry
Indiana University, Bloomington, Indiana 47401

Received January 30, 1967

Reaction for Rapid and Reversible Equilibration of γ,γ -Diphenylallylcarbinyl and Cyclopropylcarbinyl Free Radicals¹

We wish to report an example of an unusually facile reversible free-radical rearrangement in which a substituted allylcarbinyl free radical is interconverted with the corresponding cyclopropylcarbinyl radical.² Investigation of the radical rearrangement complements previous studies on analogous carbanion³ and similar carbonium ion⁴ systems. Specifically, we have found that the γ,γ -diphenylallylcarbinyl radical (I) and the cyclopropyldiphenylcarbinyl radical interconvert rapidly at 125° with respect to hy-



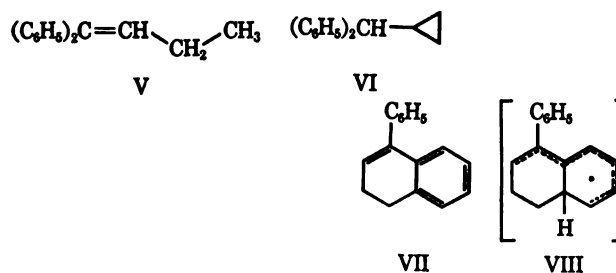
drogen abstraction by either from triethyltin hydride. Triethyltin hydrides are known to be efficient hydrogen donors. For example, decarbonylation of the acetyl radical is competitive with hydrogen abstraction from tri-*n*-butyltin hydride only at low concentrations.⁵ In the present work, the radicals were generated by thermal decomposition of either *t*-butyl (γ,γ -diphenylallyl)peracetate (III) or *t*-butyl cyclopropyldiphenylperacetate (IV). The amounts of the principal C₁₆-carbon products formed in the presence of several different hydrogen donors are listed in Table I. Of 1,1-diphenyl-1-butene (V) and cyclopropyldimethane (VI)⁶ are assumed for our purposes to arise from the radicals I and II, respectively, 1-phenyl-3,4-dihydronaphthalene (VII) is considered to arise from an *ortho* ring cyclization⁷ of I, followed by loss of a hydrogen atom.

Supported by the National Science Foundation. A preliminary report of the decomposition of *t*-butyl (γ,γ -diphenylallyl)peracetate and the theoretical problems posed thereby was presented at the Symposium on Small-Ring Compounds at the 142nd National Meeting of the American Chemical Society, Washington, D. C., March 22, 1962. For recent studies on related systems, see D. I. Schuster, Ph.D. thesis, California Institute of Technology, 1961, and A. J. Rosen, thesis, California Institute of Technology, 1964. Maercker and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 1742

L. Servis and J. D. Roberts, *ibid.*, **87**, 1331 (1965).

G. Kuivila and E. J. Walsh, Jr., *ibid.*, **88**, 571 (1966).

The formation of VI is reasonable on the basis of the stabilization of radical I by the phenyl groups. In the absence of these groups, propenes may be formed; cf. L. K. Montgomery and J. W. Matt, *ibid.*, **89**, 3050 (1967).



The relative amounts of V and VII formed in 1,4-cyclohexadiene–cyclohexane mixtures as a function of the reaction temperature and of the cyclohexadiene concentration suggest that the *ortho* ring cyclization is

Table I. Yields of C₁₆-Hydrocarbon Products in the Thermal Decomposition of *t*-Butyl (γ,γ -Diphenylallyl)peracetate and *t*-Butyl Diphenylcyclopropylperacetate in Various Solvents

Solvent	Perester ^a	Yield, %		
		V	VI	VII
Triethyltin hydride, 0.14 <i>M</i> in <i>n</i> -octane	III ^b	23.5	1.63	10.0
1,4-Cyclohexadiene	III ^d	30.0	0.3 ^c	11.9
Indene	III ^c	10.7	0.02 ^c	16.0
Cyclohexane	III ^d	1.0	0.1 ^c	26.5
Ether	III ^d	1.1	0.6 ^c	31.5
Tetrahydrofuran	III ^d	1.0	0.05 ^c	15.6
Cumene	III ^d	1.3	0.2 ^c	^e
1,4-Cyclohexadiene	IV ^c	45.0	14.6	11.0
Cyclohexane	IV ^c	1.1	7.5 ^c	23.5
Ether	IV ^c	2.0	9.5 ^c	28.5
Benzene	IV ^c	1.1	11.4	18.5

^a The decomposition temperatures were 125–131° for III and 35° for IV. ^b 0.002 *M*. ^c 0.05 *M*. ^d 0.30 *M*. ^e Not determined. ^f As identification has been made by gas chromatographic retention time alone, this figure is an upper limit to the amount formed.

irreversible and that VIII disappears mainly through disproportionation or dimerization, or through loss of a hydrogen atom to, or coupling with, a cyclohexadienyl radical. The conversion of VIII to VII appears to be fairly efficient, and one may write approximately

$$d(\text{V})/d(\text{VII}) = k_a(\text{I})(\text{ZH})/k_r(\text{I})$$

so that

$$k_a/k_r = (\text{V})/(\text{VII})(\text{ZH})_{av}$$

where k_a is the rate constant for hydrogen abstraction by I from the hydrogen donor, ZH, and k_r is the rate constant for the isomerization of I to VIII. Values of k_a/k_r estimated for triethyltin hydride, 1,4-cyclohexadiene, and indene at 125–131° are about 17, 0.4, and 0.1, respectively.⁸ All of the other solvents are much less active as hydrogen donors; in fact, the similarity in the yields of V for decomposition of III or IV in cyclohexane, ether, tetrahydrofuran, and cumene suggests that the active hydrogen donor in these cases is

(7) For a previously reported example of a rearrangement of this type, see S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12**, 138 (1956).

(8) (a) The concentration of hydrogen donor was taken to be 8.7 *M* for 1,4-cyclohexadiene and 7.4 *M* for indene. (b) The values of k_a/k_r may not be strictly comparable because recent rate studies have shown that the perester III mainly undergoes induced decomposition in the presence of triethyltin hydride. Formation of large amounts of triethyltin γ,γ -diphenylallylacetate (ca. 50%) and of hydrocarbon products (V, VI, etc.) under a variety of conditions can be rationalized in terms of attack of triethyltin radicals at either of the peroxy oxygens of III. The nature of the induced decomposition will be discussed more fully in a later publication.

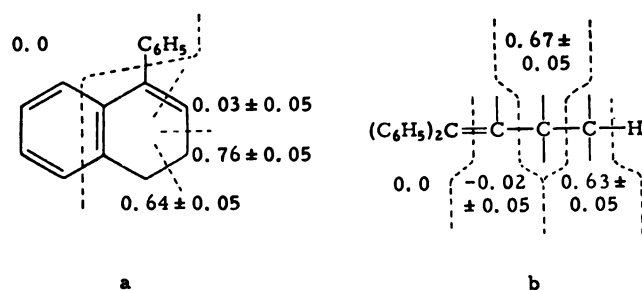


Figure 1. Distribution of the deuterium label as inferred by nmr spectroscopy in products from the decomposition of deuterium-labeled *t*-butyl (γ,γ -diphenylallyl)peracetate in (a) cyclohexane at 125°, and (b) 1.34 *M* triethyltin hydride in *n*-octane at 125°.

actually VII or a tetrahydronaphthalene believed to correspond to an as yet uncharacterized reaction product.

A detailed product analysis to be reported later indicates that relative yields of diphenylcyclopropylmethane and diphenylbutene formed from either perester in 1,4-cyclohexadiene as a function of initial perester and cyclohexadiene concentrations are compatible with VI being formed mainly through donation of hydrogen to II by cyclohexadienyl radicals while V arises similarly from I and 1,4-cyclohexadiene. In the solvents which are poor hydrogen donors, VI can be formed by hydrogen abstraction from VIII.⁹

For the decomposition of III in triethyltin hydride-*n*-octane mixtures, the ratio VI:V is independent of the tin hydride concentration. This observation indicates that the rearrangement of I to II is fast with respect to hydrogen abstraction by I from the hydride, or that there is a single "nonclassical" radical of intermediate structure which gives rise to both hydrocarbons. Thus, the degree of equivalence attained by the methylene groups in I before conversion to product is of special interest. To determine this, perester III was prepared with 1.40 g-atoms of deuterium in the α position. Following decomposition in cyclohexane at 125°, the distribution of the deuterium label in VII, the major reaction product, was determined by nmr spectroscopy. The results are summarized in Figure 1a.

It is clear that the rearrangement of I to II must be fast with respect to that of I to VIII. Here, the time during which the rearrangement may take place is limited only by the relatively slow rate at which the *ortho* ring cyclization occurs. Decomposition of III in the presence of 1.34 *M* triethyltin hydride made it possible to reduce this time by approximately a factor of 23, according to the value of k_a/k_r estimated for the tin hydride. Nonetheless, nmr analysis of the 1,1-diphenyl-1-butene (V) formed showed equilibration of

(9) The major difference in the amount of VI formed in the decomposition of the two peresters in cyclohexadiene (see Table I) can be understood essentially as follows. The half-life for decomposition of ring-opened perester, III, at 131° is about the same as that for IV at 35°. The steady-state cyclohexadienyl radical concentration goes roughly as the square root of the decomposition rate. Therefore, the cyclohexadienyl radical concentration will be about the same in the two cases. However, the steady-state concentration of the ring-closed radical, II, will be quite different. If, as we believe, II is energetically more stable than I, the ratio I:II will be greater at the higher temperature. The rates of hydrogen abstraction to give V and of conversion to ring-cyclized radical VIII will then be much faster at 131° due both to the temperature effect on k_a and on k_r , and to the greater relative amount of I. As a result, the steady-state concentration of II will be much smaller at 131° than at 35°, and the amount of VI formed will be correspondingly less.

the methylene groups to have occurred even in the presence of this active hydrogen donor (Figure 1b). Thus, the half-time for the isomerization of I to II must be short compared to that for the reaction of the former with the tin hydride.

At present there is no reason to postulate the existence of a "nonclassical" radical species to account for the experimental results and, on the whole, the radical system behaves more like the analogous carbanion system³ than like similar carbonium ion systems.⁴ Possible answers to the intriguing question¹⁰ as to the magnitude of the equilibrium constant between I and II will be considered in detail later.

(10) D. Patel, C. H. Hamilton, and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 5144 (1965).

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Received January 30, 1967

pH-Dependent Proton Absorption in Chymotrypsin Binding. Evidence for a pH-Dependent Conformation Change of the Enzyme¹

Sir:

The second-order rate constant ($k_{cat}/K_m(\text{app})$) of chymotrypsin-catalyzed reactions has long been known to decrease above pH 8, with an apparent dependence on a single ionizable group of $pK \sim 9$.² Recently this phenomenon has been identified as a pH-dependent binding by chymotrypsin, even for neutral substrates and inhibitors.³⁻⁵ A pH-dependent binding of a neutral molecule implies that a pH-dependent proton change of the enzyme occurs on binding. In fact, a pH-dependent absorption of one proton per mole of enzyme has been observed upon acylation of chymotrypsin.⁷ Is this proton phenomenon at high pH associated with the noncovalent binding of substrate to enzyme (K_s) or with the subsequent covalent acylation step (k_2)? Recent results with competitive inhibitors of chymotrypsin⁴ and with derivatized chymotrypsins⁸ favor the former possibility.

The binding of the competitive inhibitor, benzyl alcohol, to α -chymotrypsin was first investigated. This substance is particularly advantageous since it is endowed with both high solubility and partial resemblance to a natural chymotrypsin substrate; solutions with $[I]_0/K_i = 20$ can easily be prepared, leading to essentially complete saturation of the enzyme by the inhibitor even at high pH. The results of a series of experiments determining proton uptake by the enzyme upon binding of excess benzyl alcohol are shown in

(1) This research was supported by grants from the National Institutes of Health.

(2) H. Neurath and G. W. Schwert, *Chem. Rev.*, **46**, 69 (1950).

(3) A. Himoe and G. P. Hess, *Biochem. Biophys. Res. Commun.*, **23**, 234 (1966).

(4) M. L. Bender, M. J. Gibian, and D. J. Whelan, *Proc. Natl. Acad. Sci. U. S. A.*, **56**, 833 (1966).

(5) Earlier erroneous reports associated this phenomenon with a subsequent rate step.⁶

(6) M. L. Bender, G. E. Clement, F. J. Kézdy, and H. d'A. Heck, *J. Am. Chem. Soc.*, **86**, 3680 (1964).

(7) J. Keizer and S. A. Bernhard, *Biochemistry*, **5**, 4127 (1966), and references therein.

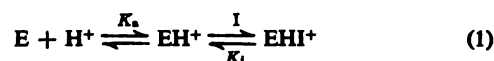
(8) H. L. Oppenheimer, B. Labouesse, and G. P. Hess, *J. Biol. Chem.*, **241**, 2720 (1966).

re 1. At pH 7, no protons are absorbed by the enzyme on binding while at pH's near 10 almost one valent of proton per mole of enzyme is absorbed. pH dependence of the proton uptake follows a sigmoidal curve (solid line) based on a single pK of 8.8, similar to the pK controlling the pH-dependent binding of the enzyme in this region.⁴ Thus, the shapes of $1/K_i$ (or $1/K_s$) vs. pH curves and the proton uptake vs. pH curves are essentially identical with one another. Likewise, plots of proton absorption vs. inhibitor concentration show saturation binding curves similar to normal (V vs. $[S]$) saturation binding curves. The results are obtained with acetonitrile, a nonspecific inhibitor, and N-acetyl-D-tryptophanamide, a specific inhibitor.

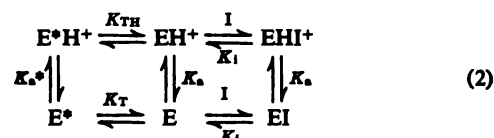
At pH 8.8 the addition of benzyl alcohol ($[BzOH] \gg$ caused 0.5 proton per mole of enzyme to be absorbed, and the further addition of acetonitrile, also in increasing concentration, caused no further changes in the state of protonation of the enzyme. Thus the effect of added inhibitor, especially acetonitrile, is due to specific enzyme-small molecule interaction and not to altered solution properties.

These results suggest that the proton uptake seen in overall acylation (k_2/K_s) actually occurs in the binding step (K_s) preceding acylation (k_2). In the acylation step *per se* no further proton uptake can occur, so it is all accounted for in the binding.

These results further indicate that a set of coupled equilibria involving binding and protonation of the enzyme must occur. A set of coupled equilibria was previously used to explain the pH-dependent binding and proton release on binding of oxygen to hemoglobin, the so-called Bohr effect.^{9,10} The simplest expression of coupling in the chymotrypsin system is



implying that EH^+ , but not E , can bind inhibitor (or vice versa) and that EH^+ , but not EHI^+ (EHS^+), can lose a proton. This set of equations, related to the hemoglobin equations,⁹ successfully describes the sigmoidal shape of Figure 1 and the corresponding sigmoidal shape of $1/K_i$ vs. pH. However, eq 1 suffers from two faults: (1) it gives no mechanistic explanation for the binding of a neutral inhibitor to a protonated enzyme, but not to a neutral enzyme, E ; and (2) it does not account for the change in state of the enzyme seen symmetrically around pH 9.¹¹ In order to meet these requirements, eq 1 has been expanded to eq 2.



This scheme, which postulates two states of the enzyme, rationalizes the pH dependence of both binding and proton uptake. Provided that $K_{TH} (= [EH]/[E^*H]) \geq 1$ and that $[H^+] \gg K_a \leq 10^{-11}$,^{12,13} sigmoidal pH

J. Wyman, *Advan. Protein Chem.*, **4**, 407 (1948).

R. A. Alberty, *J. Am. Chem. Soc.*, **77**, 4522 (1955).

B. H. Havsteen, *J. Biol. Chem.*, **242**, 769 (1967).

The assumption that $K_{TH} \geq 100$ is borne out by the data on the titration of the enzyme alone.¹¹

Equation 2 represents two sides of a cubic array. The other sides of the cube, E^*HI^+ and E^*I , have been omitted, implying that

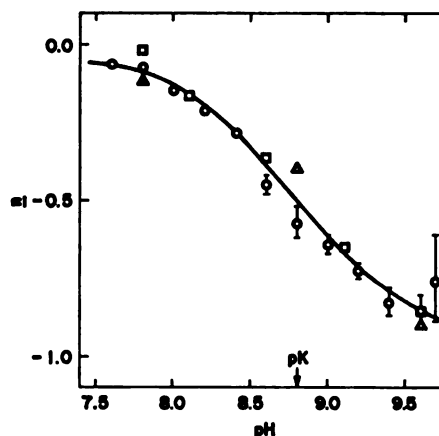


Figure 1. The pH dependence of proton absorption by α -chymotrypsin upon binding of inhibitors: O, benzyl alcohol (pH 7.9: $K_i = 10$ mM, competitive inhibition; 10 mM, proton absorption; pH 9.0: $K_i = 17$ mM, competitive inhibition; 21 mM, proton absorption; pH 9.7: $K_i = 50$ mM, competitive inhibition; 51 mM, proton absorption); Δ , acetonitrile ($K_i = 830$ mM, pH 7.9); \square , N-acetyl-D-tryptophanamide ($K_i = 2.3$ mM, pH 7.9). $[E]_0 = 0.86 \times 10^{-4}$ M; $[I]_0$ always $5 \times K_{i, \text{obsd}}$ at each pH; 25.0°, 0.1 M KCl. Observations of proton absorption by α -chymotrypsin were made using a recording pH meter: ordinary glass and calomel electrodes in a Faraday cage with a Radiometer TTT1c pH-Stat regulator unit used to drive a Sargent SR recorder, for which full scale could be varied from 1.0 to 0.01 pH unit. Inhibitor was added with a Gilson micrometer buret via a Teflon needle. Chymotrypsinogen was used as a "blank" reaction to correct for small (0–25%) pH changes due only to addition of inhibitor. The value of the pH change on addition of inhibitor to α -chymotrypsin was compared to that produced artificially by addition of 1 equiv of hydroxide ion/mole of enzyme to obtain the fraction of one proton absorbed by the enzyme per mole at the given pH. ΔpH values from 0.05 to 0.16 were observed.

dependence of both processes is predicted. Thus E is the major form of the enzyme when protonated, and E^* is the major form when unprotonated.

The symbol n is defined as the number of protons per mole of enzyme which are released as the result of forming the enzyme-inhibitor complex (cf. ref 7 for a similar definition). Using the scheme of eq 2, one may then derive eq 3 and 4. Equation 4 predicts that a plot

$$\frac{1}{K_{i, \text{obsd}}} = \frac{(1/K_i)}{\left(1 + \frac{K_a}{K_T[H^+]}\right)} \quad (3)$$

$$n = \frac{1}{\left(1 + \frac{K_a}{K_T[H^+]}\right)} - \frac{\left(1 + \frac{[I]}{K_i}\right)}{\left(1 + \frac{K_a}{K_T[H^+]} + \frac{[I]}{K_i}\right)} \quad (4)$$

of n vs. $[I]$ at a given pH will produce the usual hyperbolic saturation curve (as seen for V vs. $[S]$), leading to the same $K_{i, \text{obsd}}$ as that obtained by competitive inhibition experiments. Indeed this is observed and proven in experiments carried out at pH 7.8, 8.8, and 9.6.

The dissociation constants of these species are infinite. Havsteen¹¹ has produced kinetic evidence for the top of the cube (E^*H^+ , EH^+ , EHI^+ , and E^*HI^+) by observing at high pH one relaxation of the enzyme itself, and two relaxations of the enzyme in the presence of the inhibitor proflavin. We find that proflavin is a special case: its binding is decreased only twofold at pH 10 where the binding of many other inhibitors is decreased ca. tenfold, implying that proflavin can bind not only at the active site where the change of state occurs, but possibly at some second site also.

The change in state between E and E* in the native enzyme may be described as a change in hydration or, more probably, a conformational change of the native enzyme. Although the binding and proton absorption data require that E be the major form when protonated and E* be the major form when unprotonated, the introduction of inhibitor (or substrate) into the system transforms all of the enzyme to EHI⁺ (or EHS⁺), which explains the pH-independent catalytic steps (k_2 and k_3) in the high pH region. The conformation change thus is related to the binding of small molecules at the enzyme active site but not to the catalytic process *per se*. A pH-dependent intramolecular competitive inhibition of the active site will explain the data on the transformation given both here and elsewhere.⁴ Although this (conformational) change drastically affects the activity of chymotrypsin through an inhibition of binding, it does so only in a negative way.

(14) National Institutes of Health Predoctoral Fellow.

(15) The authors thank Professor F. J. Kézdy for assistance with the mathematical formulation.

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Received March 28, 1967

On the Mechanism of Aromatic Arylation with Nitrosoacetanilide

Sir:

Nitrosoacetanilide (1) has long been known as a source of phenyl radicals¹ and has found particular application in studies of homolytic phenylation of aromatic compounds.^{2,3} It has been established that the rate-determining step in these reactions is the first-order isomerization (eq 1) leading to benzene-diazo acetate.⁴ However, the detail of subsequent processes has been less clear. Two major difficulties challenged early mechanistic ideas. First, early schemes show the high yields of acetic acid arising by way of the acetyloxy radical, in spite of the known instability of this intermediate.⁶ Second, the initial adduct of phenyl radicals to benzene (*i.e.*, the phenylcyclohexadienyl radical, 2) is cleanly oxidized to biphenyl, while in other systems disproportionation and dimerization lead, in addition, to hydroaromatic products.⁶

The difficulties referred to have led to suggestions of concerted^{4,7} or cage⁸ processes. However, a more satisfactory mechanistic interpretation, which has received general acclaim,⁹ was advanced recently by

(1) W. S. M. Grieve and D. H. Hey, *J. Chem. Soc.*, 1797 (1934).

(2) See, for example, G. H. Williams, "Homolytic Aromatic Substitutions," Pergamon Press, Oxford, 1960, Chapter 4.

(3) R. Ito, T. Migita, N. Morikawa, and O. Simamura, *Tetrahedron*, 21, 955 (1965).

(4) R. Huisgen and G. Horeld, *Ann. Chem.*, 562, 137 (1949).

(5) See, for example, C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 493.

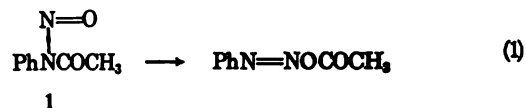
(6) D. F. DeTar and R. A. J. Long, *J. Am. Chem. Soc.*, 80, 4742 (1958); E. L. Eliel, S. Meyerson, Z. Welvert, and S. H. Wilen, *ibid.*, 82, 2936 (1960); D. H. Hey, M. J. Perkins, and G. H. Williams, *J. Chem. Soc.*, 5604 (1963); 3412 (1964); D. I. Davies, D. H. Hey, and M. Tiecco, *ibid.*, 7062 (1966).

(7) R. Huisgen and G. Sorge, *Ann. Chem.*, 566, 162 (1950).

(8) E. L. Eliel, M. Eberhardt, O. Simamura, and S. Meyerson, *Tetrahedron Letters*, 749 (1962).

(9) E. L. Eliel, J. G. Saha, and S. Meyerson, *J. Org. Chem.*, 30, 2451 (1965); B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms 1965," John Wiley and Sons, Inc., New York, N. Y., 1966,

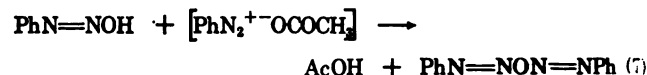
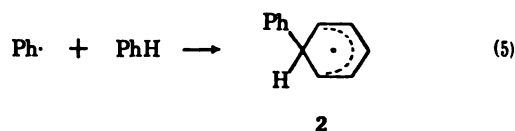
Rüchardt and his collaborators¹⁰ and was successfully extended to the Gomberg reaction.¹¹ In this new scheme, outlined below for the phenylation of benzene, the acetic acid is formed in a nonradical process involving the ion-pair form¹² of the diazoacetate. Furthermore, rapid oxidation of radical 2 by a high stationary-state concentration of the phenyldiazotate radical



Initiation

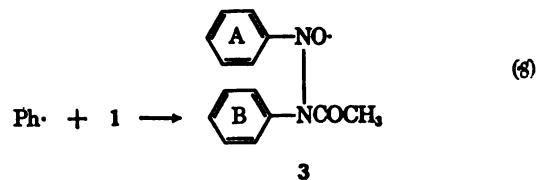


Major product-forming sequence



(PhN=NO·) accounts for the failure to observe disproportionation or dimerization products from 2. This mechanism received added support when a stable radical was detected in the reaction by electron spin resonance (esr),¹³ and its spectrum was interpreted in terms of the phenyldiazotate structure ($a_N = 1.67$, 11.61; $a_H = o$, -2.60; m , 0.89; p , -2.73). The larger nitrogen splitting has subsequently been assigned to the nitrogen atom bonded to oxygen, by means of ¹⁵N labeling experiments.¹⁴

Our interest¹⁵ in the scavenging of phenyl radicals by C-nitroso compounds (to give nitroxide radicals) led us to propose that the radical detected by Rüchardt and Binsch¹³ might, in fact, have structure 3. Any hyperfine splitting by the protons in ring B may have been too small to have been resolved.



We have redetermined the esr spectrum of the stable radical from the decomposition of nitrosoacetanilide in benzene (Figure 1) and have now been able to obtain

p 154. A related mechanism has been advanced, with little supporting evidence, for homolytic phenylation by N-phenyl-N'-tosyloxydiimide N-oxide: E. A. Dorko and T. E. Stevens, *Chem. Commun.*, 871 (1966).

(10) C. Rüchardt and B. Freudenberg, *Tetrahedron Letters*, 3623 (1964).

(11) C. Rüchardt and E. Merz, *ibid.*, 2431 (1964).

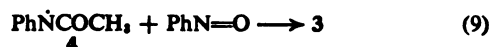
(12) P. Miles and H. Suchitzky, *Tetrahedron*, 18, 1369 (1962).

(13) G. Binsch and C. Rüchardt, *J. Am. Chem. Soc.*, 88, 173 (1966).

(14) G. Binsch, E. Merz, and C. Rüchardt, *Chem. Ber.*, 100, 247 (1967).

(15) G. R. Chalfont, D. H. Hey, K. S. Y. Liang, and M. J. Perkins, *Chem. Commun.*, 367 (1967).

essentially the same spectrum by mixing benzene solutions of nitrosobenzene and *N*-bromoacetanilide (Figure 2). We consider that the most probable structure for the radical responsible for this spectrum is therefore 3; in the second reaction this is considered to arise by addition of the nitrogen-centered radical 4 to nitrosobenzene (eq 9).¹⁶ The ¹⁵N experiments already cited¹⁴ once more allow assignment of the larger nitrogen coupling in radical 3 to the nitrogen atom bonded to oxygen. The value of 11.7 gauss seems very reason-

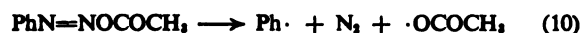


able for nitrogen in this environment, by analogy with other data on nitroxide radicals.¹⁷

Reaction of *N*-bromo-*p*-chloroacetanilide with nitrosobenzene gives a radical whose esr spectrum is indistinguishable from that of 3, consistent with the hypothesis of negligible splitting by the ring B protons. Reactions of *N*-bromoacetanilide with *p*-chloronitrosobenzene, *p*-nitrosotoluene, and 2-methyl-2-nitrosopropane also give stable radical species, the esr spectra of which have been resolved into 50, 42, and 9 lines, respectively.¹⁸ These reactions appear to constitute the first examples of addition of organic nitrogen-centered radicals to the nitroso group, though there are now numerous reports of additions by carbon-¹⁹ and oxygen-centered²⁰ radicals.

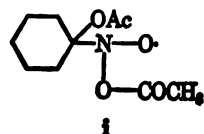
Assuming that structure 3 correctly represents the structure of the stable radical in the nitrosoacetanilide reaction, this species could then adopt the role of oxidant in a modified mechanism such as that outlined below. This finds close analogy with the mechanism proposed for the decomposition of benzoyl peroxide in the presence of diphenyl nitroxide.¹⁵

Initiation



(16) The esr spectrum developed on mixing the reagents, though photolysis of the bromo amide by stray laboratory light may have been instrumental in radical production. At room temperature, the presence of silver powder did not increase the radical concentration. In a control experiment, no radical spectrum was formed from nitrosobenzene and molecular bromine. Spectra were recorded on a modified Varian V4502 spectrometer generously placed at our disposal by Dr. G. R. Wilkinson of the Physics Department of this college. We are also indebted to Dr. Yvonne Rees for a helpful appraisal of various sources of phenylacetamido radicals.

(17) For example, compound i has $a_N = 16.2$ gauss in methylene chloride: J. W. Lown, *J. Chem. Soc., Sect. B*, 441 (1966). This value might be expected to be reduced slightly in 3 by delocalization of the unpaired electron over the aromatic ring (cf. ref 18).



(18) The last of these (nine lines) appeared as a triplet of triplets ($a_N = \text{ca. } 16 \text{ and } 1.5 \text{ gauss}$) and is ascribed to *t*-BuN(O)N(Ph)COCH₃. This radical has not yet been obtained free from di-*t*-butyl nitroxide, despite attempts to avoid direct photolysis of the nitrosobutane (see ref 19). The spectrum in Figure 1 has been analyzed in detail^{13,14} and involves considerable coincidence of lines. There must also be coincidences in the spectra of the chloro- and methyl-substituted radicals and analysis of the spectra of these and related nitroxides will be given in the full paper.

(19) A. Mackor, Th. A. J. W. Wajer, Th. J. de Boer, and J. D. W. van Voorst, *Tetrahedron Letters*, 2115 (1966), and references therein.

(20) A. Mackor, Th. A. J. W. Wajer, Th. J. de Boer, and J. D. W. van Voorst, *ibid.*, 385 (1967).

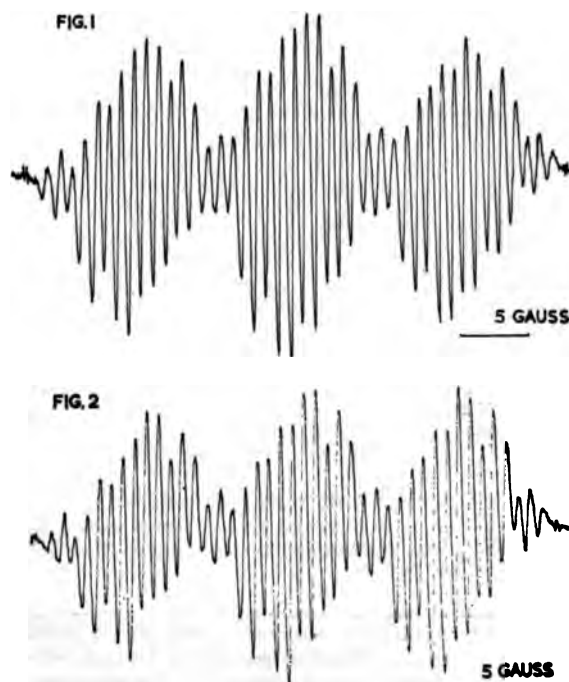
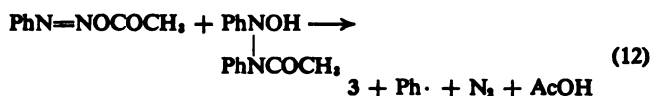


Figure 1. Esr spectrum of the radical formed during the decomposition of *N*-nitrosoacetanilide in benzene.

Figure 2. Esr spectrum of the radical formed on mixing benzene solutions of *N*-bromoacetanilide and nitrosobenzene.

Main product-forming sequence



Reaction 12 may represent more than one discrete step. The reduced yield of biphenyl with high initial concentrations of nitrosoamide might be explained in terms of increased removal of phenyl radicals in reaction 8, leading to unidentified by-products.

Other examples of phenylation reactions in which product formation is dominated by the presence of relatively stable radical intermediates have also been documented.²¹ In the light of the present work, the identity of any such species in the Gomberg reaction¹¹ merits reinvestigation.

Acknowledgment. We thank the Science Research Council for financial support (to G. R. C.), and Professor D. H. Hey for valuable discussions.

(21) D. H. Hey, M. J. Perkins, and G. H. Williams, *J. Chem. Soc.*, 110 (1965); M. J. Perkins, *ibid.*, 5932 (1964).

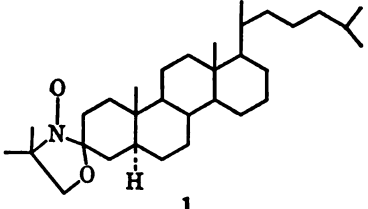
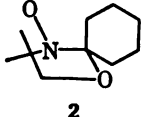
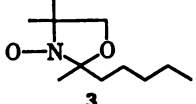
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Department of Chemistry, King's College
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Received March 13, 1967

A New Versatile Ketone Spin Label

Sir:

The study of molecular systems by esr spectroscopy is contingent on the presence within the system of un-

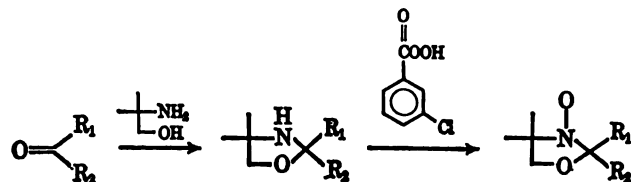
Table I. Physical and Spectral Data

Nitroxide	Mp or bp (mm), °C	a_N^a , ± 0.1 gauss	g value, ± 0.0002	λ_{\max} , $m\mu$ (ϵ)	% yield
 1	175-176 (methanol- ether)	14.3	2.0058	443 (7.2) (ether)	70 ^b
 2	57-58 (pen- tane)	14.3	2.0058	420 (7.4) (ethanol)	42 ^c
 3	~70 (0.08)	14.4	2.0058	422 (7.0) (ethanol)	26 ^{c,d}

^a X-band esr spectra were measured in ethyl acetate solution ($ca. 5 \times 10^{-4} M$) and consisted of the usual three-line nitroxide spectra. All three nitroxides were found to have 1.0 ± 0.2 spins per molecule. ^b This represents pure crystalline material. ^c Yields were determined by visible absorption spectroscopy. ^d The analytical specimen was obtained by preparative vapor phase chromatography.

paired electron spins. Elegant methods have recently been developed for the chemical attachment of relatively stable nitroxide free radicals to diamagnetic biomolecules, permitting study of the latter by esr techniques. Several workers have applied this spin-labeling method with notable success to the study of proteins such as bovine serum albumin.¹

The continuing successful development of this technique depends to a large measure on the availability of a wide variety of spin-label molecules. We wish to report the first general method for converting ketones to stable nitroxide free radicals. The reaction sequence from the ketone to the nitroxide is outlined below.



For example, refluxing a toluene solution of cholestan-3-one containing an excess of 2-amino-2-methylpropan-1-ol² and a trace of *p*-toluenesulfonic acid monohydrate for several hours with continuous water removal by means of a Dean-Stark trap led to the corresponding oxazolidine, one epimer of which had mp 124-125°. The known⁴ oxazolidines derived from cyclohexanone and heptan-2-one were similarly prepared.

In each instance oxidation of the oxazolidine to the corresponding nitroxide was effected by dropwise addition over 20 min of an ether solution of 1.50 equiv of *m*-chloroperoxybenzoic acid to an ice-cold, stirred ether

solution of oxazolidine. The resulting solution was allowed to stand at 25° for 24 hr. The ether layer was washed with cold 5% sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was removed under vacuum, affording the nitroxide. Table I summarizes pertinent physical and spectral data for the three representative nitroxides 1, 2, and 3.

The conformationally rather rigid nature of the oxazolidine ring system in these new spin labels should markedly facilitate the interpretation of rotational correlation times in terms of the local environment of the spin label.

Acknowledgments. We thank Professor O. H. Griffith for determination of the esr spectral data and the National Science Foundation (Grant GP5805) and the Office of Scientific and Scholarly Research of the Graduate School of the University of Oregon for financial support of this work.

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Concerning the Anion and Cation Radicals of Corannulene

Sir:

The consideration of valence bond structures such as 2 for the recently synthesized strained, nonalternate benzoid hydrocarbon, corannulene (1),¹ intimated the theoretical accessibility of the corresponding radical anion and radical cation derivatives. The unusual polar form 2 implies that the radical cation and anion correspondingly will have large contributions of structures such as 3 and 4 to the resonance hybrid. Because of the importance of these species to more sophisticated computations on the corannulene molecule, as

(1) W. E. Barth and R. G. Lawton, *J. Am. Chem. Soc.*, **88**, 380 (1966).

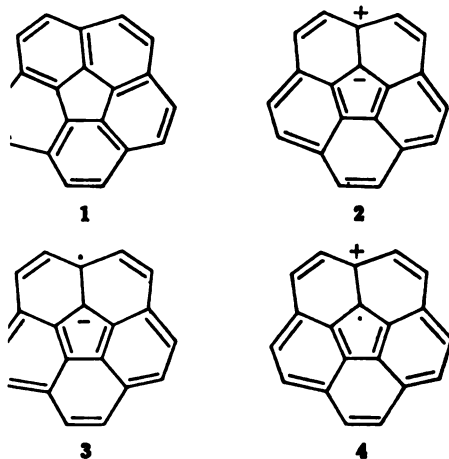
(1) T. J. Stone, T. Buckman, P. L. Nordio, and H. M. McConnell, *Proc. Natl. Acad. Sci. U. S.*, **54**, 1010 (1965); O. H. Griffith and H. M. McConnell, *ibid.*, **55**, 8 (1966); L. Stryer and O. H. Griffith, *ibid.*, **54**, 1785 (1965).

(2) Available from Aldrich Chemical Co.

(3) All new compounds gave carbon, hydrogen, and nitrogen elemental analyses within 0.3% of the theoretical values.

(4) E. M. Hancock and A. C. Cope, *J. Am. Chem. Soc.*, **66**, 1738 (1944).

of general interest in its chemistry, we were to search for these derivatives.



graphic reduction of $1 \times 10^{-3} M$ corannulene-*n*-butylammonium perchlorate solution in acetonitrile using either a stationary platinum microelectrode or a dropping mercury electrode afforded two well-resolved waves with half-wave potentials, $E_{1/2}$, of -2.36 v vs. the Ag-AgCl aqueous reference electrode. That the first wave on both electrodes indicated a reversible, one-electron reduction was confirmed by wave log analysis and controlled potential electrolysis. The corannulene radical anion product of the first reduction wave was characterized by spectroscopic and esr techniques in the following.

Controlled potential electrolysis on a macroreticulated mercury pool electrode and at a potential of -2.5 v vs. Ag-AgCl using a specially constructed flow cell² which was mounted in a Cary Model 14 spectrophotometer in the formation of a dark emerald green solution having maxima in the visible at 450 and 650 m μ (see Figure 1A, curve 1). However, the ratio of intensities of the peaks at 450 and 650 m μ varied over experiments, suggesting that these are possibly due to more than a single species. Upon exposure to oxygen the green solution became yellow. The visible spectrum of this solution exhibited a maximum at 450 m μ . Thus, it is believed, the green color is a result of the summation of the radical anion at 650-m μ maximum and a decay product 450-m μ maximum caused by trace amounts of oxygen in solution.

For green solutions were observed upon reduction of $1 \times 10^{-4} M$ solutions of corannulene in tetrahydrofuran by potassium or sodium metal. At room temperature these solutions exhibited esr spectra consisting of 11 equally spaced lines (Figure 1B), the outermost being observed only under conditions of high gain and resolution. The spectrum and its relative intensity distribution is exactly that expected for a radical with one set of ten equivalent protons. Confirmation that the chemically and electrolytically prepared species were identical was obtained by electroreduction in the esr cavity of a $10^{-3} M$ solution of corannulene in dimethylformamide at a potential of -2.5 v vs. a Ag-AgCl reference electrode, giving an identical esr spectrum with that obtained chemically. The hyperfine splitting constant for the radical anion in diethoxyethane was $a_H = 1.560 \pm 0.005$ gauss,

data and H. B. Mark, Jr., to be published.

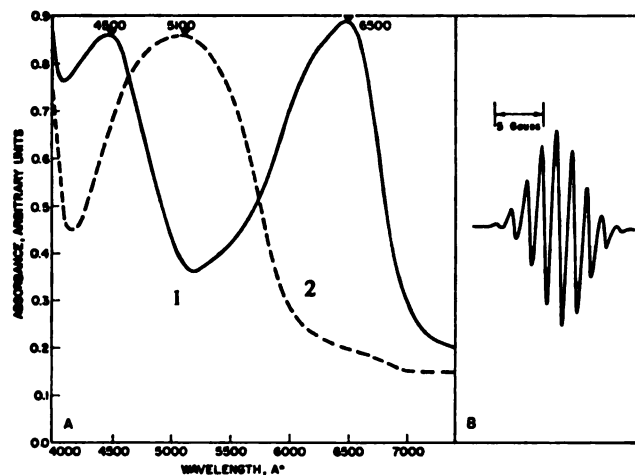


Figure 1. (A) Visible spectrum of electrolysis products produced at -2.0 (curve 1) and -2.5 v (curve 2) vs. a Ag-AgCl reference electrode. (B) ESR spectrum of corannulene anion radical.

and the g value was 2.00270 ± 0.00001 . The splitting constant in dimethylformamide is identical within experimental error.

Controlled potential electrolysis at -2.5 v vs. Ag-AgCl (diffusion plateau of second wave) produced a bright red species having a single absorbance maximum at 500 m μ . This same red substance could also be observed when corannulene solutions were subjected to long contact with alkali metals. The red species, which is not paramagnetic, is not believed to be the dianion, but rather some decay product of it. Further studies of this reaction are in progress.

Attempts to observe the radical cation (4) were uniformly unsuccessful; using a slow anodic sweep of a platinum electrode, a poorly defined oxidation wave was obtained with a half-wave potential of about 1.46 v vs. Ag-AgCl. The wave is actually peaked in shape. Apparently the oxidation product of corannulene undergoes rapid chemical reaction, producing a polymeric product which coats the electrode surface and blocks further oxidation. The passivation prevented any anodic coulometric study. Further, an attempt to observe an esr signal under similar conditions was also unsuccessful.

The neutral corannulene molecule is highly strained, and one would not expect it to be planar. A possible bowl-shaped configuration which preserves the five-fold symmetry of the planar structure was suggested by Barth and Lawton.¹ If the simple Hückel method is used to treat the π system, one possible model in which deviations from planarity can be approximately treated is by a reduction in the β_{10} for the five bonds between the inner and outer rings. The difference in π energy between planar and nonplanar forms for the radical is less than this difference for the neutral molecule. This indicates that no added stability for the planar configuration is obtained on going from the neutral species to the radical anion and hence, if the neutral molecule is nonplanar, the anion radical is likely to be also.³

A bowl-shaped configuration for the anion radical is consistent with the esr observation of ten equivalent protons. In any structure maintaining fivefold sym-

(3) Dr. Gerald J. Gleicher has carried out extensive SCFMO strain calculations, which are to be published.

metry, the unpaired electron occupies a degenerate orbital. Averaging over the ten hydrogen-bonded positions one can obtain average Hückel spin densities, $\langle \zeta \rangle$, and excess charge densities $\langle \epsilon \rangle$. For the radical anion, $\langle \zeta \rangle$ is 0.0630 in the planar configuration ($\beta_{10} = 1.00$), decreases slightly to a minimum value of 0.0616 for $\beta_{10} = 0.72$, and is 0.0667 for β_{10} zero.

For corannulene, one is not sure of the σ framework for the carbon atoms with bonded hydrogen, but if we use the McConnell and Colpa-Bolton relationships, $a^M = 27\zeta$ and $a^{CB} = -27\zeta + 12.8\epsilon$, as discussed by Snyder and Amos,⁴ we find for the planar configuration $a^M = -1.70$ and $a^{CB} = -1.66$; if $\beta_{10} = 0.72$, $a^M = -1.66$ and $a^{CB} = -1.63$. The calculation for the nonplanar configuration including the excess charge effect gives the best agreement with the experimental value $|a| = 1.56$. The agreement between the calculated and experimental values is somewhat surprising considering the nature of the approximations that have been made. However, in the case of coronene anion radical, which is alternate and planar, the calculated splitting using average Hückel spin and charge densities is -1.49 , compared with an experimental value of -1.47 .⁵

Segal, *et al.*,⁶ have found, in agreement with Stone's theory,⁷ that the g values of hydrocarbon radicals can be fitted very well by $\Delta g = g - g_0 = (31.9 - 16.6\lambda) \times 10^{-5}$. Here g_0 is the free-electron value and λ is the Hückel energy level coefficient of the unpaired electron orbital. Segal found that the g value of radicals such as coronene with the unpaired electron in a degenerate orbital do not conform to this relationship, but corannulene does. For corannulene the experimental value of Δg is 38×10^{-5} and the calculated values for planar ($\beta_{10} = 1.00$) and nonplanar ($\beta_{10} = 0.72$) are 40×10^{-5} and 38×10^{-5} , respectively.

Acknowledgment. This research was supported in part by grants from the National Science Foundation (NSF GP-6425 and GP-4620), the Petroleum Research Fund (PRF-1941-AS), and the Western Electroanalytical Theoretical Society.

(4) L. C. Snyder and T. Amos, *J. Chem. Phys.*, **42**, 3670 (1965).

(5) I. C. Lewis and L. S. Singer, *ibid.*, **43**, 2722 (1965).

(6) B. G. Segal, M. Kaplan, and G. K. Fraenkel, *ibid.*, **43**, 4191 (1965).

(7) A. J. Stone, *Mol. Phys.*, **7**, 311 (1964).

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On the Dissociation and Reassociation of the Polypeptide Chains of Tropomyosin and Paramyosin¹

Sir:

The molecules of tropomyosin and paramyosin are similar. In benign media, both consist of two α -helices arranged side by side and twisted slightly about one another.²⁻⁴ Thus, although they differ significantly in amino acid composition, the only gross difference in molecular form is in the over-all molecular length.

(1) This investigation was supported by Research Grant RG-5488 from the Division of General Medical Sciences, Public Health Service.

(2) S. Lowey, J. Kucera, and A. Holtzer, *J. Mol. Biol.*, **7**, 234 (1963).

(3) A. Holtzer, R. Clark, and S. Lowey, *Biochemistry*, **4**, 2401 (1965).

(4) C. Cohen and K. C. Holmes, *J. Mol. Biol.*, **6**, 423 (1963).

Further questions immediately arise. Among these are: (1) How many individual polypeptide chains make up each molecule? Is there one long chain with a hairpin turn between long helical segments, or two completely helical chains held side by side, etc.? (2) Are there any covalent cross-linkages (in particular, disulfide bonds) between the two helical segments? (3) Are the covalent cross-linkages, if any, necessary to maintain the native conformation?

Two of these questions have already been answered for tropomyosin.^{3,5} We report here experimental results which answer all three for both proteins. Except where otherwise noted, preparative methods and physical techniques were as reported earlier.^{2,3}

Tropomyosin. A molecule of tropomyosin has a mass of 74,000 amu.³ In a denaturing medium in which the helix content (measured by optical rotatory dispersion) is zero, the same mass is observed, and the other solution properties are not those of a linear, random coil of that mass.³ Clearly, then, this molecule has one or more covalent cross-linkages. This agrees with chemical studies, which indicate one disulfide bond/molecule.⁶ In a medium that would reduce disulfide linkages, the molecular mass is about one-half the value given above.⁵ Thus, there are two polypeptide chains in tropomyosin, as it is usually prepared, held together by at least one disulfide linkage.

To investigate further, we prepared tropomyosin samples that had all the disulfide linkages reduced to sulfhydryl, and then all sulfhydryls were masked with acetyl groups. This was accomplished by dissolution of native tropomyosin in a denaturing medium (5 M guanidine hydrochloride), reduction with β -mercaptoethanol, acetylation with iodoacetic acid, dialysis, and lyophilization. This lyophilized material ("modified" tropomyosin) was dissolved in both benign and denaturing aqueous media, and several macromolecular properties of these solutions were determined. Specifically, measurements were made of intrinsic viscosity, intrinsic sedimentation coefficient, and (light scattering) molecular weight. In parallel, measurements of intrinsic viscosity and sedimentation coefficient were made on solutions of unmodified tropomyosin. Results for both kinds of material are summarized in Table I (rows labeled TM).

The data in Table I confirm our earlier experiments on unmodified tropomyosin in both media. We have also confirmed that the molecular weight of unmodified tropomyosin, in a medium that is both reducing and denaturing, is one-half that value. It is also plain from the table that the properties of modified and unmodified tropomyosin are quite different from one another in the denaturing medium, but are indistinguishable in the benign medium.

Most striking is the drop in molecular weight (by a factor of two) suffered by the modified protein when transferred from the benign to the denaturing medium and its complete recovery upon transfer back to the benign medium.

Paramyosin. A paramyosin molecule has a mass of 220,000 amu.³ The molecule is extraordinarily stable; optical rotatory dispersion experiments show appreci-

(5) E. F. Woods, *Nature*, **207**, 82 (1965).

(6) A. G. Szent-Györgyi, R. E. Benesch, and R. Benesch in "Sulphur in Proteins," R. E. Benesch and R. Benesch, Ed., Academic Press Inc., New York, N. Y., 1959, p 291.

Data for Modified and Unmodified Tropo- and Paramyosin in Various Media^a

	Medium ^b	$[\eta]^u$	$[\eta]^m$	$10^{11}[\eta]_{20,w}^u$	$10^{11}[\eta]_{20,w}^m$	$10^{-3} M^u$	$10^{-3} M^m$
I	KCl _{1.0} K[PO ₄] _{0.1} (7.3)	34	34	2.59	2.68	74.2 ^c	77.2
I	GuHCl _{1.0} KCl _{0.5} K[PO ₄] _{0.05} (6.1)	45 ^c	33	2.38		76.2 ^c	39.5
I	KCl _{1.0} K[PO ₄] _{0.1} (7.4)	207	206	3.1	2.99	220 ^d	200
I	GuHCl _{1.0} KCl _{0.5} K[PO ₄] _{0.05} (7.4)	103	65.6	4.4	2.63		$\left. \begin{matrix} 108^e \\ 92^f \end{matrix} \right\}$

^u as whose headings contain superscript m (u) refer to the property obtained when the modified (unmodified) protein is dissolved in n given. Intrinsic viscosities are in cc/g; $[\eta]_{20,w}$ in sec⁻¹. ^b To designate aqueous solvent media, the chemical formula for each (other than water) is given with its molarity as a subscript, followed by parenthetical specification of the pH (ref 3). ^c Reference 3. ^d 2. ^e From the empirical relation: $[\eta] = 0.716r^{0.66}$ as given in C. Tanford, K. Kawahara, and S. Lapanje, *J. Am. Chem. Soc.*, 67). ^f From the Scheraga-Mandelkern equation with $\beta' = 2.5 \times 10^8$, as given in H. A. Scheraga and L. Mandelkern, *ibid.*, 75,

content, at 25°, up to a guanidine concentration of 1.0 M.^{7,8} Chemical studies have revealed no bonds.⁶

To investigate the polypeptide chain make-up of this we prepared modified paramyosin in the same tropomyosin, the only difference being that the concentration of the paramyosin solvent was 1.5 M). Measurements of the same macroscopic properties were made (Table I, rows labeled u) differences in technique used in the paramyosin study are noteworthy: (1) molecular weights in benign medium were measured by the Archibald method; (2) since it is very difficult to determine the molecular weight in 7.5 M guanidine by absolute methods (because of strong nonideality), we have to use of the intrinsic viscosity-molecular weight relationship for proteins⁹ and have confirmed this by use of the sedimentation-viscosity relationship for random coils.¹⁰

Results for paramyosin are analogous to those for tropomyosin. Modified and unmodified paramyosins, for example, markedly different intrinsic viscosities in denaturing solvent, that of the unmodified being larger. Since destruction of cross-links in a single-chain random coil would produce a size effect,⁹ this observation suggests some dissociation of chains in the modified protein. The molecular weights confirm this: the mass of the modified molecule in guanidine is one-half that of the native protein. That this chain separation is reversible is evident from comparison of the data for the modified and unmodified proteins in benign media; the results are indistinguishable.

From these conclusions can be drawn from the experimental results: (1) the molecules of both tropomyosin and paramyosin contain two individual polypeptide chains; (2) in both proteins, at least as they are usually found, the chains are joined by at least one disulfide bond (which has not been detected chemically in paramyosin⁶); and (3) the disulfide cross-bridging is, in some cases, unnecessary for maintenance of the native conformation—even after all disulfides have been reduced and the resulting sulfhydryls acetylated, the α -helix is recovered in benign media.

At least one of the three conclusions noted above should be stated without some equivocation. There is a

John and A. G. Szent-Györgyi, *J. Am. Chem. Soc.*, 79, 248

Noelken, Ph.D. Thesis, Washington University, St. Louis,

Table I, footnote e.

Table I, footnote f.

chance that the two chains are unanimously parallel, or unanimously antiparallel, in the unmodified double-helical molecules, but that after modification and redissolution in benign medium a mixture of double-helical molecules results, some having parallel chains and some antiparallel. The measurements reported here are responsive only to comparatively gross changes in molecular shape and cannot resolve this ambiguity. However, if a coiled coil owes its stability to knobs-into-holes packing, as has been suggested,¹¹ it seems quite unlikely that any side-to-side packing other than that characteristic of the native protein would be very stable.

Needless to say, several questions remain; among these is whether the two chains within an individual molecule are identical or different, and, if the latter, whether they can be chemically separated. If so, it would be particularly interesting, for the fundamental theory of stability of protein conformations, to see if a system containing only one of the chains would form an α -helix in a benign medium. Thus far, no instance of a single protein α -helix has been reported.

(11) F. H. C. Crick, *Acta Cryst.*, 6, 689 (1953).

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Relief by Modification of Carboxylate Groups of the Calcium Requirement for the Activation of Trypsinogen

Sir:

The activation of bovine trypsinogen involves the removal of a highly anionic hexapeptide from the N-terminal region of the molecule.^{1,2} MacDonald and Kunitz³ had shown earlier that this process is greatly enhanced by divalent cations such as calcium. These ions seem to exert a directing influence by both promoting the formation of active trypsin from trypsinogen and precluding the formation of an "inert protein." Thus in the presence of calcium ions proteolysis is restricted to the single peptide bond between lysine-6 and isoleucine-7, all other lysyl and arginyl bonds being resistant to tryptic cleavage. In the absence of calcium ions proteolysis is retarded and becomes relatively

(1) E. W. Davie and H. Neurath, *J. Biol. Chem.*, 212, 515 (1955).

(2) P. Desnuelle and C. Fabre, *Biochim. Biophys. Acta*, 18, 29 (1955).

(3) M. R. MacDonald and M. Kunitz, *J. Gen. Physiol.*, 25, 53 (1941).

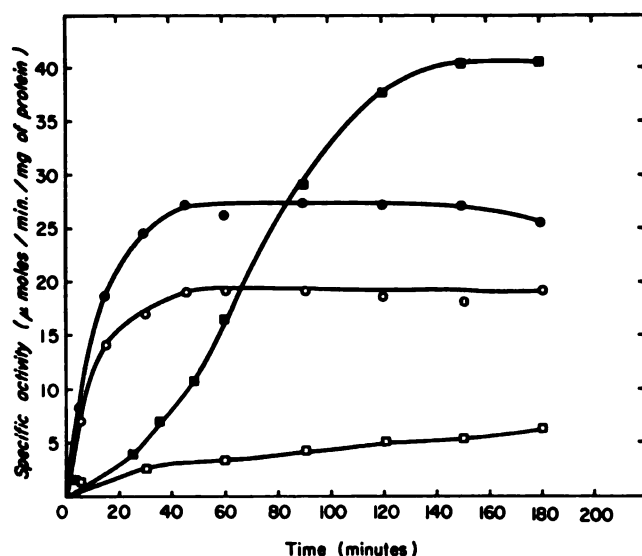


Figure 1. The course of activation in 0.1 M Tris-Cl, pH 8.1, at 0° of native (squares) and modified (circles) trypsinogen (3.5 mg/ml) in the presence (filled symbols) and absence (open symbols) of 0.05 M CaCl₂.

nonspecific.⁴ It is not clear how calcium confers specificity on the limited proteolysis.

A possible site of interaction of calcium with trypsinogen is suggested by the amino acid sequence of the activation peptide, which contains a cluster of four β -carboxylates in a tetrapeptide sequence¹ adjacent to the bond being cleaved. The present experiments were designed to examine the effect on the activation process of modification of these free carboxylate groups with amines under the influence of water-soluble carbodiimides. In recent years⁵⁻⁷ such treatments at acid pH have proven to be specific for other protein carboxylates.

Preliminary experiments showed that trypsin (0.2 mM) retained 68% of its activity during a 15-min treatment at pH 4.5, 25°, with a 25-fold molar excess of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in 1.0 M glycine ethyl ester.⁸ The reaction was stopped by the addition of 1.0 M acetate, pH 3.6, and the reagent was removed by dialysis against 10⁻³ M HCl at 0°.

Similar treatment of trypsinogen resulted in a derivative which could be 64% activated relative to the unmodified control (Figure 1). Significantly, even in the absence of CaCl₂, the modified protein could be activated to the extent of about 46%, whereas with unmodified trypsinogen in the absence of CaCl₂ activation did not exceed 15%. The number of active sites estimated by measuring the ³²P incorporation during inactivation with ³²P-labeled diisopropyl phosphorofluoridate corresponded to the activity determined by rate assay with benzoyl-L-arginine ethyl ester as substrate.

A series of anionic peptides was isolated from the activation mixture containing glycine ranging from 0.6 to 2.5 g residues per mole in addition to valine, aspartic

acid, and lysine (Table I). In contrast, activation of unmodified trypsinogen yielded a single acidic peptide of the expected composition (Val, Asp₄, Lys). The anionic peptides in Table I represent a 60% yield of the N-terminal peptides from the modified trypsinogen. This is greater than the amount predicted from its activability (42%), suggesting that not every tryptic cleavage between lysine-6 and isoleucine-7 was productive. This observation is in accord with the end group analyses (Table II) which invariably exceeded the expected yield of DNP-isoleucine. However, in the latter case autolysis could account for high values for these N-terminal residues.

Table I. Peptides Derived from the Activation of Modified Trypsinogen*

Peptide	g residues of glycine found	Yield of peptide, μ moles	Yield, %
A	0.6	0.106	14
B1	1.7	0.140	18
B2	1.3	0.194	26
C	2.3	0.166	22
D	2.5	0.150	20
Total		0.756	100

* The modified protein (13.4 mg/ml) was activated for 1.5 hr at 0° in the absence of CaCl₂ in mixtures containing trypsin (0.67 mg/ml) and 0.05 M N-ethylmorpholine acetate, pH 8.1. Peptides were separated from the protein on Sephadex G-25 and purified by paper electrophoresis at pH 6.5 and chromatography in 1-butanol-acetic acid-water, 3:1:1. Acid hydrolysis of the anionic peptides yielded valine, aspartic acid, and lysine in the ratio 1:4:1 in all cases, in addition to the indicated amounts of glycine. Peptides B1 and B2 were not completely separated from each other. The stoichiometric yield of activation peptide (assuming 100% activation), after correcting for analytical losses during the isolation procedure, would be 1.31 μ moles.

Table II. Protein N-Terminal Residues in Activation Mixtures*

	Trypsinogen	Moles of DNP-amino acid/mole of protein		
		Trypsinogen + Ca ²⁺ + trypsin	Trypsinogen + trypsin, no Ca ²⁺	Modified trypsinogen + trypsin, no Ca ²⁺
Val	0.78	0.07	0.77	0.39
Ile + Leu	..	0.67	0.26	0.68
Ser	0.08	0.32

* Trypsinogen or modified trypsinogen was activated with trypsin (3.5 mg/ml) with or without CaCl₂ as in Table I for 2 hr. The protein component was precipitated with trichloroacetic acid and end-group analysis was carried out with FDNB (H. Fraenkel-Conrat, J. I. Harris, and A. L. Levy, *Methods Biochem. Anal.*, 2, 359 (1955)) in 8 M urea.

The number of peptides found indicates that the extent of substitution with glycine ethyl ester varied. Further fractionation is required to determine whether the peptide fractions on the electropherogram are molecularly homogeneous. The nonintegral values of glycine may be due to molecular heterogeneity resulting from multiple substitution, partial ester hydrolysis, or side reactions of undetermined character.

The activability of carboxylate-modified trypsinogen in the absence of CaCl₂ suggests that the directive influence of calcium on the normal activation may be by an interaction with carboxylate groups of the native zymogen. The present data show that carboxylate

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(5) J. C. Sheehan and J. J. Hlavka, *J. Am. Chem. Soc.*, 79, 4528 (1957).

(6) J. P. Riehm and H. A. Scheraga, *Biochemistry*, 5, 99 (1966).

(7) D. G. Hoare and D. E. Koshland, Jr., *J. Am. Chem. Soc.*, 88, 2057 (1966).

(8) A similar modification of trypsin had been previously described by Hoare and Koshland.⁷

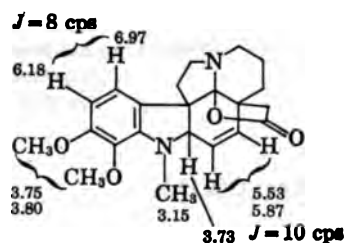
of the activation peptide have been amidated with ethyl ester and suggest that calcium binding carboxylate modification can be functionally involved in the activation process.

Acknowledgment. This work has been supported in part by the National Institutes of Health (GM-04617, 154) and the National Science Foundation (10).

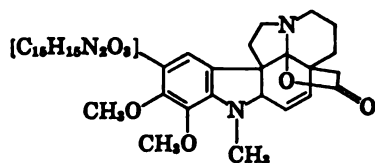
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lytine

Haplophytine¹ was first isolated by Snyder and his co-workers, who carried out an extensive investigation of its chemistry.² It is obtained as the principal alkaloid from *Haplophyton camicidum* (Apocynaceae).³⁻⁴ High resolution mass spectrometry⁵ required the determination of its formula to $C_{27}H_{40}N_4O_7$ (calcd mol wt, 500; found, m/e 652.29148).⁶ Acid cleavage of the crystalline compound (76%), $C_{22}H_{30}N_2O_4$, mol wt, 382; found: m/e 382, mp 201–203°, gave structure I on the basis of its nmr spectrum (see δ values) and the following data. Its infrared spectrum ($CHCl_3$) shows a strong $C=O$ band at 1715 cm^{-1} (cf. cimicine,⁴ cimicidine,⁴ and dichotamine⁷),



I



II

OH or NH bands. Its ultraviolet spectrum [220 $m\mu$ (ϵ 28,700), 256 (5900), and 304 (2400)] is consistent with an indoline chromophore. Its mass spectrum shows a strong peak at m/e 44, character-

istic of the earlier work on haplophytine has been summarized by Snyder and his co-workers, *Alkaloids*, 8, 673 (1965).

¹ Rogers, H. R. Snyder, and R. F. Fischer, *J. Am. Chem. Soc.*, 74, 1952; H. R. Snyder, R. F. Fischer, J. F. Walker, H. E. Els, Nussberger, *ibid.*, 76, 2819, 4601 (1954); H. R. Snyder, H. F. Walker, and R. A. Mooney, *ibid.*, 80, 3708 (1958).
² P. Cava, S. K. Talapatra, K. Nomura, J. A. Weisbach, B. and E. C. Shoop, *Chem. Ind. (London)*, 1242 (1963).
³ P. Cava, S. K. Talapatra, P. Yates, M. Rosenberger, A. G. Douglas, R. F. Raffauf, E. C. Shoop, and J. A. Weisbach, *ibid.* (1963).
⁴ Thank Mr. L. Weiler, Harvard University, for the mass spec-

trifactory elemental analytical data have been obtained in these investigations⁵ for all compounds whose molecular formulas

3. Brown, Jr., H. Budzikiewicz, and C. Djerassi, *Tetrahedron* 19, 731 (1963).

istic of lactonic alkaloids of the aspidospermine skeletal type.^{7,8} Hydrogenation of the cleavage product gave a zwitterionic tetrahydro derivative, mp 265° dec, formed by saturation of the ethylenic double bond accompanied by hydrogenolysis of the lactone (cf. dihydrocimicine and dihydrocimicidine⁴). Esterification with diazomethane gave a glass, $C_{22}H_{32}N_2O_4$, whose mass spectrum showed the molecular ion peak m/e 400 (base peak) and a single prominent fragment ion at m/e 168, a pattern very characteristic of non-lactonic alkaloids of the aspidospermine type.⁹ Reduction of the cleavage product with sodium borohydride gave a zwitterionic product the spectra of whose methyl ester demonstrated that reductive cleavage of the lactone alone had occurred. The mass spectrum of this ester showed a molecular ion at m/e 398, confirming the extent of reduction; the absence of significant fragment ions at m/e 166 and 179 excluded a formulation in which the ethylenic double bond of I is placed at C-6-7.⁹ The position assigned to the double bond is also in better accord with the chemical shift of the C-2 proton and the fine splitting of the olefinic proton signals in the nmr spectrum of I.

The many common features of the spectra of I and those of haplophytine [λ_{max}^{EtOH} 220 $m\mu$ (ϵ 48,500), 265 (14,300), and 305 (4500); $\lambda_{max}^{CHCl_3}$ 5.72 and 6.05 μ ; δ^{CDCl_3} (ppm) 2.40 (~3 H), 3.00 (3 H), 3.17 (3 H), 3.65 (3 H), 3.72 (1 H), 5.55 (1 H, doublet, $J = 10$ cps), 5.85 (1 H, doublet, $J = 10$ cps), 6.27 (1 H, doublet of doublets, $J = 7$ and 2.5 cps), 6.9–7.2 (3 H, multiplet), 9.04 (1 H, absent after D_2O wash)] showed that the structure of haplophytine is related to that of I by replacement of a hydrogen atom in the latter by a moiety $C_{15}H_{16}N_2O_2$. That the linkage is at C-15 as in II is indicated by the absence of a doublet ($J = 8$ cps) in the nmr spectrum of haplophytine corresponding to the C-15 proton signal in the spectrum of I. Catalytic hydrogenation of haplophytine gave tetrahydrohaplophytine, $C_{27}H_{44}N_4O_7$, accompanied by spectral changes analogous to those occurring when I was converted to tetrahydro-I; acid cleavage of the methyl ester of O-methyltetrahydrohaplophytine, $C_{31}H_{48}N_4O_7$, gave tetrahydro-I.

The intensities of the ultraviolet maxima of haplophytine indicated that the $C_{15}H_{16}N_2O_2$ moiety also possesses an indoline system. This can be expanded to a 7-hydroxy-1-acylindoline system on the basis of the relationship between the infrared and nmr spectra of haplophytine and the spectra of its O-substituted derivatives, as earlier deduced by Snyder.^{2,10} The nmr signal at 6.27 ppm, which can be assigned to an aromatic proton coupled with *ortho* and *meta* protons, requires that the 7-hydroxy-1-acylindoline system be unsubstituted at the C-4, -5, and -6 positions. The signal at 2.40 ppm indicated the presence of an aliphatic $N-CH_3$ in the $C_{15}H_{16}N_2O_2$ moiety, while the infrared spectrum showed that the third oxygen atom can only be present in an ether linkage.

(8) K. S. Brown, Jr., W. E. Sanchez L., A. de A. Figueiredo, and J. M. Ferreira Filho, *J. Am. Chem. Soc.*, 88, 4984 (1966).

(9) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 7.

(10) The presence of this second aromatic ring is considered to account for the unusual shielding of the protons of one of the methoxyl groups in haplophytine; in I, where this second ring is absent, the chemical shifts of the protons of both methoxyl groups are normal.

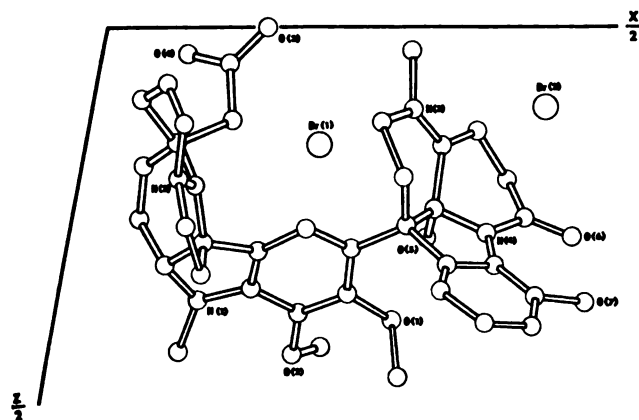
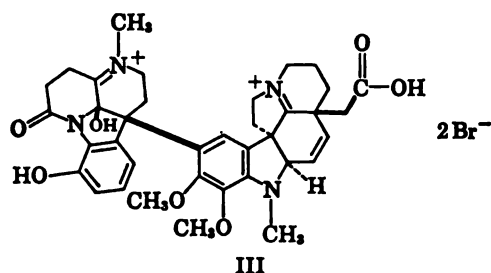


Figure 1.

A single-crystal X-ray diffraction study of haplophytine dihydrobromide revealed the structure shown in III (see Figure 1). The following crystal data were



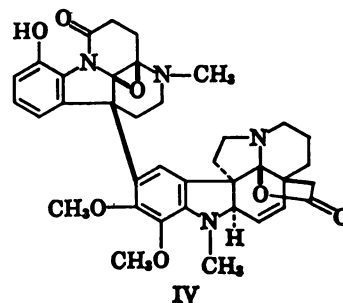
obtained for the dihydrobromide with Cu K α radiation: monoclinic, space group C2, with $a = 25.535$, $b = 7.490$, $c = 18.861$ Å, $\beta = 101^\circ 19'$, $V = 3537.2$ Å³, $Z = 4$, $D_x = 1.530$, $D_m = 1.528$ g/cm³.

Three-dimensional diffraction intensity data were recorded at room temperature on a Picker four-circle automatic diffractometer for 2001 independent reflections. The positions of the bromine atoms in the unit cell were deduced from a three-dimensional Patterson synthesis. After fixing the origin of the unit cell by setting the y coordinate of one of the bromine atoms at zero, the positions of these heavy atoms were used to calculate the phases of the observed structure amplitudes. Successive three-dimensional Fourier syntheses and structure factor calculations progressively disclosed the electron-density distribution of the molecule. The R factor $(\sum ||F_o| - |F_c||) / \sum |F_o|$, is 8.4% with anisotropic temperature factors for the bromine atoms and isotropic for the light atoms excluding hydrogen. The bond distances and angles are within the range of accepted values.

There are two intramolecular hydrogen bonds in the molecule, as indicated by oxygen-oxygen distances of 2.6 Å. One of these is in the 7-hydroxy-1-acylindole system, and the other is between the tertiary alcoholic hydroxyl group and the oxygen atom of the most proximal methoxyl group. The effect of the latter bond is to fix the orientation of the two large moieties with respect to one another in the crystal lattice. The absolute configuration of the molecule was determined by the anomalous dispersion method and is as shown in III and in the accompanying perspective diagram, in which the positive y direction extends out of the page toward the viewer (*i.e.*, conventional right-handed co-

ordinate system). Further refinements of the structure will be reported in detail in due course.

Consideration of structure III in relation to the chemical and spectroscopic properties of haplophytine and the observation that the dihydrobromide is reconverted to the latter at pH 8 lead to the assignment of structure IV to haplophytine. This structure also permits the assignment of structures to the transformation products of haplophytine described earlier.³



Acknowledgment. Acknowledgment is gratefully made by P. Y. to the National Research Council of Canada for a grant which supported this work in part.

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Trimethylenemethane, C(CH₂)₃

Sir:

Theoretical treatments^{1,2} of trimethylenemethane (II) predict a triplet ground state and a high delocalization energy relative to the classical structure of one double bond and two localized electrons. Trimethylenemethane, stable in low-temperature matrixes, has recently been prepared by the photolysis of 4-methylen-1-pyrazoline^{3a} or 3-methylenecyclobutanone,^{3b} and the esr spectrum confirmed a triplet ground state. Trimethylenemethane and its derivatives have been postulated to explain the formation of "rearranged" methylenecyclopropanes in the pyrolyses⁴ or photolyses⁵ of 4-alkylidene-1-pyrazolines and in the thermal isomerization of methylenecyclopropanes.⁶

We have examined the gas-phase reaction of 2-iodomethyl-3-iodopropene (I)⁷ with alkali metal vapor

(1) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 43.

(2) D. P. Chong and J. W. Linnett, *J. Chem. Soc.*, 1798 (1965).

(3) (a) P. Dowd, *J. Am. Chem. Soc.*, **88**, 2587 (1966); (b) P. Dowd and K. Sachdev, *ibid.*, **89**, 715 (1967).

(4) R. J. Crawford and D. M. Cameron, *ibid.*, **88**, 2589 (1966).

(5) (a) A. C. Day and M. C. Whiting, *J. Chem. Soc., Sect. C*, 464 (1966); (b) S. D. Andrews and A. C. Day, *Chem. Commun.*, 667 (1966).

(6) (a) J. K. Crandall and D. R. Paulson, *J. Am. Chem. Soc.*, **88**, 4302 (1966); (b) J. P. Chesick, *ibid.*, **85**, 2720 (1963); (c) E. F. Ullman, *ibid.*, **82**, 505 (1960).

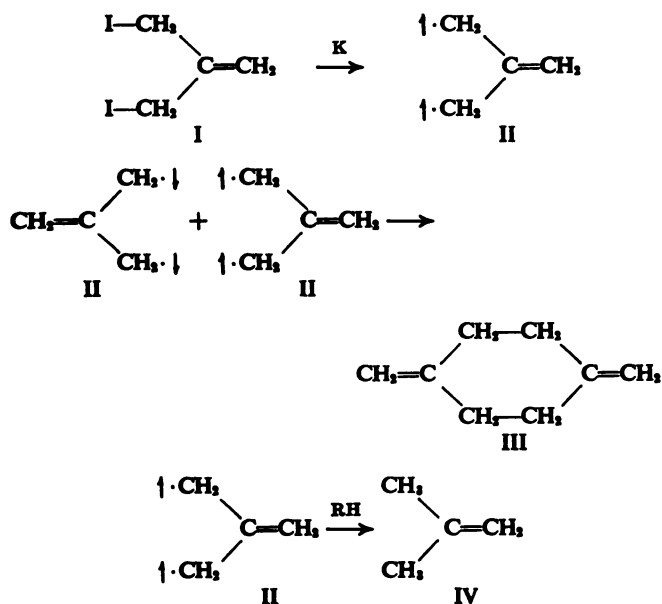
(7) 2-Iodomethyl-3-iodopropene (mp 32–33°, bp 83–85° (10 mm)) was prepared by the reaction of KI in acetone on 2-chloromethyl-3-chloropropene (see ref 8).

as a possible method of generating trimethylenemethane (II). The diiodide I was vaporized and carried in a helium stream, which was then saturated with alkali metal vapor by passage through a fine spray of sodium-potassium alloy (<10 sec in the spray zone) at 228–267°. The products consisted of 1,4-dimethylenecyclohexane (III),⁸ *p*-xylene, isobutene (IV), 1-butene, *cis*- and *trans*-2-butenes, and methylenecyclopropane.⁸

The sum of the yields of III and *p*-xylene remained constant from one reaction to another, totaling about 35%. However, their ratio varied considerably, suggesting that III is converted to *p*-xylene.

The C₄ products, formed in yields of about 30%, were consistently about one-half isobutene. Methylenecyclopropane is partially converted to the straight-chain butenes under the reaction conditions.

The high yields of 1,4-dimethylenecyclohexane and isobutene suggest the intermediacy of triplet-state trimethylenemethane. 1,4-Dimethylenecyclohexane is the expected product from the dimerization of two molecules of trimethylenemethane having opposite spins. Isobutene is also expected, being formed by abstraction of two hydrogen atoms from hydrocarbon or potassium hydride.

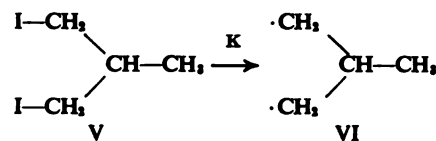


Methylenecyclopropane could result from (1) initial production of singlet trimethylenemethane or (2) ring closure of the triplet species with spin relaxation by contact with an alkali metal atom or a surface.

In contrast to the behavior of trimethylenemethane, the corresponding saturated diradical VI, formed from the reaction of 1,3-diiodo-2-methylpropane (V) with alkali metal vapor at 227–228°, gives methylenecyclopropane, isobutene, and isobutane in yields of 76.7, 3.3, and 0.2%, respectively. 1,4-Dimethylcyclohexane or other products due to dimerization were not detected.

(8) The same products were obtained from 2-chloromethyl-3-chloropropene, but in lower yield. The dichloride was prepared by the method of B. C. Anderson, *J. Org. Chem.*, 27, 2720 (1962), and J. T. Gragson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, 75, 3344 (1953).

(9) 1,4-Dimethylenecyclohexane was identified by comparison of the infrared spectrum and the melting point of its tetrabromide with those given in the literature [F. Lautenschlaeger and G. F. Wright, *Can. J. Chem.*, 41, 1972 (1963)]. The nmr spectrum had two singlets at 2.20 and 4.64 ppm in a respective ratio of 2:1.



Extensive studies^{10,11} of 1,2-, 1,3-, 1,4-, and 1,5-diradicals testify to the insignificance of bimolecular reactions, such as dimerization and disproportionations, in competition with unimolecular ring closure and rearrangement.

Although the reaction of 2-iodomethyl-3-iodopropene with alkali metal vapor is a two-step process, formation of 1,4-dimethylenecyclohexane cannot be due to the coupling of two monoiodo radicals. If this were the case, the saturated diiodide would also give dimeric material.¹² Hence, the preference for the bimolecular formation of 1,4-dimethylenecyclohexane and isobutene rather than the unimolecular formation of methylenecyclopropane is due to the greater stability, the greater reluctance to internal cyclization, and the longer lifetime of triplet trimethylenemethane relative to the saturated 1,3-diradical.

The failure to isolate the trimethylenemethane dimers by the pyrolysis⁴ or photolysis⁵ of 4-alkylidene-1-pyrazolines, or the pyrolysis of methylenecyclopropanes,⁶ indicates that either the concentration of triplet trimethylenemethane was too low for bimolecular coupling to be observed or that triplet trimethylenemethane was not an intermediate in these reactions. Dimerization would be the expected reaction of the triplet molecule, formation of methylenecyclopropanes for the singlet. Theoretical considerations support these conclusions.¹³

Triplet tetramethylcyclobutadiene (VII) has been proposed as an intermediate in the reaction of *cis*-3,4-dichlorotetramethylcyclobutene and alkali metal vapor.¹⁴ It would thus be expected that reaction of a mixture of this dichloride and 2-iodomethyl-3-iodopropene with alkali metal vapor would lead to the simultaneous production of triplet tetramethylcyclobutadiene (VII) and trimethylenemethane (II), which could then couple to produce 3-methylene-1,5,6,7-tetramethylbicyclo[3.2.0]heptene (VIII).¹⁵ The experiment yielded, in addition to the expected products from the individual reactions of II and VII, a single cross-coupling product VIII, in 7% yield based on either reactant. This result suggests that both trimethylenemethane and tetramethylcyclobutadiene had the same electronic state, triplet. Had trimethylenemethane

(10) E. J. Goldstein, Ph.D. Thesis, The Pennsylvania State University, 1964; R. J. Petersen, Ph.D. Thesis, The Pennsylvania State University, 1964.

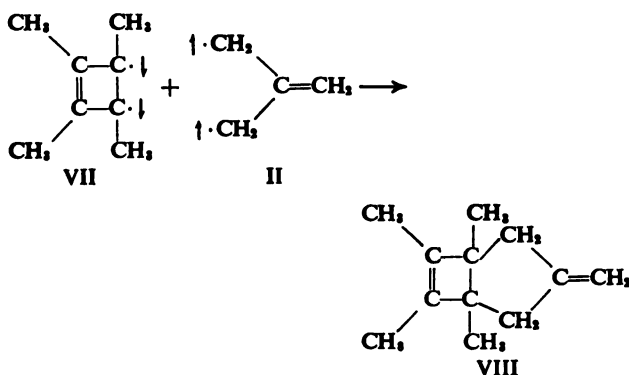
(11) R. J. Crawford and A. Mishra, *J. Am. Chem. Soc.*, 88, 3963 (1966).

(12) Iodoalkanes react at nearly every collision with atomic sodium [E. Warhurst, *Quart. Rev. (London)*, 5, 44 (1951)]. Since the iodine atoms in the precursor to trimethylenemethane are both allylic, they should react as fast or slightly faster than those in the saturated diiodide. Consequently, the rate of formation of trimethylenemethane is as great as or greater than the rate of formation of the saturated diradical.

(13) W. T. Borden, *Tetrahedron Letters*, 259 (1967).

(14) P. S. Skell and R. J. Petersen, *J. Am. Chem. Soc.*, 86, 2530 (1964).

(15) The cross-coupling product VIII was identified on the basis of the following evidence: the mass spectrum had a parent peak at *m/e* 162 corresponding to the formula C₈H₁₄; the infrared spectrum showed absorbances at 5.91 (cyclobutene double bond), 7.28 (methyl group), 3.30, 6.00, and 11.35 μ (terminal methylene group); the nmr spectrum consisted of singlets at 1.02 and 1.41 ppm and multiplets centered at 2.00 and 4.64 ppm in ratio of 3:3:2:1, respectively.



added to a singlet tetramethylcyclobutadiene, the resulting triplet adduct would not have been expected to give only a single cross-coupling product, but rather a number of monocyclic compounds *via* reduction, or internal or external disproportionation. Therefore the cross-coupling product VIII was formed in a one-step process involving the simultaneous formation of both bonds. The analogous bicyclic product¹⁶ was obtained using *cis*-3,4-dichlorocyclobutene¹⁷ and 2-chloromethyl-3-chloropropene, thus implicating a triplet cyclobutadiene intermediate.

The combined observations indicate that trimethyl-enemethane was produced and that it exists in a relatively stable triplet state, as predicted by theoretical calculations and in agreement with the esr results.

(16) 3-Methylenebicyclo[3.2.0]hept-6-ene was identified on the basis of the following spectral evidence: the mass spectrum had a parent peak at m/e 106 corresponding to the formula C_8H_{10} ; the infrared spectrum showed absorption bands at 3.29 (vinyl hydrogen), 5.93 (cyclobutene double bond), 6.00, and 11.15 μ (terminal methylene group); the nmr spectrum consisted of a singlet at 5.91 ppm and multiplets at 4.83, 3.20, and 2.12 ppm in a ratio of 1:1:1:2, respectively.

(17) A generous sample of *cis*-3,4-dichlorocyclobutene was furnished by Professor C. D. Nenitzescu.

(18) This work was supported by the National Science Foundation.

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A Simple Floating Localized Orbital Model of Molecular Structure

Sir:

Most molecules have an even number of electrons which are generally paired off to create a ground state which is a spectroscopic singlet. For such molecules and states the following quantum mechanical model is proposed.

Let there be a minimal set of n floating localized orbitals φ_i which are, in general, nonorthogonal and real, and let each one be occupied by a pair of electrons with opposing spin. The $2n$ -electron wave function can then be written as a single normalized Slater determinant

$$\psi = |\varphi_1(1)\bar{\varphi}_1(2)\varphi_2(3)\bar{\varphi}_2(4)\dots\varphi_n(2n-1)\bar{\varphi}_n(2n)|$$

$$[1/(\sqrt{(2n)!} \det S)]$$

where the bars over certain orbitals indicate β spin as opposed to α for the others, and $\det S$ is the determinant of the orbital overlap matrix S with elements

$$S_{ij} = \int \varphi_i^* \varphi_j d\tau$$

Given the set of orbitals and the appropriate nonrelativistic Hamiltonian operator H , the mean energy E is calculated according to a formula adapted from one derived by Löwdin¹

$$E = \int \psi^* H \psi d\tau = 2 \sum_{i,j} (ij|f) T_{ij} + \sum_{i,j,k,l} (ij|kl) (2T_{ij}T_{kl} - T_{il}T_{jk})$$

where

$$(ij|f) = \int \varphi_i^* h \varphi_j d\tau$$

are the kinetic and potential energy integrals with the one-electron operator h , and

$$(ij|kl) = \int \varphi_i^*(1)\varphi_j(1)\varphi_k^*(2)\varphi_l(2)(1/r_{12}) d\tau(1)d\tau(2)$$

are the electron repulsion energy integrals. T_{ij} 's are elements of the reciprocal orbital overlap matrix

$$T = S^{-1}$$

For a given set of nuclear coordinates E is minimized, according to the variation method, by a variation in parameters defining the orbitals. This will generate a potential energy surface. If a "full minimization" of E with respect to nuclear coordinates as well as orbital parameters is carried out, then the equilibrium configurations of the molecule will be predicted. The calculation is strictly *ab initio* with no semiempirical parameters.

In this simple model the orbitals are taken to be floating spherical Gaussian functions²

$$\varphi_i = (2/\pi\rho_i^2)^{1/4} \exp[-(r_i/\rho_i)^2]$$

where r_i is the radial distance from the center of the orbital and ρ_i is an "orbital radius" parameter which defines a sphere which includes about 74% of the orbital charge density. For each orbital the coordinates of the center as well as the orbital radius are parameters to be varied.

Minimization of E with respect to all parameters will automatically lead to a result which will satisfy both the virial theorem and the Hellmann-Feynman theorem.³

Table I presents typical results for a series of diatomic and polyatomic molecules by the full minimization procedure.

The calculated energies are, of course, well above experimental values since no electron correlation is included other than that between electrons of like spin due to the antisymmetrization inherent in the determinantal wave function. Also the energies must be higher than those of Hartree-Fock calculations since the latter are by definition the values obtained by all possible variations of the orbitals in a single determinantal wave function. Because the total energies are crude, it would be expected that dissociation energies would be unsatisfactory and no attempt has been made to calculate them.

(1) P.-O. Löwdin, *J. Chem. Phys.*, **18**, 365 (1950).

(2) S. F. Boys, *Proc. Roy. Soc. (London)*, **A200**, 542 (1950), introduction of gaussian orbitals; H. Preuss, *Z. Naturforsch.*, **11a**, 823 (1956); **19a**, 1335 (1964); **20a**, 18, 21, 1290 (1965); J. L. Whitten, *J. Chem. Phys.*, **39**, 349 (1963); **44**, 359 (1966); J. L. Whitten and L. C. Allen, *ibid.*, **43**, S170 (1965), use of off-center spherical Gaussian "pure" or "lobe" functions to simulate nonspherical atomic orbitals.

(3) A. C. Hurley, *Proc. Roy. Soc. (London)*, **A226**, 170, 176, 193 (1954).

Table I. Calculated Energies and Bond Lengths According to the Floating Localized Orbital Model with Spherical Gaussian Functions

Molecules	Negative total energy (hartrees)		Bond length, Å	
	This work	Hartree-Fock	Calcd	Obsd ^a
H ₂	0.956	1.1336 ^a	0.780	0.741
LiH	6.572	7.9851 ^b	1.712	1.595
Li ₂	12.282	14.8718 ^c	2.807	2.672
HF	84.635	100.0580 ^d	0.779	0.917
		(min at R = 0.920 Å)		
BeH ₂ linear	13.214		1.412	
BH ₃ planar D _{3h}	22.297	26.2358 ^e (min at R = 1.16 Å)	1.245	1.19 (av)
CH ₄ tetrahedral	33.992	39.8660 ^f (min at R = 1.10 Å)	1.115	1.093
NH ₃ pyramidal C _{3v}	47.568	55.9748 ^g (min. at R = 1.04 Å)	1.008	1.012
			1.489	...
H ₂ O angular C _{2v}	64.290	75.9224 ^h (min at R = 0.963 Å)	0.880	0.957
			1.621	...
linear C ₂ H ₂	64.203		1.210	1.205
linear, sym	64.684	76.7916 ⁱ	C≡C 1.073 C=H 1.350	1.059 1.337
C ₂ H ₄ planar, D _{2h}	65.836	78.0012 ^j	C=C 1.104 C-H 1.085	1.085

^a W. Kolos and C. C. J. Roothaan, *Rev. Mod. Phys.*, **32**, 205 (1960). ^b D. D. Ebbing, *J. Chem. Phys.*, **36**, 1361 (1962). ^c P. E. Cade and A. C. Wahl, quoted by G. Das, *ibid.*, **46**, 1568 (1967). ^d E. Clementi, *ibid.*, **36**, 33 (1962). ^e B. D. Joshi, *ibid.*, **46**, 875 (1967). ^f R. Moccia, *ibid.*, **37**, 910 (1962); **40**, 2164, 2176, 2186 (1964). ^g R. J. Buenker, S. D. Peyerimhoff, and J. L. Whitten, *ibid.*, **46**, 2029 (1967). ^h Observed values are taken from L. E. Sutton, Ed., "Interatomic Distances," Special Publication No. 18, The Chemical Society, London, 1965.

The calculated bond lengths are surprisingly close to the experimental values, on the average within 4.4%. Considering the crudeness of the model no such direct quantitative similarity would be expected. However, the model should give general trends which certainly are present.

Bond angles are not as successfully calculated although NH₃ and H₂O are properly predicted to be pyramidal and bent, respectively. The angles are: H-N-H, 88.0° (obsd 106.6°); and H-O-H, 89.5° (obsd 104.5°).

Dipole moments (Debyes) are calculated to be: LiH, 6.56 (obsd 5.882); HF, 1.66 (obsd 1.98); H₂O, 1.92 (obsd 1.84); and NH₃, 1.71 (obsd 1.46).

LiH is a simple example which shows how the orbital parameters behave. One orbital turns out to have a small "radius," ρ , equal to 0.707 bohr and is located 0.0076 bohr from the Li nucleus on the side opposite from the proton. This can be considered an inner-shell Li orbital. The other orbital has a radius of 2.44 bohrs and is located about 89% of the way from Li to H. The bond could therefore be interpreted to be predominantly ionic.

This model has a simpler relation to the original electron pairing and shared pair concepts of Lewis⁴

than does the quantum mechanical valence bond method since the present model uses only one orbital per electron pair bond instead of two. It is also related to molecular orbital theory through the use of a single determinantal wave function. Localized molecular orbitals have been discussed particularly by Lennard-Jones and co-workers⁵ and by Edmiston and Ruedenberg.⁶

This model constitutes an extension of the Kimball-Neumark⁷ spherical Gaussian orbital model which was applied by Neumark to the simple systems He and H₂. The "charge cloud" model of Kimball⁷ which conceives of uniformly charged spheres for electron pairs resembles the present model but does not allow for overlap of the spheres and is only pseudo-quantum mechanical. Likewise the tangent-sphere model of Bent⁸ and related ideas of King,⁹ although giving considerable qualitative insight into molecular structure, are not sufficient for quantitative calculations. Details of the calculations and additional results will be published elsewhere.

Acknowledgment. This research has been supported by a grant from the National Science Foundation to Northwestern University.

(4) G. N. Lewis, *J. Am. Chem. Soc.*, **38**, 762 (1916); "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., New York, N. Y., 1923.

(5) J. E. Lennard-Jones, *Proc. Roy. Soc. (London)*, **A198**, 1, 14 (1949); G. G. Hall and J. E. Lennard-Jones, *ibid.*, **A202**, 155 (1950); J. E. Lennard-Jones and J. A. Pople, *ibid.*, **A202**, 166 (1950); A. C. Hurley, J. E. Lennard-Jones, and J. A. Pople, *ibid.*, **A220**, 446 (1953).

(6) C. Edmiston and K. Ruedenberg, *Rev. Mod. Phys.*, **35**, 457 (1963).

(7) Ph.D. Dissertations by G. F. Neumark, L. M. Kleiss, H. R. Westerman, and J. D. Herniter, Columbia University; reviewed by J. R. Platt in "Encyclopedia of Physics," Vol. 37, Part 2, S. Flügge, Ed., Springer-Verlag, Berlin, 1961, p 258.

(8) H. A. Bent, *J. Chem. Educ.*, **40**, 446, 523 (1963); **42**, 302, 348 (1965).

(9) L. C. King, *Chemistry*, **37**, 12 (1964).

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The Coordination Number of Aluminum(III) in Liquid Ammonia¹

Sir:

Various nmr techniques²⁻⁴ have been used to determine hydration numbers of ions in aqueous solutions. We have attempted to extend these methods to liquid ammonia and wish to report the results for Al(III) solutions. The method used was to determine the area under the ¹⁴N nmr absorption line in the species Al(NH₃)₂³⁺ after broadening the solvent line beyond detection by addition of Cu(II). The exchange of bound ammonia in the Cu(II) complex is very rapid.⁵ The area measurements were calibrated using various known species.

(1) Report No. RLO-1031-6 of work supported by the U. S. Atomic Energy Commission.

(2) J. A. Jackson, J. F. Lemons, and H. Taube, *J. Chem. Phys.*, **33**, 553 (1960).

(3) R. E. Connick and D. N. Fiat, *ibid.*, **38**, 1349 (1963).

(4) D. N. Fiat and R. E. Connick, *J. Am. Chem. Soc.*, **88**, 4754 (1966).

(5) J. P. Hunt, H. W. Dodgen, and F. Klanberg, *Inorg. Chem.*, **2**, 478 (1963).

Anhydrous aluminum iodide was prepared by standard methods and dissolved in anhydrous ammonia which was also prepared and handled by standard techniques. The Al(III) concentration was ca. 1.35 M. In other experiments it had been found that addition of $\text{Cu}(\text{NH}_3)_4(\text{NO}_3)_2$ to the extent of ca. 0.2 M broadened the solvent ammonia line beyond detection (the bound ammonia line and solvent line occur at essentially the same frequency) and that Cu(II) and I⁻ were stable in ammonia. Addition of the Cu(II) nitrate salt caused precipitation of some Al(III) the amount of which was determined, and an appropriate correction was made. The ^{14}N nmr absorption line for the bound ammonia (and references) was measured at ca. 9300 gauss using equipment previously described.⁶ The areas under the curves were measured in various ways and compared with areas obtained for standard aqueous NaNO_3 , $\text{Co}(\text{NH}_3)_6^{3+}$ in ammonia, $\text{Co}(\text{NH}_3)_6 \cdot \text{H}_2\text{O}$ in water, and others. The known solutions gave internally consistent results and were chosen to give line widths and intensities comparable to that found for the Al(III) species. This was done so that all the nmr measurements could be made under essentially identical conditions of radiofrequency level, modulation amplitude, etc. The full width at half-maximum absorption for the bound ammonia line was 1.35 ± 0.14 gauss at 27°. The coordination number of Al(III) was found to be 6.03 ± 0.45 (as an average of four signals).

We were unable to shift the solvent line sufficiently to be useful using either Cu(II) (which produces relatively small shifts) or Co(II) without causing excessively large amounts of broadening. Dysprosium nitrate was found to be too insoluble in ammonia to be useful for shifting the solvent line.

The results imply a relatively long lifetime for the $\text{Al}(\text{NH}_3)_6^{3+}$ species in ammonia consistent with the results of Sutter and Hunt⁷ using ^{15}N tracer techniques. A coordination number of six was also found for the hydrated species.³ The precision of the measurements was limited because of the broad, weak signals involved. Attempts to measure solvation number for Be(II) and Ga(III) have failed so far because of solubility problems. The use of ^{15}N and improved nmr equipment may make it possible to study other species in the future.

(6) H. H. Glaeser, G. A. Lo, H. W. Dodgen, and J. P. Hunt, *Inorg. Chem.*, **4**, 206 (1965).

(7) J. R. Sutter and J. P. Hunt, *J. Am. Chem. Soc.*, **82**, 6420 (1960).

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Oxidation of Coordinated Ligands.

Sulfato and Nitrato Complexes of Platinum

Sir:

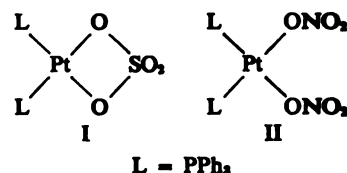
During the recent upsurge in interest in the behavior of d^{10} and d^8 complexes, a variety of working models have been suggested in an attempt to rationalize and predict the chemistry of these species.^{1,2} Recently

(1) C. D. Cook and G. S. Jauhal, *Inorg. Nucl. Chem. Letters*, **3**, 31 (1967).

(2) J. P. Collman and J. W. Kang, *J. Am. Chem. Soc.*, **88**, 3459 (1966).

we have inclined strongly to the view that the behavior in solution of the zerovalent complexes $\text{M}(\text{PPh}_3)_4$ ($\text{M} = \text{Ni}, \text{Pd}, \text{Pt}$) is essentially that of solvated metal atoms. The characteristics¹ of the oxygen and ethylene complexes, $(\text{PPh}_3)_2\text{PtO}_2$ and $(\text{PPh}_3)_2\text{Pt}(\text{C}_2\text{H}_4)$, helped to reinforce this concept and prompted an investigation under homogeneous conditions² of those reactions in which platinum has traditionally served as a heterogeneous catalyst; e.g., the contact process.

Passage of SO_2 into a solution of $(\text{PPh}_3)_2\text{PtO}_2$ at room temperature results in the rapid formation of an air-stable complex which we believe to be the sulfato complex I. Anal. Calcd for $\text{C}_{36}\text{H}_{30}\text{O}_4\text{P}_2\text{S}\text{Pt}$: C, 53.00; H, 3.68; mol wt, 815. Found: C, 52.92; H, 3.66; mol wt, 795.



The infrared spectrum (Nujol) shows four strong bands with some splitting at 1279, 1165 and 1150, 880 and 871, and 650 cm^{-1} , which is in accord with the symmetry of the SO_4 group acting as a bidentate ligand (C_{2v}) and is in reasonable agreement with the spectrum reported by Barraclough and Tobe⁴ for the complex $[\text{Co}(\text{en})_2\text{SO}_4]\text{Br}$, one of the few monomeric complexes known to contain bidentate sulfate. The possibility of a sulfur-bonded sulfito complex⁵ cannot be ruled out in terms of the number of bands observed, but is, we feel, unlikely in view of the high frequency of the band which we assign to the asymmetric S-O stretch (1279 cm^{-1}). Reaction between SO_2 and a solution of the ethylene adduct, $(\text{PPh}_3)_2\text{Pt}(\text{C}_2\text{H}_4)$, results in displacement of ethylene and formation of a brown crystalline complex⁶ which loses SO_2 readily on warming (50°) to yield the air-stable, green complex $(\text{PPh}_3)_2\text{Pt}(\text{SO}_4)$. Anal. Calcd for $\text{C}_{36}\text{H}_{30}\text{O}_4\text{P}_2\text{S}\text{Pt}$: C, 55.17; H, 3.83; S, 4.09. Found: C, 54.92; H, 3.94; S, 4.68. Two strong infrared bands (Nujol) are found at 1182 and 1149 and 1035 cm^{-1} , resulting from asymmetric and symmetric S-O stretching vibrations. The spectrum is strongly indicative of a sulfur-bonded SO_2 adduct, and the complex is presumably of a similar type to $(\text{SO}_2)\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ recently reported by Vaska.⁷ Passage of oxygen through a solution of the green SO_2 adduct, or heating the complex in air (110°), results in the formation of the sulfato complex already described.

Similar results are obtained when the oxygen adduct is treated with NO_2 , the dinitrato complex (II) being obtained pure and in high yield. Anal. Calcd for $\text{C}_{36}\text{H}_{30}\text{N}_2\text{O}_6\text{P}_2\text{Pt}$: C, 51.25; H, 3.56; N, 3.32. Found: C, 51.43; H, 3.65; N, 3.16. The complex

(3) It has recently been shown by G. Wilke, H. Schott, and P. Heinbach, *Angew. Chem. Intern. Ed. Engl.*, **6**, 92 (1967), that a solution of complex $(\text{PPh}_3)_2\text{NiO}_2$ functions as a catalyst for the oxidation of triphenylphosphine.

(4) C. G. Barraclough and M. L. Tobe, *J. Chem. Soc.*, 1993 (1961).

(5) G. Newman and D. B. Powell, *Spectrochim. Acta*, **19**, 213 (1963).

(6) We have learned of closely related experiments by J. I. Levison and S. D. Robinson, *Chem. Commun.*, 198 (1967), following submission of this paper. They report the preparation of the brown, apparently four-coordinated adduct, $(\text{PPh}_3)_2\text{PtSO}_2$, and its ready oxidation to the sulfato complex, $(\text{PPh}_3)_2\text{PtSO}_4$, described herein.

(7) L. Vaska and S. S. Bath, *J. Am. Chem. Soc.*, **88**, 1333 (1966).

absorbs strongly at 1502 and 1491, 1272 and 1263, 974, and 787 cm^{-1} in the infrared (Nujol) and is evidently comparable to a series of four-coordinate dinitrato complexes reported by Bannister and Cotton.⁸

The dinitrato complex is decomposed rapidly by boiling water with the liberation of nitrate ion; the sulfato complex is considerably more resistant to hydrolysis, but reaction with cyanide ion results in displacement of the coordinated sulfate group and formation of a cyano complex of Pt(II) (infrared band at 1332 cm^{-1}).

The mechanistic aspects of some of these reactions are currently receiving attention.

Acknowledgment. We thank the National Research Council of Canada and Engelhard Industries (Canada) Ltd. for their support.

(8) E. Bannister and F. A. Cotton, *J. Chem. Soc.*, 2276 (1960).

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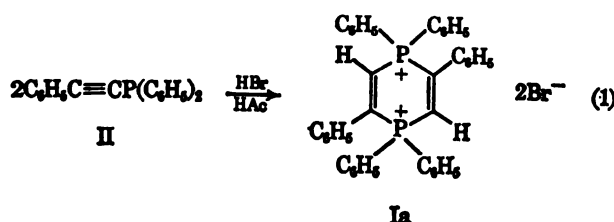
Delocalization of the π -Electron System in 1,4-Dihydrophospha(V)pyrazines

Sir:

The nature of π -electron delocalization in the phosphonitrilic system has been the subject of some controversy.^{1,2} The few cyclic phosphorus-carbon six- π -electron systems capable of 3d-2p π delocalization thus far synthesized have been rather unstable.^{3,4}

We wish to report the synthesis of a stable 1,4-dihydrophospha(V)pyrazine in which there appears to be delocalization of the four π electrons over the phosphorus atoms.

We have isolated 1,1,2,4,4,5-hexaphenyl-1,4-diphosphoniacyclohexadiene-2,5 dibromide (Ia) in over 60% yield from the 100-hr reaction of phenylethynyl-diphenylphosphine⁵ (II) with hydrogen bromide in glacial acetic acid at room temperature (eq 1). The orange solid



Ia melted at 286–290° (from ethyl acetate-methanol). *Anal.* Calcd for $\text{C}_{40}\text{H}_{32}\text{P}_2\text{Br}_2 \cdot \text{H}_2\text{O}$: C, 63.83; H, 4.52; P, 8.24; Br, 21.28. Found: C, 63.85; H, 4.49; P, 8.30; Br, 21.05.

The water solubility, the infrared spectrum, and the fact that it gives an immediate yellow precipitate (Ib)

(1) D. P. Craig and N. L. Paddock, *Nature*, **181**, 1052 (1958); *J. Chem. Soc.*, 4118 (1962).

(2) M. J. S. Dewar, E. A. C. Lucken, and M. A. Whitehead, *ibid.*, 2423 (1960).

(3) G. Markl, *Angew. Chem.*, **75**, 168 (1963); **75**, 669 (1963); *Z. Naturforsch.*, **18b**, 1136 (1963).

(4) E. A. Cookson and P. C. Crofts, *J. Chem. Soc., Sect. C*, 2003 (1966).

(5) W. Chodkiewicz, P. Cadiot, and A. Willemant, *Compt. Rend.*, **250**, 866 (1960); K. Issleib and G. Harzfeld, *Chem. Ber.*, **95**, 268 (1962).

when treated with aqueous sodium picrate show that Ia is a phosphonium salt.

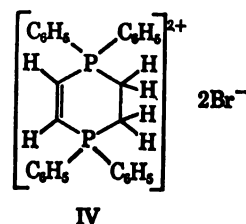
Elemental analysis establishes Ia as a 1:1 adduct of II and HBr, i.e., $[(\text{C}_6\text{H}_5)_2\text{PC}\equiv\text{CC}_6\text{H}_5 \cdot \text{HBr}]_n$, while the lack of covalently bound bromine in the adduct is deduced from the analysis of the picrate Ib, mp 245–248° (from acetonitrile). *Anal.* Calcd for $\text{C}_{82}\text{H}_{66}\text{N}_6\text{O}_{14}\text{P}_2$: C, 60.58; H, 3.50; N, 8.16; Br, 0.00. Found: C, 60.50; H, 3.37; N, 8.14; Br, 0.00.

Table I*

Compd	Protons	Multiplicity	$J_{\text{P-H}}$, cps	τ , ppm	Area ratio
Ia	Vinyl	Broad complex		0.60	1
				1.04	
				1.5	
IIIa	Phenyl-P	Complex		2.0	10
	Phenyl-C	1		2.38	5
	CH	Complex		~4.6	1
	Phenyl	Complex		~2.2	15
	CH ₂	Complex		~5.6	2
IV	Vinyl	Broad complex		1.00	1
				1.42	
				1.84	
	Phenyl-P	Complex		2.15	10
	CH ₂	2 (broad)	8.0	6.11	2

* Proton nmr at 60 Mc/sec employing tetramethylsilane as an internal standard and trifluoroacetic acid as solvent.

The proton nmr spectrum of a trifluoroacetic acid solution of Ia at 60 Mc (Table I) shows two sharp peaks at τ 0.6 and 1.5 with a shallow broad complex centered between them. This is similar to the proton nmr spectrum of 1,1,4,4-tetraphenyl-1,4-diphosphoniacyclohexene-2 dibromide (IV)⁶ (Table I). These data



fit a polymeric vinylenebis(diphenylphosphonium) bromide.



Furthermore, the melting point and complete absence of covalently bound bromine strongly suggest a cyclic structure in which n is not very large.

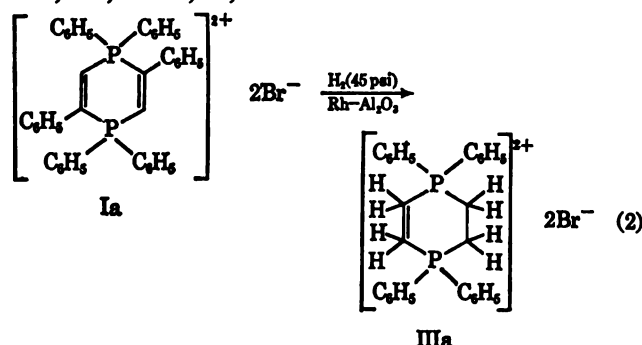
Osmotic pressure depression of methanol solutions of Ia over a range of concentrations (Table II) showed that association occurs at higher concentrations and that the effective molecular weight, obtained by extrapolation, approaches the value of 245 (where $n = 2$).

Table II. Molecular Weight Determination of Ia in Methanol Solution by Osmometric Method

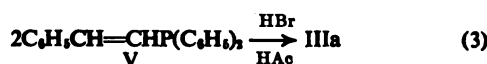
mg/ml	Concentration		Mol wt
		M	
9.470		0.0320	296
5.995		0.0212	283
3.280		0.0123	267

(6) A. M. Aguiar and H. J. Aguiar, *J. Am. Chem. Soc.*, **88**, 4090 (1966).

Hydrogenation of Ia employing 5% rhodium on alumina at 45 psi in methanol gave colorless 1,1,2,4,4,5-hexaphenyl-1,4-diphosphoniacyclohexane dibromide (IIIa), mp 269–272° (from acetonitrile-methanol). *Anal.* Calcd for $C_{40}H_{48}Br_2P_2 \cdot H_2O$: C, 63.49; H, 5.03; Br, 21.16; P, 8.70. Found: C, 63.33; H, 4.89; Br, 20.40; P, 8.77.



Compound IIIa was also produced by the reaction of *cis*- or *trans*- β -styryldiphenylphosphines⁷ (V) with hydrogen bromide in glacial acetic acid (eq 3). As in



the case of Ia, the structure of IIIa was established through elemental analysis, solubility, infrared spectrum, formation and analysis of a picrate (IIIb), and proton nmr spectra (Table I).

Compound IIIb had mp 230–233° (from acetonitrile). *Anal.* Calcd for $C_{42}H_{40}N_6O_{14}P_2$: N, 8.12; Br, 0.00. Found: N, 8.00; Br, 0.00. Absorption in the visible region by Ia is not understandable in terms of the delocalization present in a β -styryldiphenylphosphonium salt since the benzyl bromide salts of *cis*- and *trans*- β -styryldiphenylphosphine (VI) are colorless.

Table III lists the ultraviolet absorbances of Ia and IIIa, along with those of *cis*- and *trans*-VI for comparison. Only a shoulder from the ultraviolet region was found in the visible spectrum of Ia.

Table III. Ultraviolet Absorptions of Methanol Solutions

Compd	λ , m μ	ϵ
Ia	267 (peak emerging from large shoulder)	18,600
IIIa	269 (shoulder covering the 218 region)	4,600
<i>cis</i> -VI	270	1,100
	218	2,400
<i>trans</i> -VI	278	2,500
	217	3,000

Support for extensive delocalization of the π cloud is obtained from the ^{31}P nmr data listed in Table IV.

Table IV*

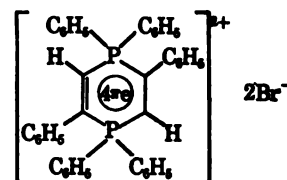
Compd	Shift
Ia	+3.5
IIIa	-20.4
IV	-2.8
<i>cis</i> -VI	-13.0

* At 40.5 Mc/sec; ^{31}P nmr shifts in parts per million of methanol solutions relative to an external standard of 85% H_3PO_4 .

(7) A. M. Aguiar and T. G. Archibald, *Tetrahedron Letters*, 45, 5541 (1966).

It is seen that the shielding of the phosphorus nucleus is substantially greater in Ia than in any other model compounds. In fact, Ia represents the first report of a phosphonium salt with a positive ^{31}P nmr shift. Most simple phosphonium salts display ^{31}P shifts in the -20- to -30-cps region.^{8,9}

The above data are most easily accommodated by assuming delocalization of the π -electronic charge over the phosphorus atoms.



Acknowledgment. This work was supported by National Science Foundation Grant No. GP-3823.

(8) M. M. Crutchfield, Monsanto Co., St. Louis, Mo., private communication.

(9) NASA Fellow, 1964–1967.

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Heavy-Atom Solvent Effect on the Photodimerization of Acenaphthylene

Sir:

Owing to their ability to enhance spin-orbit coupling, heavy-atom solvents have been used extensively in the study of singlet-triplet absorption and emission spectra.¹ In addition to an effect on the radiative processes, it is known that these solvents often promote nonradiative singlet-to-triplet intersystem crossing.¹ Two recent studies have attempted to make use of this external heavy-atom effect to affect increased intersystem crossing in photochemical reactions. However, no change was observed when heavy-atom solvents were used in a study of the type II photoelimination reactions of aliphatic ketones,² nor was an effect observed in the photodimerization of coumarin.⁴ Both of these systems contain $n-\pi^*$ excited states. El-Sayed⁵ has pointed out that in carbonyl compounds the spin-orbit perturbation due to the carbonyl group is comparable to or larger than an internal heavy-atom perturbation due to halogen substitution on the carbonyl-containing molecule. In addition, the internal heavy-atom perturbation is expected to be much larger than the external perturbation due to a heavy-atom solvent.

In this note we wish first to present evidence to document the heavy-atom solvent effect on the photodimerization of a system not containing $n-\pi^*$ states and second to show that in the two cases easily com-

(1) D. S. McClure, *J. Chem. Phys.*, 17, 905 (1949); M. Kasha, *ibid.*, 20, 71 (1952); S. P. McGlynn, T. Azumi, and M. Kasha, *ibid.*, 40, 507 (1964); R. F. Borkman and D. R. Kearns, *Chem. Commun.*, 446 (1966).

(2) A. R. Horrocks, T. Medinger, and F. Wilkinson, *Photochem. Photobiol.*, 6, 21 (1967); S. P. McGlynn, J. Daigre, and F. J. Smith, *J. Chem. Phys.*, 39, 675 (1963); S. Siegel and H. S. Judelkis, *ibid.*, 42, 3060 (1965).

(3) P. J. Wagner, *ibid.*, 45, 2335 (1966).

(4) H. Morrison, H. Curtis, and T. McDowell, *J. Am. Chem. Soc.*, 88, 5415 (1966).

(5) M. A. El-Sayed, *ibid.*, 41, 2462 (1964).

pared that the effect is proportional to the square of the spin-orbit coupling factor (ζ^2).

It has been shown^{6,8a} that the *cis* and *trans* dimers from the photolysis of acenaphthylene arise from two distinct excited states. The *cis* dimer is formed predominantly *via* an excited singlet state or more probably from a singlet excimer, while the *trans* dimer is formed *via* the triplet state. Since the probability of a singlet-triplet transition resulting from spin-orbit coupling depends inversely upon the square of the energy separation between the two states, one would expect a greater probability of crossing from a perturbed excited singlet to the triplet state than from the triplet to the ground state. Therefore, in the acenaphthylene system an increased triplet yield should result in an increased conversion to the *trans* isomer. The results of our experiments are shown in Table I. All photolyses were carried out using the apparatus and analytical procedure previously described.⁶ As can be seen in Table I, both the total conversion to products and the relative amount of the *trans* dimer produced are markedly affected by the presence of a heavy atom in the solvent. For example, a change from pure cyclohexane to cyclohexane containing 10 mole % ethyl iodide increased, by a factor of 2, the total conversion and produced an 11-fold increase in the amount of *trans* dimer formed.⁷ The amount of *trans* produced in propyl bromide solvents was found to be linearly dependent upon the mole per cent of propyl bromide for percentages where the total amount of conversion did not appreciably affect the probability of bimolecular reaction.

Table I. Heavy-Atom Solvent Effect on Photodimerization of Acenaphthylene

Solvent ^a	Total amount of dimer formed, g	Acenaphthylene recovered, g	<i>trans</i> , g	<i>cis</i> , g
Cyclohexane	6.51	8.40	1.09	5.42
Benzene	9.62	5.27	2.82	6.80
<i>n</i> -Butyl chloride	7.14	7.76	2.12	5.02
<i>n</i> -Propyl bromide in cyclohexane				
10 mole %	5.98	9.05	3.45	2.53
25 mole %	8.03	7.01	5.03	3.00
50 mole %	10.99	4.05	7.49	3.50
100 mole %	14.07	0.84	10.01	4.06
10% Ethyl iodide in cyclohexane	13.74	1.14	10.96	2.78

^a All determinations were made with 15.2 g of acenaphthylene in 150 ml of solvent; irradiation time 15 hr.

The probability of a radiationless transition is proportional to the square of the perturbing operator in an expectation value equation involving the two states between which the transition is occurring. For transitions between states of different multiplicity, vibronic and/or spin-orbit perturbation operators are important.

(6) D. O. Cowan and R. L. Drisko, *Tetrahedron Letters*, 1255 (1967); D. O. Cowan, "Photochemistry: Recent Developments and Applications," Symposium, Houston, Texas, Feb 17, 1967; R. Livingston and K. S. Wei, *J. Phys. Chem.*, 71, 541 (1967).

(6a) NOTE ADDED IN PROOF. All solvents were essentially transparent at the wavelengths used (>3300 Å).

(7) A discussion of the *cis* dimer production is deferred until publication of the full paper since we have shown that the *cis* dimer arises from more than one excited state.

However, if there is strong electronic coupling of the excited states with the heavy-atom solvent states, the most important operator may generally be the spin-orbit operator.⁸

The probability then of an intersystem crossing from a singlet to a triplet state may be directly related to the square of the spin-orbit coupling factor ζ , the values of which are known for atoms. Since the coupling is related to the atomic number of the perturbing nucleus, the relative magnitude of coupling may be approximated by using the coupling factor for the heaviest atom in the solvent. Thus, to a first approximation, the relative probability of intersystem crossing in proceeding from *n*-PrBr to EtI would be given by $(\zeta_{\text{I}}/\zeta_{\text{Br}})^2$. Using the values $\zeta_{\text{I}} = 5060$ and $\zeta_{\text{Br}} = 2460$,⁹ this ratio becomes equal to 4.2. Using the data for the formation of *trans* dimer in Table I (10% *n*-PrBr, EtI) and correcting for the amount of *trans* formed in pure cyclohexane, the ratio $\text{trans}_{\text{EtI}}/\text{trans}_{\text{PrBr}}$ is equal to 4.18. The agreement between these two ratios is excellent. Investigations of the effect of other heavy-atom solvents as well as a comparison of external and internal heavy-atom effects on the photodimerization are currently in progress.

Acknowledgment. This investigation was supported in part by Research Grant GM12988 from the Division of General Medical Sciences, Public Health Service, National Institutes of Health.

(8) S. K. Lower and M. A. El-Sayed, *Chem. Rev.*, 66, 199 (1966).

(9) E. V. Condon and G. H. Shortley, "Theory of Atomic Spectra," Cambridge University Press, London, 1959.

(10) Du Pont Postgraduate Teaching Fellow, 1965-1967.

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Formation of Spiroonatriene and Heptafulvalene from an Attempt to Generate Cycloheptatrienylidene

Sir:

If the normal electrophilicity¹ of a singlet carbene is sufficiently suppressed by delocalization of electrons into its vacant p orbital, its behavior should resemble that of a nucleophile as a result of the nonbonded pair of electrons on the carbene carbon. In a number of cases² where adjacent heteroatoms (oxygen, nitrogen)

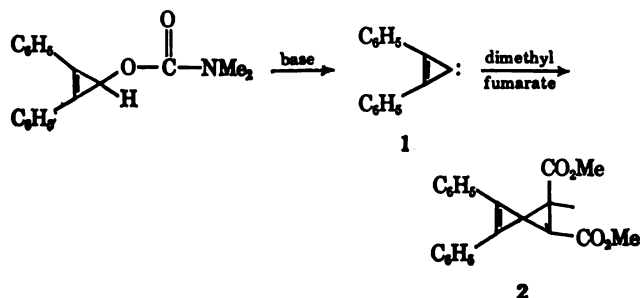
(1) Cf. J. Hine, "Divalent Carbon," The Ronald Press, New York, N. Y., 1964, p 43; W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964, p 164.

(2) Although the question of the actual intermediacy of nucleophilic carbenes in many cases has been clouded by the fact that the carbene dimers (e.g., tetraaminoethylenes) give the same products with electrophiles³ as would be expected from the carbene itself, there are still a number of cases that probably do indeed involve intermediate carbene formation (including, in fact, reactions of the dimer with electrophiles⁴). For examples of these as well as lead references to earlier work, see: D. M. Lemal, E. P. Gosselink, and S. D. McGregor, *J. Am. Chem. Soc.*, 88, 582 (1966); R. W. Hoffmann and H. Hauser, *Tetrahedron*, 21, 1891 (1965); H. Quast and S. Hunig, *Chem. Ber.*, 99, 2017 (1966); *Angew. Chem. Intern. Ed. Engl.*, 3, 800 (1964); H. Balli, *ibid.*, 3, 809 (1964); H. Quast and E. Frankenfeld, *ibid.*, 4, 691 (1965); H. W. Wanzlick and A. Hanns, *Chem. Ber.*, 99, 1580 (1966); H. W. Wanzlick and H. J. Kleiner, *Angew. Chem. Intern. Ed. Engl.*, 3, 65 (1964). For an excellent review of earlier work in this area, see H. W. Wanzlick, *ibid.*, 1, 75 (1962). For the first example of an intermediate of this type, see R. Breslow, *J. Am. Chem. Soc.*, 80, 3719 (1958).

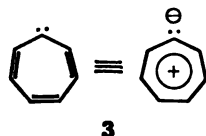
(3) D. M. Lemal, R. A. Lovald, and K. I. Kawano, *ibid.*, 86, 2518 (1964); H. E. Winberg, J. E. Carnahan, D. D. Coffman, and M. Brown, *ibid.*, 87, 2055 (1965); N. Wiberg and J. W. Buchler, *Chem. Ber.*, 96, 3000 (1963).

have served as the electron-donating groups this anticipated effect has manifested itself in an inertness to typical alkenes but reactivity with a wide variety of electrophiles.

A second mechanism for delocalizing electrons into the vacant p orbital of a singlet carbene and thereby accentuating its nucleophilicity is its incorporation into a conjugated ring in such a way as to make the vacant orbital an integral part of an aromatic system. The simplest example of this type of system, the two- π -electron cyclopropenylidene (1), has defied standard techniques for generating carbenes^{4,5} but has been suggested as a possible intermediate in the reaction of a substituted cyclopropenyl carbamate with base. The evidence for this as an intermediate consists simply of the fact that it gives spiropentenones with electrophilic olefins⁶ and no reaction with simple alkenes.⁴



At this time we wish to report the results of our attempts to generate a potentially nucleophilic carbene in which the vacant p orbital is an integral part of a six- π -electron aromatic system—cycloheptatrienyldene⁷ (3).



As a potential precursor to this species, tropone tosylhydrazone was synthesized in high yield from tropone *via* 7,7-dichlorocycloheptatriene. The tosylhydrazone was converted to its sodium salt (a muddy brown solid) with sodium hydride in tetrahydrofuran. Photolysis of the salt in tetrahydrofuran in the presence of typical alkenes gave the salt of *p*-toluenesulfonic acid and up to 50% of a photolytically unstable, almost black crystalline solid, but no indication of the spiro-natriene adduct that would result from carbene addition to the alkene double bond. The dark solid was identified as heptafulvalene (5) by comparison of its properties with those reported for an authentic sample.⁹

(4) Unpublished results from these laboratories.

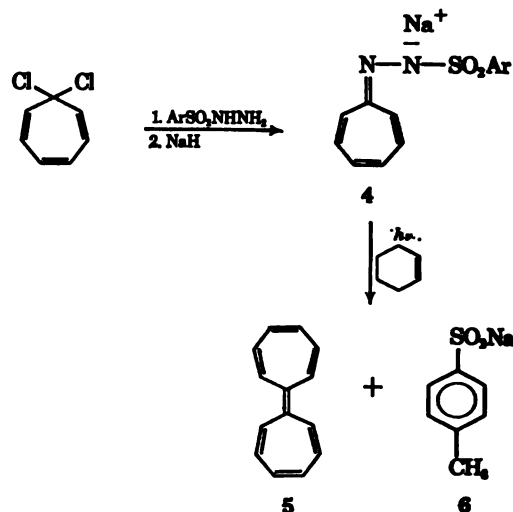
(5) R. Breslow and L. J. Altman (*J. Am. Chem. Soc.*, **88**, 504 (1966)) have pointed out that perhaps one factor contributing to the acidity of the ring hydrogen of *n*-propylcyclopropenone is contribution of a cyclopropenylidene resonance form.



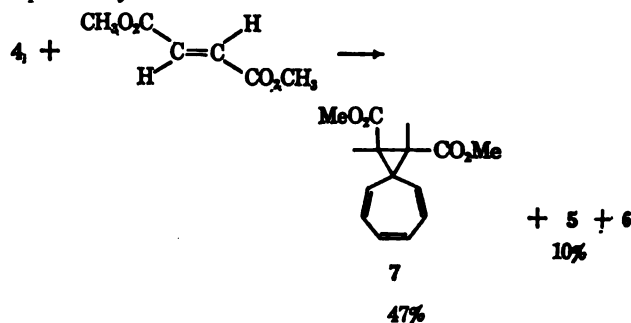
(6) W. M. Jones and M. E. Stowe, *Tetrahedron Letters*, 3459 (1964).

(7) Generation of di- and triannelated cycloheptatrienyldenes has been recently reported by Murahashi, Moritani, and Nishino.⁸ In view of the involvement of the aromatic rings in the conjugated systems of these intermediates, it is not surprising that their chemical properties resemble typical aryl-substituted alkylidenes.

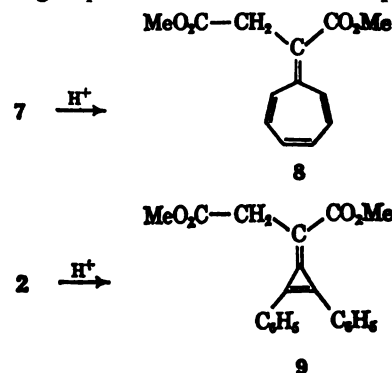
(8) Cf. S. Murahashi, I. Moritani, and M. Nishino, *J. Am. Chem. Soc.*, **89**, 1257 (1967).



Even in the presence of electron-rich alkenes (*e.g.*, enamines) there was observed none of the spiro adduct but, again, only the dimer and sodium *p*-toluenesulfinate. However, when the photolysis was carried out in the presence of the electrophilic olefin, dimethyl fumarate, there was isolated, in addition to the sulfinate salt and the dimer, a 47% yield of the spiro-natriene 7 which, formally, would arise from addition of cycloheptatrienyldene to the fumarate double bond.



Both analyses¹⁰ and spectra support the interesting structure assigned to 7. In the infrared it showed a single carbonyl absorption at 1720 cm^{-1} , in the ultraviolet it showed a single maximum at 262 $\text{m}\mu$ (ϵ 2800), and in the nmr it showed single peaks at τ 7.65 (cyclopropyl hydrogens) and 6.32 (methyl hydrogens), a doublet at τ 4.59 (*ortho* ring hydrogens), and a multiplet at τ 3.52 (remaining cycloheptatriene ring hydrogens), with areas in the ratio 2:6:2:4, respectively. Additional support for the assigned structure resides in its facile conversion under acidic conditions to the corresponding heptafulvene 8. For example, 1% HCl



(9) W. von E. Doering in "Theoretical Organic Chemistry. The Kekule Symposium," Academic Press Inc., New York, N. Y., 1959, p 44.
(10) All new compounds gave acceptable analyses.

in ethanol effects complete conversion in 30 min, acid alumina causes rapid isomerization, etc. Both analyses and spectra confirm the assigned structure. This reaction finds analogy in the highly facile acid-induced ring opening of the spiro-pentene 2 to the triafulvene 9.⁶

The nature of the intermediate(s) that leads to heptafulvalene and spirononatriene is, of course, questionable.¹¹ However, whatever its structure, the products that it gives rise to are those anticipated for a carbene (dimer formation) of low electrophilicity (no reaction with alkenes) and relatively high nucleophilicity (reaction with electrophilic double bonds).

Acknowledgment. The authors gratefully acknowledge the support of this research by the U. S. Army Research Office, Durham.

(11) Reaction of heptafulvalene with dimethyl fumarate in a reaction analogous to that proposed by Lemal³ to explain the products of reaction of electrophiles with tetraaminoethylenes was independently excluded as the source of the spirononatriene.

(12) (a) Alfred P. Sloan Fellow, 1963-1967. (b) Gulf Oil Fellow, 1966-1967.

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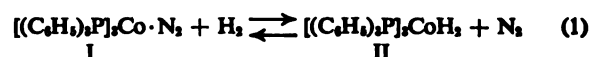
Reversible Combination of Molecular Nitrogen with a Cobalt Complex. Exchange Reactions of Nitrogen-Tris(triphenylphosphine)cobalt with Hydrogen, Ethylene, and Ammonia

Sir:

Previously we reported that molecular nitrogen combines with a cobalt complex in the reaction of cobalt acetylacetonate, diethylaluminum monoethoxide, and triphenylphosphine carried out in an atmosphere of nitrogen.¹ We wish to report now on some exchange reactions of the isolated complex, nitrogen-tris(triphenylphosphine)cobalt (I), with molecular hydrogen, ethylene, and ammonia. Recently, ruthenium^{2,3} and iridium⁴ complexes, which are combined with molecular nitrogen, have been reported, but no report has been made, as far as we know, on the reaction of a nitrogen-coordinated complex with these gases.

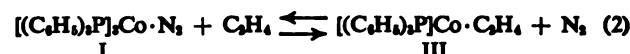
When a benzene solution of nitrogen-tris(triphenylphosphine)cobalt (I) is swept or shaken with purified hydrogen gas, the original red color changes to yellow with a loss of molecular nitrogen from the complex, as proved by infrared and mass spectrometry. The sharp strong band at 2088 cm⁻¹ assigned to the stretching vibration of the coordinated nitrogen molecule disappears rapidly with the appearance of new bands at about 1940 and 1760 cm⁻¹. Sweeping the benzene solution of I with argon gas does not affect the original spectrum at all. On concentrating the yellow benzene solution, light yellow crystals are isolated which can be recrystallized from toluene. *Anal.* Calcd for C₁₈H₁₅P₃Co (II): C, 76.50; H, 5.59. Found: C, 76.72; H, 6.00; N, 0. Thermal decomposition of the yellow complex II releases hydrogen and benzene. On sweeping the yellow

solution of II with nitrogen, the ν_N band at 2088 cm⁻¹ resumes the original intensity and the solution regains its initial red color. The cycle can be repeated many times, showing a reversible equilibrium.



On sweeping the benzene solution of I with deuterium, a band is observed at 1260 cm⁻¹ which may be assigned to a Co-D stretching vibration which is shifted from the band of Co-H stretching vibration at 1760 cm⁻¹ by a factor of 1.4. The band at 1940 cm⁻¹ was not observed in the spectrum of the benzene solution swept with deuterium, but no corresponding new band due to deuterium substitution appeared. The origin of the band at 1940 cm⁻¹ is not clear at the moment.

When a benzene solution of I is swept with purified ethylene, the original red color darkens with the loss of the coordinated nitrogen molecule. The ν_N band at 2088 cm⁻¹ disappears and new bands, which may be assigned to the C-H stretching vibration of the coordinated ethylene molecule, appear at about 2950 and 2850 cm⁻¹. Similar bands are observed in the spectrum of [(C₆H₅)₃P]₂Ni·C₂H₄ prepared according to Wilke and Hermann.⁵ On passing nitrogen through the solution, these bands disappear and the ν_N band resumes the original intensity, suggesting a reversible exchange reaction of the type



Tris(triphenylphosphine)cobalt coordinated with ethylene (III) can be isolated by the reaction of cobalt acetylacetonate, triphenylphosphine, and diethylaluminum monoethoxide in an argon atmosphere.⁶ Combination of nitrogen with cobalt also takes place in the reaction of tris(triphenylphosphine)methylcobalt¹ with nitrogen gas.

Analogous reversible reaction of the nitrogen-cobalt complex is observed with ammonia as indicated by the reversible change of the ν_N band. The complex reacts irreversibly, however, with carbon monoxide and carbon dioxide. The details will be reported later.

(5) G. Wilke and G. Hermann, *Angew. Chem.*, **74**, 693 (1962).

(6) Unpublished results.

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Reaction of Benzyne with Benzene. Effect of Silver Ion

Sir:

The decomposition of suspensions of benzenediazonium-2-carboxylate (1) in excess benzene at 45° is reported¹ to yield benzobarrelene (2), benzocyclooctatetraene (3), and biphenyl (4) (cf. run 8, Table I). The products were postulated to occur by 1,4 addition,¹ 1,2 addition (followed by valence bond isomerism),¹ and insertion^{2a} reactions of benzyne (from 1) on benzene, respectively. These are the "accepted" prod-

(1) R. G. Miller and M. Stiles, *J. Am. Chem. Soc.*, **85**, 1798 (1963).

(1) A. Yamamoto, S. Kitazume, L. S. Pu, and S. Ikeda, *Chem. Commun.*, **79** (1967).

(2) A. D. Allen and C. V. Senoff, *ibid.*, **621** (1965).

(3) A. E. Shilov, A. K. Shilova, and Yu. G. Borodko, *Kinetika i Kataliz*, **7**, 768 (1966).

(4) J. P. Collman and J. W. Kang, *J. Am. Chem. Soc.*, **88**, 3459 (1966); **89**, 169 (1967); **89**, 844 (1967).

ucts and reaction paths.² However, if benzenediazonium-2-carboxylate (1'), prepared directly from anthranilic acid and amyl nitrite,³ is similarly decomposed, the reaction products⁴ are 2 and biphenylene (5), accompanied with only *trace* amounts of 3 and 4 (run 1). These results are all the more unusual inasmuch as it has been shown⁵ that benzyne generated from several different sources appears to behave the same.

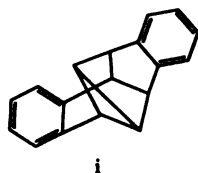
The essential difference between 1 and 1' is that 1 is prepared in a silver ion environment¹ and 1' is not.³ The apparent dependence of product distribution on the method of synthesis of benzenediazonium-2-carboxylate is a result of *silver ion contamination*. This was adequately demonstrated (Table I) by decomposing 1' in benzene, at 45°, containing known amounts of added Ag⁺ as the oxide, trifluoroacetate, and perchlorate.⁶ The effect of Ag⁺ is clearly evident by observing the change in product composition in the absence of added Ag⁺ (run 1) to that when the Ag⁺:1' is ~10⁻³ (run 2). By increasing the Ag⁺:1' to ~10⁻² the amount of 2 formed is reduced to 3.7%.⁷

The results from reaction of benzyne with benzene in the presence of Ag⁺ are best explained by proposing a benzyne-silver complex (6)⁸ which would be more electrophilic than benzyne. The complex could attack benzene to give 7 which, by intra- or intermolecular H⁺ transfer and ejection of Ag⁺, gives biphenyl (4) or,

(2) *E.g.*: (a) E. K. Fields and S. Meyerson, *Chem. Commun.*, 474 (1965); (b) S. F. Dyke, A. R. Marshall, and J. P. Watson, *Tetrahedron*, 22, 2515 (1966).

(3) Amyl nitrite (5 ml) was added to a solution of anthranilic acid (3.0 g) and trifluoro- or trichloroacetic acid (0.03 g) in THF (30 ml). After 1-1.3 hr the mixture is cooled to ~10°, and the off-white to pale yellow solid is collected and washed with THF until washings are colorless, and then with benzene. The yield of 1' varies between 92 and 95%. Dry 1' is *exceedingly hazardous*. Solvent (benzene) moist material (much less hazardous) was used in this study.

(4) Several other hydrocarbons are formed in this reaction. A major product, C₁₈H₁₄, mp 154-155° (6-10% yield), was identified (on the basis of its nmr spectrum) as hexacyclo[8.7.1.0^{2,7}.0^{4,17}.0^{11,16}]octadeca-2,4,6,11,13,15-hexaene (i). From reaction of 1' with 2 in refluxing



ethylene chloride i was prepared in >80% yield. This compound was also discovered in Professor Stiles' laboratory (M. Stiles, U. Burckhardt, and G. Freund, *J. Org. Chem.*, in press). The structure of i was confirmed by an X-ray crystallographic study: J. W. Schilling and C. E. Nordman, American Crystallographic Association Meeting, Atlanta, Ga., Jan 1967, Abstracts, p 22.





(5) R. Huisgen and R. Knorr, *Tetrahedron Letters*, 1017 (1963).

(6) The ratio of 3:4 is somewhat dependent of the anion, but not that of 2:(3 + 4). Compare 3:4 = 0.9 from run 8 which appears to be contaminated with about 0.1% Ag⁺ as AgCl and/or Ag₂O with that of ~0.6 from runs 2-7 containing AgClO₄. This will be discussed in detail in the full paper.

(7) (a) 2, 3, 4, and 5 are not interconverted nor destroyed by the action of Ag⁺. (b) 1,4 Addition seems to be the usual reaction path of arynes with arenes. Cf. Reaction of tetrachlorobenzyne (from the Grignard reagent) and mesitylene (H. Heany and J. M. Jablonski, *Tetrahedron Letters*, 4529 (1966)); formation of dibenzobarralene in 30% yield from 1' and 2 equiv of naphthalene (this study) or from 1 and excess naphthalene in 7% yield;¹ ring A adducts (1,4) from benzyne and anthracenes (G. H. Klanderma, *J. Am. Chem. Soc.*, 87, 4649 (1965)). 4-Me-1' behaves similarly.

(8) Structures can be drawn which involve overlap of d orbitals of Ag⁺ with the sp² orbitals and/or with the benzene π systems. For examples of silver olefin and silver dialkylacetylene complexes see F. R. Hapner, K. N. Trueblood, and H. J. Lucas, *ibid.*, 74, 1333 (1952); A. E. Comyns and H. J. Lucas, *ibid.*, 79, 4339, 4341 (1957), and references contained therein.

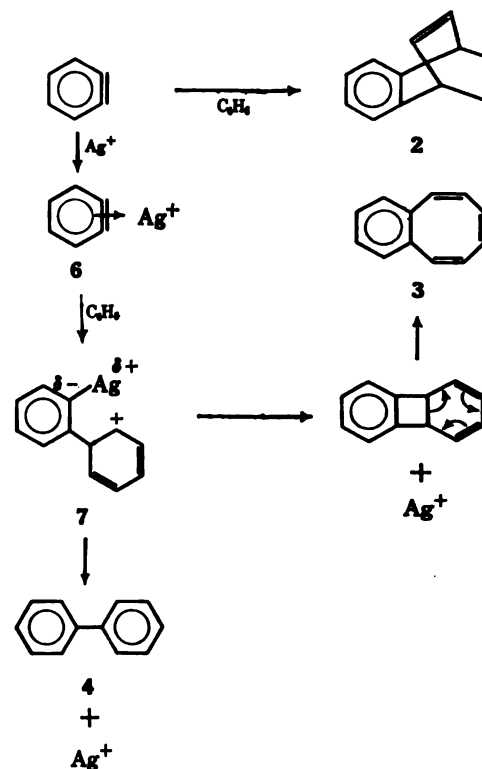
Table I. Decomposition of Benzenediazonium-2-carboxylate (6.7 mmoles) in Benzene (200 ml)^a

Run ^d	AgClO ₄ mmoles × 8.5	% compositions ^{b,c}				2 (3 + 4)
						
1	0	88	0.4	1.1	11	59
2	10 ⁻³	67	7.9	13	12	3.2
3	10 ⁻³	55	13	22	10	1.6
4	10 ⁻³	46	17	29	8.4	1.0
5	10 ⁻³	17	31	52	0.7	0.2
6	10 ⁻³	6.8	35	58	0	0.07
7	10 ⁻³	3.7	35	61	0	0.04
8 ^e	7.4	44	49	0	0	0.08

^a Reaction temperature 45°. ^b Yield of C₁₈ hydrocarbons is ca. 20%. ^c Hydrocarbons separated on 10 ft × 0.25 in. o.d. 20% SE 30 on Chromosorb W 60-80 mesh, column 135°. Relative retention time: 2, 0.75; 3, 0.89; 4, 1.00; 5, 1.37; acenaphthene, 1.60 (internal standard). ^d Typical data. ^e Benzenediazonium-2-carboxylate prepared as described in ref 1.

by ring closure followed by valence bond isomerism, yields benzocyclooctatetraene (3). Thus, the ratio 2:(3 + 4) is a measure of the two competitive processes: (1) 1,4 addition of benzyne to benzene, and (2) benzyne-silver complex (6) formation and subsequent reaction with benzene⁹ (Scheme I). The magnitude of the effect

Scheme I



of trace amounts of Ag⁺ is indicative of the extraordinary catalytic ability of Ag⁺ to "trap" benzyne and of the reactivity of 6.

In the "complete" absence of Ag⁺, benzyne reacts with benzene to give benzobarralene by 1,4 addition.¹⁰

(9) The distribution of the isomeric methylbiphenyls formed from 1' and toluene in the presence of Ag⁺ should either support or vitiate the proposed mechanism.

(10) (a) Pyrolysis of phthalic anhydride in benzene-*d*₆ at 690° gave a mixture of C₁₈ hydrocarbons in 48% yield (based on unrecovered phthalic anhydride) which consisted of biphenyl-*d*₈ (from benzyne and benzene!) (~9.4%), naphthalene-*d*₈ (~81%), acenaphthylene (*d*₈-*d*₈) (~6%), and acenaphthene (*d*₈-*d*₈) (~5%). In addition extensive

iphenylene (5) is a result of benzyne dimerization insured since 5 obtained by decomposing 1' in benzene- d_6 was found to be deuterium free, 2, C-D stretch absent in the infrared.

of the other metal ions (Tl^+ , Cu^+ , Cu^{2+} , Hg^{2+})¹¹ screened thus far altered the course of benzyne-benzene reaction. The study is being extended however, to transition metals and their combination in anticipation that an isolable benzyne compound may result.¹²

of biphenyl- d_{10} were formed *via* benzene- d_6 thermal dimerization of biphenyl- d_{10} :biphenyl- d_{10} ~ 0.1 . Biphenylene was not detected. Acenaphthylene and acenaphthene are formed only by thermal decomposition of 3. Based on isolated and characterized hydrocarbon, it can be concluded that at 690° the major reaction of benzyne is 1,4 addition ($\sim 75\%$) to give 2, followed by loss of H_2 to give thermally stable naphthalene. The balance is electrocyclic (*vide supra*) to give 4 ($\sim 10\%$) and 3 ($\sim 15\%$) (which reverts (60%) to form acenaphthene, which in turn is partially degraded to acenaphthylene) and pyrolysis (40%) to naphthalene. Results are somewhat different from earlier reports¹³ (D. F. unpublished data). (b) Cf. G. M. Badger, *Progr. Phys. Org. Chem.*, 1 (1966).

The absence of any effect is a strong argument against benzyne as a benzene-metal complex.

The assistance of L. R. Rice and D. F. Lindow in carrying out the initial experiments is gratefully acknowledged.

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Cyclopropenone

Studies of various cyclopropenones, including dicyclopentenone,¹ the earliest example, and the recent monoalkylcyclopropenones,² have fully shed the unusual stability of this strained system. Chemical properties of importance have also been investigated on these derivatives.¹⁻³ However, although the parent ketone III is clearly of interest, it resisted our synthetic attempts to prepare it by the methods used to make substituted derivatives. We have now succeeded in synthesizing unsubstituted cyclopropenone.

Reaction of tetrachlorocyclopropene⁴ (I) with 2 equivalents of tri-*n*-butyltin hydride at room temperature in an oil produced a volatile mixture⁵ of chlorocyclopropenes containing 3,3-dichlorocyclopropene (II) (δ 8.0), 1,3-dichlorocyclopropene (δ 7.2, 4.5, 2 cps), and mono- and trichlorocyclopropene. The distilled mixture was taken up in CCl_4 and immediately hydrolyzed with cold water (or D_2O). The aqueous phase contained as the only detectable product (the solvent peak could be moved by adding sodium phosphate or removed by using D_2O) a

Breslow, R. Haynie, and J. Mirra, *J. Am. Chem. Soc.*, **81**, 9; M. E. Vol'pin, Y. D. Koshkov, and D. N. Kursanov, *Dokl. Akad. Nauk SSSR*, 506 (1959); R. Breslow, T. Eicher, A. Krebs, and J. Posner, *J. Am. Chem. Soc.*, **87**, 1320 (1965).

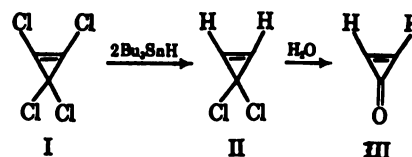
Breslow and L. J. Altman, *ibid.*, **88**, 504 (1966).

Krebs, *Angew. Chem. Intern. Ed. Engl.*, **4**, 10 (1965).

Tobey and R. West, *J. Am. Chem. Soc.*, **88**, 2481 (1966).

though the allylic chlorides must be most reactive, the resulting cyclopropenyl radical may pick up hydrogen on any ring and the cyclopropenyl chlorides undergo rapid allylic isomerization.

Under appropriate conditions the essentially pure mixture of isomers can be prepared. On treatment with $AgBF_4$ in a variety of solvents Mr. John Groves has found that this affords chlorocyclopropenone, with an nmr singlet at δ 9.6 ($J_{13C-H} = 242$ cps, $J_{H-H} = 2$



sharp singlet at δ 9.0 which we assign to the protons of cyclopropenone (III).

The nmr spectrum unambiguously establishes this structure. Thus the singlet shows ^{13}C satellites with the very large coupling ($J_{13C-H} = 230$ cps) characteristic of a cyclopropene⁶ or acetylene. The latter is, of course, excluded by the chemical shift of δ 9.0; this also excludes nonketonic cyclopropene structures since 1,3,3-trimethylcyclopropene has its vinyl proton at δ 6.7 and the 3,3-dichlorocyclopropene signal is at δ 8.0, while methylcyclopropenone is at δ 8.7. The ^{13}C satellites of III appear, as expected, as a doublet ($J_{H-H} = 3$ cps).

The aqueous solution of III shows broad infrared absorption centered at 1850 cm^{-1} . On standing it slowly ($t_{1/2}$ at $25^\circ > 1$ week) is hydrolyzed to acrylic acid.⁸ Treatment with alkali produces a dark polymer, but the compound is stable to a variety of strong mineral acids. Although III is very polar, it can be extracted from the water solution with methylene chloride or ethylene chloride by salting out. The protons in III are still at δ 8.9-9.0, there are no other signals in the nmr, and the infrared spectrum shows a strong cyclopropenone doublet⁹ at 1835 and 1870 cm^{-1} and no absorption in the O-H region. Thus III is apparently present as the free ketone, rather than a gem-diol, even in aqueous solution.

Attempts to isolate III by removal of solvent, distillation, or vapor phase chromatography under a variety of conditions have so far failed, leading to at least partial polymerization of the compound; the parent ketone is apparently more sensitive than its derivatives. However, the low reactivity of III compared with cyclopropanone,¹⁰ and in particular its retention of the unhydrated carbonyl group in water solution, confirm our previous conclusion that the cyclopropenone system has considerable conjugative stabilization.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health, and thank Mr. John Groves for several experimental contributions.

(6) Methylcyclopropenone⁶ has $J_{13C-H} = 213$ cps and 1,3,3-trimethylcyclopropene⁷ has $J_{13C-H} = 218$ cps.

(7) G. L. Closs, *Proc. Chem. Soc.*, 152 (1962).

(8) Identified by comparison of vpc, nmr, and mass spectra with those of an authentic sample.

(9) The spectra in aqueous and nonaqueous solution mirror those for alkylcyclopropenones³ and indicate that the carbonyl group is still present in water, albeit hydrogen bonded.

(10) N. J. Turro and W. B. Hammond, *J. Am. Chem. Soc.*, **88**, 3672 (1966).

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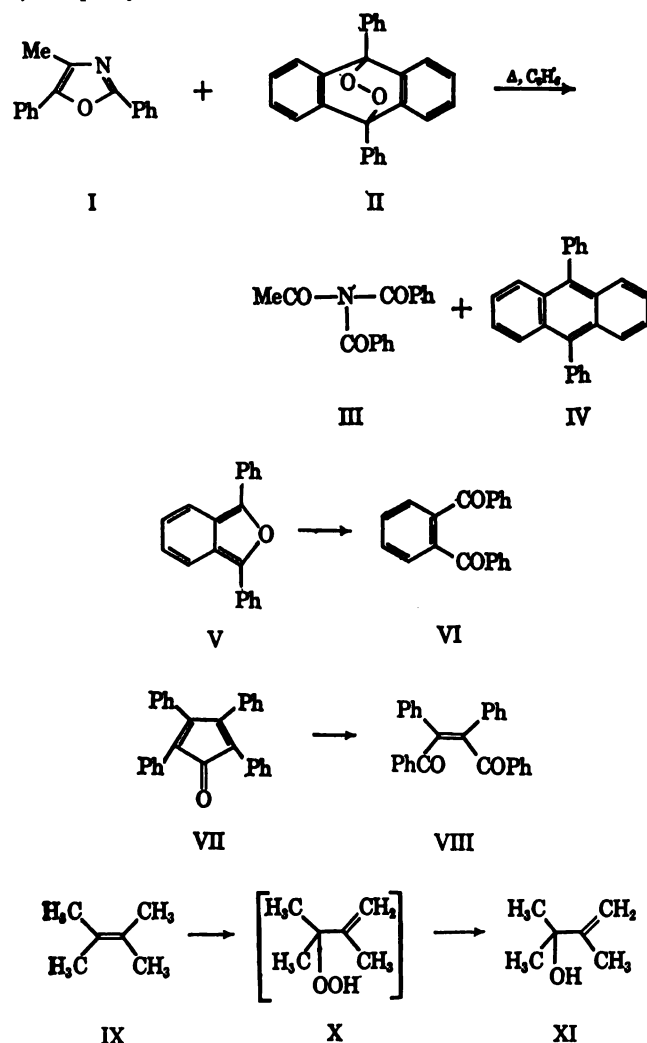
Received May 5, 1967

Singlet Oxygen Reactions from Photoperoxides

Sir:

It has been known for some time that aromatic hydrocarbons such as anthracene, rubrene, and tetra-

Chart I. Oxidation of Singlet Oxygen Acceptors by 9,10-Diphenylanthracene Peroxide



cene undergo photosensitized autoxidation to form transannular peroxides,¹ and a number of recent reports have provided strong evidence indicating that singlet oxygen is involved in the formation of these "photoperoxides."² It is also well known that many of these peroxides undergo dissociation on heating to regenerate oxygen and the parent hydrocarbon. The ease of oxygen release from these systems depends on the polycyclic aromatic system and the nature of the substituents in the *meso* positions.³

We now report that 9,10-diphenylanthracene peroxide (**II**) may be used to bring about typical singlet oxygen reactions when it is allowed to decompose^{4,5}

(1) The first example of an aromatic transannular peroxide, rubrene peroxide, was reported by C. Moreau, C. Dufraisse, and P. M. Dean, *Compt. Rend.*, **182**, 1440, 1584 (1926). For a recent review, see Y. A. Arbuzov, *Russ. Chem. Rev.*, **34**, 558 (1965).

(2) C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3879, 3880 (1964); C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Letters*, **46**, 4111 (1965); E. J. Corey and W. C. Taylor, *J. Am. Chem. Soc.*, **86**, 3881 (1964); T. Wilson, *ibid.*, **88**, 2898 (1966); E. McKeown and W. A. Waters, *J. Chem. Soc., Sect. B*, 1040 (1966).

(3) For a review, see W. Bergmann and M. J. McLean, *Chem. Rev.*, **28**, 367 (1941).

(4) C. Dufraisse and L. Enderlin, *Compt. Rend.*, **191**, 1321 (1930); C. Dufraisse and J. LeBras, *Bull. Soc. Chim. France*, **4**, 349 (1937).

(5) Preliminary kinetic studies on the thermal decomposition of 9,10-diphenylanthracene peroxide in methylene chloride at 90° indicate a first-order rate constant for oxygen release of $2.5 \times 10^{-4} \text{ sec}^{-1}$ ($t_{1/2}$ 8 hr). This value is considerably faster than the rate of decomposition of tertiary peroxides such as *t*-butyl or trityl (which, furthermore, decomposes by peroxide bond cleavage) and suggests that 9,10-diphenyl-

anthracene peroxide undergoes a concerted oxygen release (B. Hedaya, private communication).

in the presence of a variety of known singlet oxygen acceptors. Examples of the oxidations studied are given in Chart I. In each case the reaction was carried out by heating a mixture of peroxide and acceptor (ratio 2:1) in benzene or chloroform for 2–4 days. The products isolated were identical with those formed in parallel dye-photosensitized autoxidation reactions and were characterized by comparison (mixture melting point or vpc retention time, infrared and nmr spectra) with authentic samples. Thus, 2,5-diphenyl-4-methyloxazole (**I**) was converted to N-acetyldibenzamide (**III**)⁶ (82%) along with 10% of dibenzamide. 1,3-Diphenylisobenzofuran (**V**) was oxidized to *o*-dibenzoylbenzene (**VI**)⁷ in 95% yield, while treatment of tetracyclone **VII** with **II** afforded *cis*-dibenzoylstilbene (**VIII**) in 50% yield.⁸ The intermediate hydroperoxide **X** from the tetramethylethylene oxidation was not isolated, but was reduced with triphenylphosphine to form the unsaturated alcohol **XI**. No attempt was made to optimize yields in these initial runs. Control reactions using 9,10-diphenylanthracene (**IV**) in place of the photoperoxide **II** resulted in essentially quantitative recovery of starting materials either in air or under nitrogen.

The oxidation of 2,5-diphenyl-4-methyloxazole (**I**) by the peroxide **II** is outlined as a typical procedure. A solution of 0.724 g (0.002 mole) of 9,10-diphenylanthracene peroxide¹⁰ and 0.235 g (0.001 mole) of 2,5-diphenyl-4-methyloxazole¹¹ in 50 ml of anhydrous benzene was stirred at reflux temperature in the dark for 94 hr under a positive pressure of nitrogen. Benzene was removed *in vacuo*, yielding a solid residue, 0.960 g, which, after chromatography on deactivated silica gel using ether–hexane as eluent, could be separated into a mixture of N-acetyldibenzamide¹² (0.17 g, mp 64–65°, dibenzamide (0.062 g, mp 147–149°,¹³ as well as 9,10-diphenylanthracene (0.538 g) and unreacted 9,10-

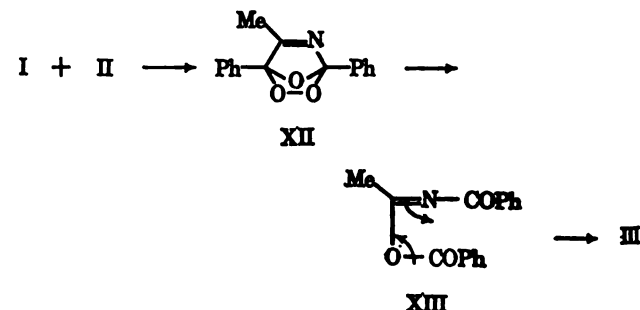
anthracene peroxide undergoes a concerted oxygen release (B. Hedaya, private communication).

(6) H. H. Wasserman and M. B. Floyd, *Tetrahedron Suppl.*, **7**, 441 (1966).

(7) A. Guyot and J. Catel, *Bull. Soc. Chim. France*, **35**, 1124 (1906); C. Dufraisse and S. Ecury, *Compt. Rend.*, **223**, 735 (1946).

(8) C. F. Wilcox, Jr., and M. P. Stevens, *J. Am. Chem. Soc.*, **84**, 1258 (1962); G. O. Schenck, *Z. Elektrochem.*, **56**, 855 (1952).

(9) Earlier studies⁴ on dye-photosensitized autoxidations have shown that oxazoles are remarkably sensitive to the action of singlet oxygen. Formation of the triamide in this process appears to involve rearrangement of the intermediates **XII** and **XIII**.



(10) C. Dufraisse and A. Etienne, *Compt. Rend.*, **201**, 280 (1935).

(11) G. H. Cleland and C. Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).

(12) Identical (mixture melting point, infrared and nmr spectra) with the product formed in the dye-photosensitized autoxidation of **I**.

(13) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5841 (1951). Dibenzamide apparently results from hydrolysis of the triamide during chromatography since this diamide could not be detected (infrared spectrum) in the crude reaction mixture before work-up.

diphenylanthracene peroxide (0.08 g). The over-all yield of di- and triamide was 92%.

We are investigating mechanistic aspects of the process by which oxygen is transferred from photoperoxide to acceptor, as well as the possibility that other types of cyclic peroxides may provide sources of singlet oxygen.

Acknowledgment. This work was supported in part by Grant GM-13854 from the National Institutes of Health.

(14) National Institutes of Health Postdoctoral Fellow, 1966-1967.

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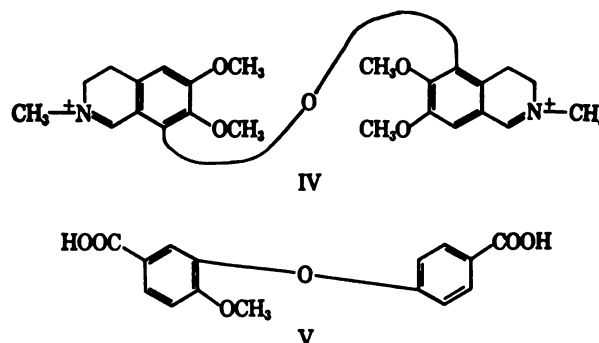
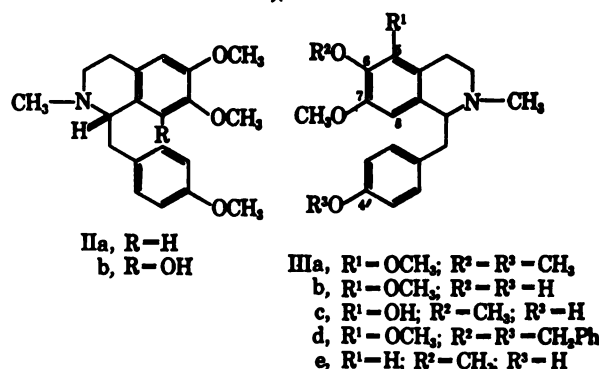
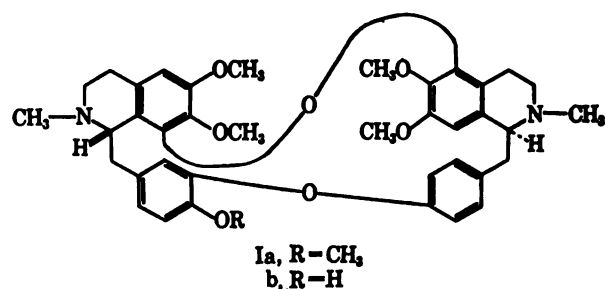
The Isolation and Structural Elucidation of Thalidasine, a Novel Bisbenzylisoquinoline Alkaloid Tumor Inhibitor from *Thalictrum dasycarpum*^{1,2}

Sir:

The genus *Thalictrum* has served as a uniquely profuse source of new and novel benzylisoquinoline and aporphine alkaloids.³⁻⁶ We report herewith the isolation and elucidation of the structure (Ia) of thalidasine, a new alkaloid tumor inhibitor⁷ from *T. dasycarpum*. Thalidasine appears to be the first bisbenzylisoquinoline recognized to contain a diphenyl ether terminus at C-5 and the first unsymmetrical bisbenzylisoquinoline recognized to contain a 20-membered ring.⁸ Furthermore, the alkaloid thalfoetidine, from *T. foetida*,⁹ is shown to possess structure Ib on the basis of evidence which includes interrelation with thalidasine.

Thalidasine (Ia), C₃₉H₄₄N₂O₇, mol wt (mass spectroscopy)¹⁰ 652, is an amorphous solid, mp 105-107°, [α]_D²⁰ -70° (c 0.89, MeOH), $\lambda_{\text{max}}^{\text{EtOH}}$ 275 m μ (ϵ 4560), 282 m μ (ϵ 4530), and nmr signals (in CDCl₃) at τ 7.38, 7.75 (6 H, two NCH₃), 6.09, 6.13, 6.25, 6.50, 6.73 (15 H, five OCH₃), and 2.46-3.70 (9 H, aromatic H). The alkaloid was characterized as the oxalate, mp 160-

162°, picrate, mp 175-177°, and methiodide, mp 182-183°. Permanganate oxidation of Ia yielded 2-methoxydiphenyl ether 4',5-dicarboxylic acid (V), characterized by mixture melting point and infrared comparison with an authentic sample.¹¹ Sodium in liquid ammonia reduction of Ia afforded, as principal products, L-O-methylarmepavine (IIa), mp 61-62°, [α]_D²⁰ +99° (c 1.10, CHCl₃), and a dihydroxydimethoxybenzylisoquinoline (A), C₁₉H₂₃NO₄, mp 194-196°, [α]_D²⁰ +51° (c 0.50, MeOH), $\lambda_{\text{max}}^{\text{EtOH}}$ 279 m μ (ϵ 2750), nmr signals at τ 7.48 (3 H, NCH₃), 6.13, 6.45 (6 H, two OCH₃), 4.33 (1 H, C-8 H), 3.92 (2 H, two OH), 3.08, 3.35 (4 H, two doublets, J = 8.5 cps). Methylation of phenol A with diazomethane gave 1-(4-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (IIIa), characterized by infrared and nmr comparison with the *dl* compound.¹² Nmr spectral characteristics and reactivity toward Gibbs reagent¹³ led to consideration of 4',6-diphenol (IIIb) and 4',5-diphenol (IIIc) structures as most likely for



phenol A. However, the infrared spectrum of synthetic [via the dibenzyl ether IIIId, mp 83-86°, nmr signals at τ 7.49 (3 H, NCH₃), 6.19, 6.55 (6 H, two OCH₃), 4.97, 5.02 (4 H, two OCH₂Ph), 3.02, 3.13 (4 H, two doublets, J = 8.5 cps, disubstituted aromatic

(11) The authors thank Professor M. Tomita cordially for the authentic sample of 2-methoxydiphenyl ether 4',5-dicarboxylic acid.

(12) M. Tomita and Y. Kondo, *J. Pharm. Soc. Japan*, **77**, 1019 (1957); H. Inouye, Y. Kanaya, and Y. Murata, *Chem. Pharm. Bull. (Tokyo)*, **7**, 573 (1959).

(1) Tumor Inhibitors. XXIV. Part XXIII: S. M. Kupchan, A. H. Gray, and M. D. Grove, *J. Med. Chem.*, **10**, 337 (1967).

(2) Supported by grants from the National Heart Institute (HE-02952) and the National Cancer Institute (CA-04500).

(3) (a) S. M. Kupchan, K. K. Chakravarti, and N. Yokoyama, *J. Pharm. Sci.*, **52**, 985 (1963); (b) M. Tomita, H. Furukawa, S.-T. Lu, and S. M. Kupchan, *Tetrahedron Letters*, 4309 (1965).

(4) (a) E. Fujita and T. Tomimatsu, *J. Pharm. Soc. Japan*, **79**, 1082 (1959); (b) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).

(5) (a) J. Padilla and J. Herran, *Tetrahedron*, **18**, 427 (1962); (b) M. Shamma, B. S. Dudock, M. P. Cava, K. V. Rao, D. R. Dalton, D. C. DeJongh, and S. R. Shrader, *Chem. Commun.*, 7 (1966).

(6) (a) S. M. Kupchan, Symposium on Selected Recent Advances in Natural Products Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, Abstracts, p 31P; (b) H. B. Dutschewski and N. M. Mollov, *Chem. Ind. (London)*, 770 (1966).

(7) Thalidasine showed significant inhibitory activity against Walker intramuscular carcinosarcoma 256 in rats at 200 mg/kg. Tumor inhibitory activity was assayed, under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, by the procedures described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

(8) Cissampareine was the first symmetrical bisbenzylisoquinoline recognized to contain a 20-membered ring (S. M. Kupchan, S. Kubota, E. Fujita, S. Kobayashi, J. H. Block, and S. A. Telang, *J. Am. Chem. Soc.*, **88**, 4212 (1966)).

(9) N. M. Mollov and V. St. Georgiev, *Chem. Ind. (London)*, 1178 (1966).

(10) The authors thank Professor A. L. Burlingame and Dr. H. K. Schnoes, University of California, Berkeley, for the mass spectral data and helpful discussions.

ring), 2.63 (10 H, monosubstituted aromatic ring)] *dl*-IIIb [mp 136–140°, $\lambda_{\text{max}}^{\text{EtOH}}$ 281 m μ (ϵ 3200), nmr signals at τ 7.43 (3 H, NCH₃), 6.15, 6.47 (6 H, two OCH₃), 5.18 (2 H, two OH), 4.23 (1 H, C-8 H), 3.11, 3.29 (4 H, two doublets, J = 8.5 cps)] differed from that of phenol A. Hence phenol A was assumed to have the 4',5-diphenol structure IIIc, and thalidasine, an unprecedented diphenyl ether terminus at C-5. Evidence for both structures was adduced from the experimental results which follow.

Characterization of the *minor* phenolic products of reduction with sodium in liquid ammonia and mass spectroscopic evidence¹⁰ strongly support assignment of structure Ia for thalidasine. One minor phenolic cleavage product was L-armepavine (IIIe), [α]_D²⁰ +99° (c 0.14, CHCl₃), infrared and nmr spectra superimposable with those of authentic sample.¹¹ A second minor phenolic product was L-1-(4-methoxybenzyl)-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisquinoline (IIb), [α]_D²⁰ +32° (c 0.40, CHCl₃), infrared and nmr spectra superimposable with those of a sample of *dl* compound.¹⁴ The most intense peak in the mass spectrum of thalidasine is a doubly charged ion (IV) of m/e 213 (C₂₄H₃₀N₂O₅). This type of fragmentation has been shown to be characteristic of alkaloids of the unsymmetrical bisbenzylisoquinoline type.^{5b,15} Fragments with compositions C₂₇H₂₉NO₄, C₁₈H₁₄O₂, C₁₄H₁₁O₂, C₁₂H₁₀NO₂, and C₁₂H₁₀NO₂, are readily explicable on the basis of structure Ia.

Thalfoetidine's chemistry supports the structural features assumed earlier,⁹ apart from the termini of the diphenyl ether linkage. Methylation of thalfoetidine with diazomethane yielded O-methylthalfoetidine,^{9,16} and direct comparison (infrared, nmr) has established the identity of the methylation product with thalidasine. Hence thalfoetidine possesses structure Ib.

(13) S. M. Kupchan, B. Dasgupta, E. Fujita, and M. L. King, *Tetrahedron*, **19**, 227 (1963).

(14) A. Brossi and S. Teitel, *Helv. Chim. Acta*, **49**, 1757 (1966). We thank Dr. Brossi cordially for a sample of *dl*-IIb.

(15) M. Tomita, T. Kikuchi, K. Fujitani, H. Kato, H. Furukawa, Y. Aoyagi, M. Kitano, and T. Ibuka, *Tetrahedron Letters*, 857 (1966); D. C. DeJongh, S. R. Shrader, and M. P. Cava, *J. Am. Chem. Soc.*, **88**, 1052 (1966).

(16) We thank Dr. N. Mollov cordially for a sample of thalfoetidine.

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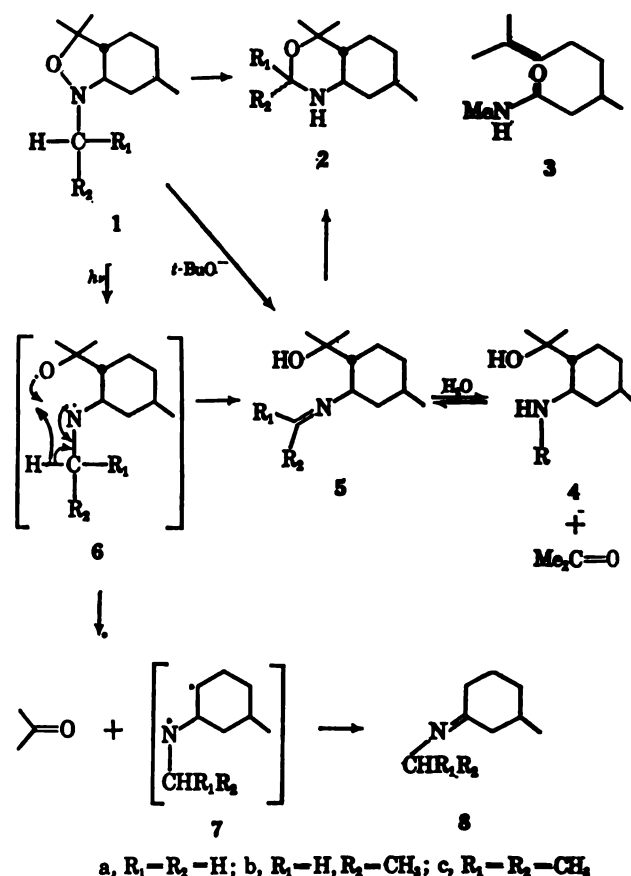
Photochemical and Base-Catalyzed Rearrangements of Isoxazolidines

Sir:

Intra-¹ and intermolecular² cycloadditions of nitrones and olefins have provided a new method for the formation of carbon-carbon bonds. Adaptation of this reaction as a synthetic method of broadest possible scope has stimulated investigations of the chemistry of the product isoxazolidine ring system. It is the purpose of this report to disclose our discovery of a rearrangement of N-alkylisoxazolidines to tetrahydro-1,3-oxa-

zines, an isomerization that can be effected both by ultraviolet irradiation and by strong base.

Irradiation of the fused bicyclic isoxazolidine **1a** ($\lambda_{\text{max}}^{\text{isooctane}}$ 213 m μ (ϵ 1940)) in hexane solution (0.027 M) with 2537-A light³ afforded a product mixture from which the bicyclic tetrahydro-1,3-oxazine **2a** could be isolated. Minor amounts of the amide **3** were also obtained, and the identity of **3** was established by synthesis from citronellic acid. The photochemical conversion of **1a** to **2a** could be efficiently photosensitized by the use of benzophenone and fluorenone (anthracene, $E_T \sim 42$ kcal/mole, proved to be a poor sensitizer). Under these conditions, the yields of **2a** were 43 and 54%, respectively, and no amide **3** was detected. Similarly, isoxazolidine **1b** was photoisomerized to **2b**.



The structures of **2a** and **2b** were supported by their nmr spectra, which for the former showed an AB quartet at 4.25 ppm (2 H, J_{AB} = 10.5 cps), whereas **2b** showed a regular quartet at 4.35 ppm (1 H, J = 5.6 cps). Reduction of each with lithium aluminum hydride produced the known¹ secondary amino alcohols **4**, R = CH₃, and **4**, R = C₂H₅, respectively.

When **1a** and **1b** were heated with 0.5 equiv of potassium *t*-butoxide in DMSO for 5 hr at $\sim 80^\circ$, the tetrahydro-1,3-oxazines were again obtained in good yield.

We propose that these reactions are mechanistically similar in that the imino alcohol **5** is a common intermediate. Cyclization of γ -hydroxy imines to tetrahydro-1,3-oxazines is well established.⁴ For the photochemical transformation, energy transfer from triplet

(3) A. Srinivasan-Griffin "Rayonet" reactor was employed, with a quartz vessel for the direct photolysis; 3000- and 3500-A sources and a Pyrex vessel were used for the sensitized runs.

(4) R. C. Elderfield, "Heterocyclic Compounds," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1957, p 541.

(1) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Am. Chem. Soc.*, **86**, 3759 (1964).

(2) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963), and references cited therein.

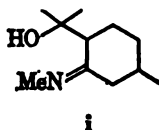
sensitizer to give the excited triplet of 1 followed by bond cleavage would result in the diradical 6. Intramolecular hydrogen transfer *via* a seven-membered transition state leads directly to 5. Because 6 is a *t*-alkoxy radical, competing fragmentation could occur. In support of this postulated mechanism, we have succeeded in trapping acetone (as the 2,4-DNP) by sweeping the reaction mixture with nitrogen. The newly generated diradical 7 would be expected to rearrange to an imine (8), and 3-methylcyclohexanone was characterized after work-up with aqueous acid.⁵

Production of 5 in the base-promoted rearrangements can take place *via* β elimination. Direct evidence for the occurrence of this pathway in the reaction of 1c and *t*-butoxide has been obtained by isolation of imino alcohol 5c. When the reaction mixture was quenched by pouring into water, the primary amino alcohol 4 (R = H) was obtained; however, if sufficient acid was present to neutralize the base, both 4 (R = H) and 5c were detected. The isopropylideneimine 5c was synthesized by condensation of 4 (R = H) with acetone. Presumably 5c does not cyclize readily to a tetrahydro-1,3-oxazine because of steric hindrance.

Other polycyclic isoxazolidines have been subjected to these rearrangement conditions, and studies to define the limitations of such reactions are in progress.

Acknowledgment. This work was supported by a grant from the National Science Foundation.

(5) An alternate pathway to acetone and 8 is also possible: intramolecular hydrogen transfer involving a five-membered ring to give i which could undergo a retroaldol reaction.



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A Novel Photoinduced Ring Expansion of 1-*t*-Butyl-2-phenyl-3-benzoylazetidines¹

Sir:

As part of our broad interest in the ground-state and electronically excited-state behavior of small-membered rings,² we have investigated the photochemical behavior of *cis*-1-*t*-butyl-2-phenyl-3-benzoylazetidine³ (I) and wish to describe an unusual photoinduced ring expansion of the four-membered azetidine ring. To our knowledge this represents the first example of a photochemical migration of an alkyl group from the α position to the carbonyl carbon of an $n-\pi^*$ excited state.

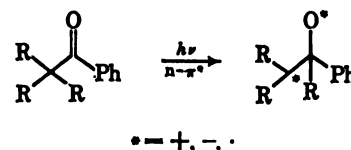
The initial experiments were carried out in a nitrogen atmosphere using an internal water-cooled mercury arc

(1) Photochemical Transformations of Small Ring Carbonyl Compounds, part XV. For part XIV, see A. Padwa, D. Crumrine, R. Hartman, and R. Layton, *J. Am. Chem. Soc.*, in press.

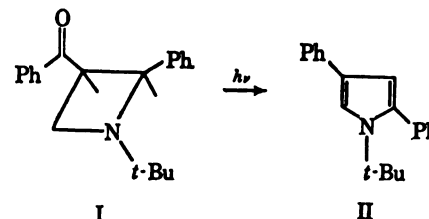
(2) A. Padwa in "Organic Photochemistry," Vol. I, O. L. Chapman Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 91.

(3) Before the completion of our investigation a report appeared describing the synthesis of azetidine I.⁴ Our spectral data are in good agreement with those reported.

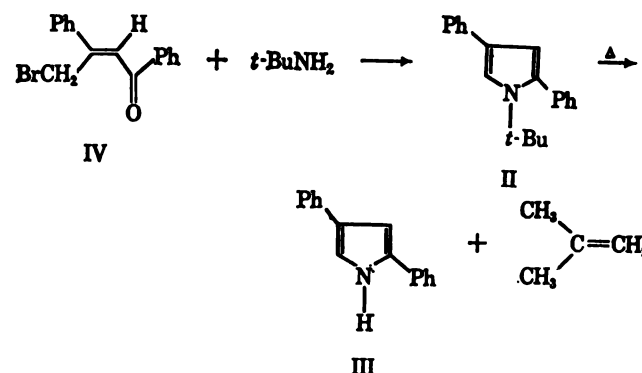
(4) J. L. Imbach, E. Doomes, R. P. Rebman, and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).



lamp (Hanovia Type L, 450 w) with a Pyrex filter to eliminate wavelengths below 300 m μ . In a typical case a solution of 0.5 g of I in 150 ml of 95% ethanol was flushed with nitrogen and irradiated for 3 hr. Conventional isolation procedures afforded 0.46 g of a solid (95%), mp 102–103°, whose structure is assigned as 1-*t*-butyl-2,4-diphenylpyrrole (II) on the basis of the chemical and physical data cited. The infrared spec-



trum of II was characterized by a series of sharp bands at 6.24, 8.21, 12.47, 13.08, 13.50, 14.25, and 14.40 μ . The ultraviolet spectrum (λ_{\max} (95% alcohol) 235 m μ (ϵ 15,800) and 276 m μ (ϵ 16,200)) of II shows an absorption curve very similar to 2,4-diphenylfuran, with peaks occurring at approximately the same wavelengths (λ_{\max} (95% alcohol) 242 m μ (ϵ 19,400) and 277 m μ (ϵ 20,000)).⁵ The nmr spectrum in deuteriochloroform exhibits a singlet at τ 8.60, a pair of doublets at τ 3.80 and 2.96 (J = 1.9 cps), and a multiplet centered at τ 2.62. The peak areas are in the ratio of 9:1:1:10. The doublet pattern of the 3- and 5-protons is to be expected, as it has been shown that the cross-ring or *meta* coupling constant ($J_{3,5}$) in the pyrrole system has a value of approximately 2 cps.⁶ The elemental analysis of this component (*Anal.* Calcd for $C_{20}H_{21}N$: C, 87.22; H, 7.69; N, 5.09. Found: C, 87.20; H, 7.85; N, 5.09) is also consistent with structure II. Chemical confirmation was obtained by pyrolysis of II at 225°. The product obtained in better than 97% yield was identical with an authentic sample of 2,4-diphenylpyrrole (III) synthesized by the method of Allen and Wilson.⁷ Structure II was further confirmed by its unequivocal synthesis from 1,3-diphenyl-4-bromobuten-2-one-1 (IV) and *t*-butylamine.



(5) S. M. King, C. R. Bauer, and R. E. Lutz, *J. Am. Chem. Soc.*, **73**, 2253 (1951).

(6) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **37**, 1056 (1959).

(7) C. F. H. Allen and C. V. Wilson, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 348.

The mechanism by which I undergoes rearrangement and the identification of the excited state(s) responsible for the reaction were deemed of considerable interest. That the $n-\pi^*$ singlet configuration is first populated and is the lowest energy state of this multiplicity seems to be a valid assumption since the absorption spectrum of I showed the $n-\pi^*$ band at 320 m μ , whereas the $\pi-\pi^*$ transition is at 246 m μ .^{8,9} The nature of the lowest lying triplet configuration remains somewhat questionable at this time, although in the present instance the benzoyl group is involved, and the lowest triplet configuration of such a moiety is $n-\pi^*$. The quantum yield for formation of II in 95% ethanol is 0.046 at 3660 Å.¹⁰ In an attempt to determine the rate constant for the unimolecular rearrangement of the excited state, we have studied the variation of quantum yield *vs.* quencher concentration. Surprisingly, the photolysis of I could not be quenched by a moderate concentration (0.3 mole) of piperylene, 1,3-cyclohexadiene, naphthalene, or ferric dipivaloylmethide. The failure to quench could mean that the rearrangement of the $n-\pi^*$ triplet is too rapid for diffusion of the excited state to quencher molecules or that most of the reaction proceeds from the singlet manifold.

With acetophenone present in a concentration so as to absorb 99% of the light a twofold increase in quantum yield resulted, despite the negligible direct excitation of azetidine I. The observation that the same product was obtained in the sensitized photolysis as in the direct irradiation provides proof that the azetidine triplet can rearrange to pyrrole II. Since the quantum yield of II increases by sensitization, we can conclude that either the intersystem crossing efficiency of the $n-\pi^*$ singlet is low or the rate of crossing in this case may be much slower than in benzophenone or acetophenone, thereby allowing for a competing unimolecular rearrangement.¹¹ The increased quantum yield can also be equally well explained by reaction *via* singlets in the direct irradiation which is less efficient than reaction *via* triplets in the sensitized reaction, both configurations leading to the same product.

These results are consistent with a picture involving reaction of the $n-\pi^*$ state as depicted in terms of the ensuing mechanism.

A possible explanation for the exclusive formation of the 2,4 isomer may be related to the preferred migratory aptitude of methyl *vs.* benzyl toward an electron-deficient center.¹⁴ In view of the uncertainties in the electronic nature of the carbonyl carbon atom, we prefer to postpone further discussion of the reaction mechanism until a more thorough study can be undertaken.

(8) Pyrex filters were used in all irradiations to remove all light below 300 m μ .

(9) Irradiation of alcohol solutions of I with 2537-Å light so as to populate the $\pi-\pi^*$ manifold produced 2,4-diphenylpyrrole. The effect of different wavelengths of light on I and the photochemistry of the *trans* isomer will be the subject of a future publication.

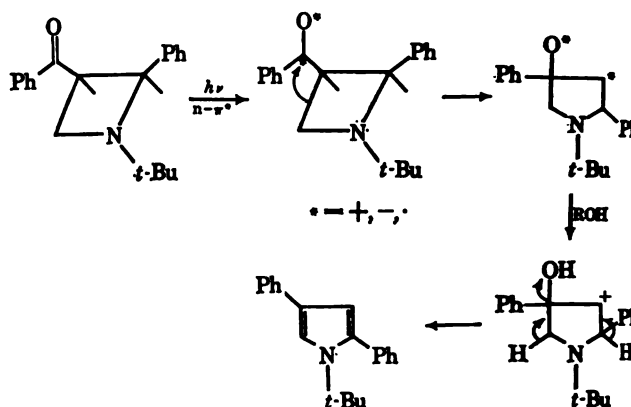
(10) Quantum yield measurements were carried out on a rotating photochemical assembly in sealed degassed Pyrex ampoules. Irradiation from a 450-w Hanovia lamp was filtered through Corning 7-51 filters. All the light is taken up by I under these conditions.

(11) A similar situation has been noted in the photochemistry of dibenzoyl ethylene, although in that case reaction proceeded predominantly by way of a $n-\pi^*$ singlet.^{15,16}

(12) G. Griffin and E. J. O'Connell, *J. Am. Chem. Soc.*, **84**, 4148 (1962).

(13) H. E. Zimmerman, H. Durr, R. S. Givens, and R. G. Lewis, *ibid.*, **89**, 1863 (1967).

(14) J. R. Owen and W. H. Saunders, Jr., *ibid.*, **88**, 5809 (1966).



Acknowledgment. We gratefully acknowledge support of this work by the Air Force Office of Scientific Research (Grant No. AF-AFOSR-1213-67).

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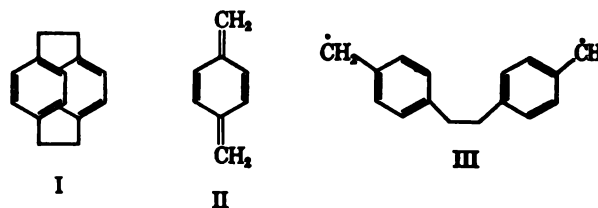
Received February 11, 1967

Racemization, Ring Opening, and Ring Expansion of the [2.2]Paracyclophane Nucleus through a Diradical Intermediate¹

Sir:

The smallest of the $[m.n]$ paracyclophanes in which $m = n = 2$ (I) exhibits a strain energy of 31.3 kcal/mole^{2a} which is reflected in the highly deformed crystal structure of the molecule.^{2b} The photochemical ring opening of [2.2]paracyclophane by both heterolytic and homolytic cleavage of the benzyl-benzyl bond results in release of this compression energy.³ The thermal ring opening of the substance at 400° to give *p,p'*-dimethylbibenzyl and *p,p'*-dimethylstilbene⁴ and at 600° to give *p*-xylylene⁵ (II) also reflect the innate instability of the system. Octamethyl[2.2]paracyclophane is much more thermally unstable, a property attributed to diradical formation followed by polymerization.⁶

We wish to report the results of three types of experiments, all of which point to thermal cleavage of [2.2]paracyclophane to the *p,p'*-dimethylenbibenzyl diradical (III) whose fate depends on the medium.



When 40 mg of (–)-4-carbomethoxy[2.2]paracyclophane⁷ (IV), mp 174–175°, $[\alpha]^{25}_{D_{436}} -583^\circ$ (*c* 1, chloro-

(1) The authors wish to thank the National Science Foundation for a grant used in support of this research.

(2) (a) R. H. Boyd, *Tetrahedron*, **22**, 119 (1966); (b) P. K. Gantzel and K. N. Trueblood, *Acta Cryst.*, **18**, 958 (1965).

(3) R. C. Helgeson and D. J. Cram, *J. Am. Chem. Soc.*, **88**, 509 (1966).

(4) J. R. Schaefgen, *J. Polymer Sci.*, **15**, 203 (1955).

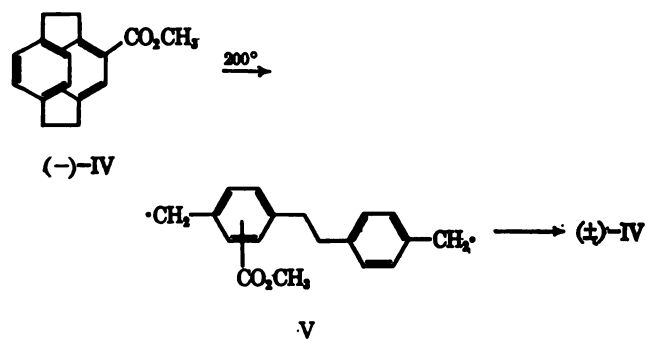
(5) W. F. Gorham, *ibid.*, **4** (A-1), 3027 (1966).

(6) D. T. Longone and L. H. Simanyi, *J. Org. Chem.*, **29**, 3245 (1964).

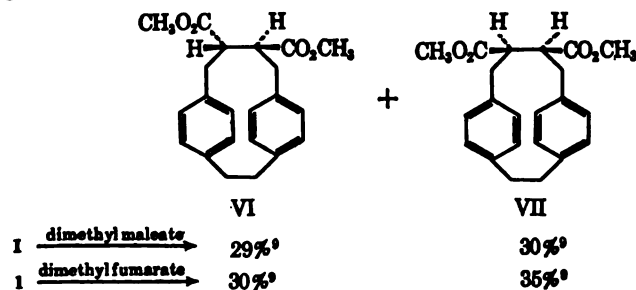
(7) (a) Elemental analyses, nmr, and infrared spectra of all new compounds were in accord with the assigned structures. (b) Optically pure (–)-4-carboxy[2.2]paracyclophane [D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.*, **77**, 6289 (1955)] was previously reported.

form here and elsewhere), was heated in 0.96 g of dimethyl sulfone for 13.3 hr at 200°, 33 mg of ester with $[\alpha]^{25}_{435} -77.5^\circ$ (13% optically pure) was isolated after purification by column chromatography and sublimation. A reaction conducted under identical conditions in *n*-tridecane gave 33 mg of material, $[\alpha]^{25}_{435} -32.5^\circ$ (5.6% optically pure). The ratio of one-point first-order rate constants calculated from these data is $k_{DS}/k_{TD} = 0.7$. The constrictions of the ring system of IV preclude racemization as occurring by a path which does not involve ring cleavage. The insensitivity of the rate to solvent polarity suggests either the derived *p*-xylylene (carbomethoxy derivative of II) or diradical³ (carbomethoxy derivative V) rather than a zwitterion as a reaction intermediate in the racemization.

When 1.0 g of [2.2]paracyclophane (I) was heated at 250° in 30 ml of *p*-diisopropylbenzene, 211 mg (21% yield) of *p,p'*-dimethylbibenzyl (mp 81–82°, undepressed by admixture with an authentic sample⁹) was isolated by column chromatography. This product suggested that diradical III intervened as the intermediate in this reduction, and that V was the intermediate in the above racemization reaction.



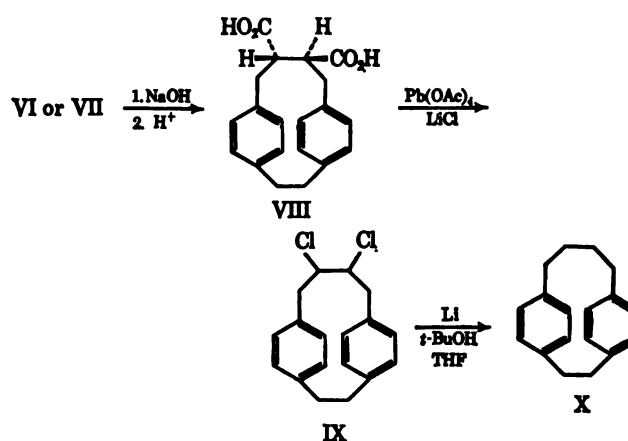
Dimethyl maleate and dimethyl fumarate esters exhibit particularly favorable tendencies to form ABAB copolymers in styrene radical polymerization under conditions that produce little homopolymerization.⁸ Thus, it seemed possible that if diradical III were an intermediate in the thermolysis of I, then I might ring expand to a diester of [2.4]paracyclophane (VI) or VII) when heated with either of the two esters. Accordingly, 3.0 g of I was heated in 8.0 g of dimethyl fumarate in the absence of air at 200° for 40 hr. The product was subjected to silica gel chromatography and fractional crystallization; 0.902 g of starting material (I) was recovered, and 0.867 g of VI (mp 202.5–203.5°)^{7a} and 0.800 g of VII (mp 88–89°)^{7a} were isolated. A parallel experiment conducted in dimethyl maleate gave similar results.



(8) (a) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 132; (b) F. R. Mayo and C. Walling, *Chem. Rev.*, **46**, 191 (1950).

(9) These yields were determined by a combination of gravimetric and nmr procedures.

The nmr spectra of VI and VII exhibit high-field aromatic absorption bands (above τ 3.3) characteristic of the smaller [*m,n*]paracyclophanes.¹⁰ The ultraviolet spectra of VI and VII are similar to that of [2.4]paracyclophane but distinctly different from other [*m,n*]paracyclophanes and open-chain materials.¹¹ Both VI and VII have carbonyl absorptions at 5.79 μ in their infrared spectra. Unambiguous proof that VI and VII possess the indicated ring structure is provided by degradation experiments. The diacid VIII^{7a} derived from either VI or VII by alkaline hydrolysis was decarboxylated¹² with lead tetraacetate and lithium chloride in pyridine to give a 15–35% yield of dichloride IX,^{7a} mp 147–148°. Treatment of IX with lithium in refluxing *t*-butyl alcohol–tetrahydrofuran¹³ gave a 57% yield of [2.4]paracyclophane (X), identical with authentic material^{11a} (melting point, mixture melting point, and nmr comparisons).



The assignment of the *trans* structure to VI and the *cis* structure to VII was made as follows. Treatment of VII with sodium methoxide in refluxing methanol–dimethoxyethane gave a high yield of VI (less than 0.5% of VII by nmr analysis remained). Thus, VI is more thermodynamically stable than VII by at least 3.5 kcal/mole. Molecular models indicate unambiguously that the *cis* structure is highly compressed compared to the *trans*. The rigid geometry of the ring system forces one of the carbomethoxy groups between the two benzene rings in the *cis* isomer.

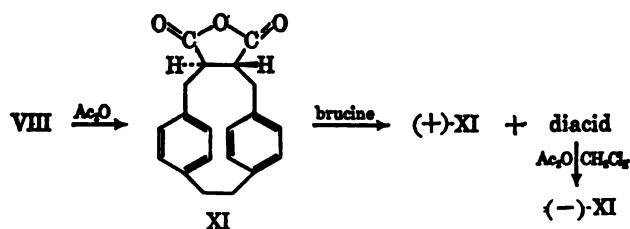
Alkaline hydrolysis of either VI or VII gave the same diacid, VIII, which when reesterified gave only VI. Apparently VII isomerized during hydrolysis. Diacid VIII, when heated in acetic anhydride, readily formed the stable cyclic anhydride XI,^{7a} 87% yield, mp 234.5–235.5°, carbonyl frequencies at 5.37 and 5.62 μ in the infrared. A sample of XI was hydrolyzed 25% in benzene with brucine hydrate at 80° for 20 min. The recovered anhydride gave $[\alpha]^{25}_{435} 0.67^\circ$ (c 8, dichloromethane). The diacid formed was reconverted to anhydride, which had $[\alpha]^{25}_{435} -2.68^\circ$ (c 8, dichloromethane). These experiments demonstrate unambiguously that XI, VIII, and VI possess the *trans* structures and are racemates, and that VII has the *cis* structure and is a *meso* form.

(10) (a) L. A. Singer and D. J. Cram, *J. Am. Chem. Soc.*, **85**, 1080 (1963); (b) D. J. Cram and R. C. Helgeson, *ibid.*, **88**, 3515 (1966).

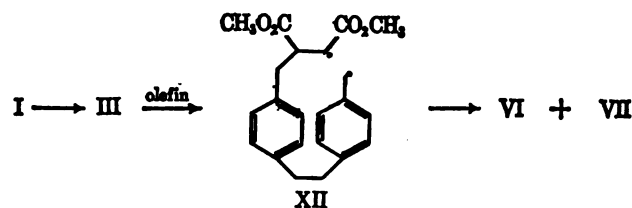
(11) (a) D. J. Cram and H. Steinberg, *ibid.*, **73**, 5691 (1951); (b) D. J. Cram, *Record Chem. Progr.*, **20**, 71 (1959).

(12) J. K. Kochi, *J. Am. Chem. Soc.*, **87**, 2500 (1965).

(13) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960).



The olefin insertion reaction undoubtedly involves production of the diradical III, one benzyl carbon atom of which adds to olefin to produce a second diradical, XII, which in turn ring closes to give VI and VII. Intermediate XII must have a sufficient lifetime to destroy the stereochemical memory of the adding olefin before ring closure. The lack of stereospecificity¹⁴ of the insertion reaction precludes any concerted addition to the diradical III or to [2.2]paracyclophane itself.



(14) Appropriate control experiments demonstrated that dimethyl maleate, dimethyl fumarate, and VII are essentially configurationally stable under the reaction conditions.

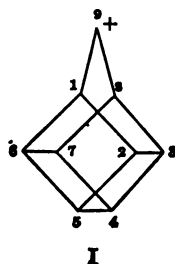
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Contribution No. 2083, Department of Chemistry
 University of California, Los Angeles, Los Angeles, California 90024
 Received April 7, 1967

Stereospecific Rearrangements in the Homocubyl Cation

Sir:

Of the fluconal molecules now known, bullvalene remains the most remarkable in that *via* a series of Cope rearrangements the system can undergo degenerate valence tautomerism which ultimately leads to complete scrambling of the carbon atoms in the framework.¹ Among other systems which can, in principle, behave similarly is the 9-homocubyl cation I; in this case, a succession of Wagner-Meerwein rearrangements continually regenerates the 9-homocubyl



cation and results in scrambling of the nine methine units.

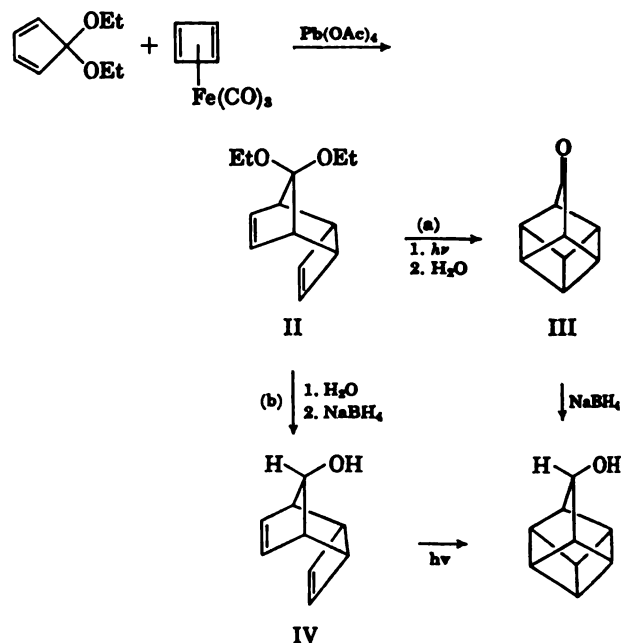
In a recent communication, Schleyer and co-workers² have reported preliminary studies dealing with the synthesis and rearrangement of the homocubyl cation.

(1) W. von E. Doering and W. Roth, *Tetrahedron*, **19**, 715 (1963); G. Schröder, J. F. M. Oth, and R. Merenyi, *Angew. Chem. Intern. Ed. Engl.*, **4**, 752 (1965).

(2) P. von R. Schleyer, J. J. Harper, G. L. Dunn, V. J. Di Pasquo, and J. R. E. Hoover, *J. Am. Chem. Soc.*, **89**, 698 (1967).

We have independently been investigating this same problem and wish to report our initial results at this time. These results, based upon both a different synthesis and method of rearrangement detection, are in agreement with those of Schleyer, *et al.*,² in showing that the homocubyl cation when generated in acetic acid does undergo several degenerate rearrangements before forming the acetate. In addition, evidence indicates the reaction to be stereospecific and that much of the scrambling proceeds *via* internal return of the tosylate employed.

9-Homocubyl tosylate was prepared by two related pathways. Oxidative decomposition of cyclobutadieneiron tricarbonyl with lead tetraacetate in pyridine in the presence of cyclopentadienone diethyl ketal³ afforded the adduct II.⁴ In path a irradiation of II in acetone gave 9,9-diethoxyhomocubane which upon



hydrolysis yielded homocubanol III. Reduction of III with sodium borohydride produced 9-homocubanol which was converted to the tosylate in the usual manner. The tosylate (mp 73–73.5°) displayed absorptions in the nmr at τ 2.42 (area 4), 5.12 (1), 6.33–7.00 (8), and 7.56 (3).⁶ In path b, hydrolysis of the ketal II followed by reduction with NaBH_4 afforded predominantly the alcohol IV in which the stereochemistry of the hydroxyl group is as indicated.⁷ Irradiation of IV gave homocubanol.

(3) P. E. Eaton and R. A. Hudson, *ibid.*, **87**, 2769 (1965).

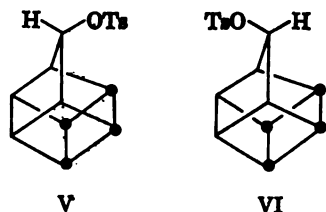
(4) Decomposition with ceric ion⁴ was unsatisfactory in that the ketal was rapidly hydrolyzed and dimerized to dicyclopentadienone.

(5) J. C. Barborak, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **88**, 1328 (1966).

(6) The physical properties of 9-homocubanol and its acetate and tosylate were identical with those reported by Schleyer and co-workers.¹

(7) This isomer is formed in better than 90% yield. The stereochemistry is indicated by the nmr pattern of the 7,8-olefinic protons (triplet) characteristic of 7-antisubstituted norbornenes [see E. I. Snyder and B. Franzus, *J. Am. Chem. Soc.*, **86**, 1166 (1964)]. In addition, in the mixture of tetradeuterated 9-homocubyl tosylates made *via* pathway a (see text) there exists two distinct regions of absorptions for the ring protons other than C₉; these occur in the regions τ 6.4–6.6 and 6.6–7.0 of areas 1:3, respectively. The lower field set (τ 6.4–6.6) must therefore be associated with those protons situated beneath the tosylate group rather than those β to the tosylate group. In the *d*₄ tosylate made *via* path b there is no absorption in the region τ 6.4–6.6 but all four protons appear at τ 6.65–6.9; therefore, the tosylate must be *syn* to two deuterium atoms, which requires the stereochemistry shown in IV.

In order to follow the extent of possible rearrangement of the homocubyl ion accompanying solvolysis, the tetradeuterio derivative of homocubanol was prepared in an analogous manner starting with perdeuterio-cyclobutadieneiron tricarbonyl.⁸ Path a afforded an equal mixture of the two tosylates V and VI, while path b afforded the single isomer V.



A sample of V and another consisting of an equal mixture of V + VI was solvolysed in acetic acid at 120° for 30 hr, and the acetates and unreacted tosylates were recovered.¹⁰ The unique chemical shift of the C₉ proton in both the acetate and the tosylate allows a direct measure of the extent of rearrangement; however, the amount of deuterium appearing at C₉ will also depend on the stereospecificity of the process. In a stereospecific process involving repeated migration of the carbon atom *trans* to the leaving group, the sample of V should show twice as much deuterium at C₉ as that of the mixture V + VI since VI in such a process cannot generate deuterium at C₉. However, in a nonstereospecific process, the two samples should produce the same amount of deuterium at C₉.

The acetate produced from V showed $26.1 \pm 3\%$ deuterium at C₉, while that from V + VI showed $12.3 \pm 3\%$. The scrambling process under these conditions is clearly stereoselective if not entirely stereospecific. The relationship between the number of rearrangements which occur and the amount of deuterium they generate at C₉ for the stereospecific process is shown in Table I.¹¹

Table I. Percentage of D at C₉ Accompanying 1,2 Shifts of V

No. of 1,2 shifts	0	1	2	3	4	5	6	∞
% D at C ₉	0	0	12.5	21.9	28.1	32.2	35.0	40.0

On the average close to four Wagner-Meerwein shifts had therefore occurred in the over-all solvolysis. The recovered tosylates also contained deuterium at C₉ and to a larger degree than that observed for the acetates;¹² again approximately twice as much deuterium appeared at C₉ in the reaction of V as with the mixture V + VI. This indicated stereospecific rearrangement *via* internal return of the tosylate ion pair.¹³ The results of Schleyer and co-workers, however,

(8) Prepared by repeated treatment of cyclobutadieneiron tricarbonyl with CF₃COOD.⁹ Analysis by nmr methods indicated the starting perdeuterio complex contained at least 98% deuterium.

(9) J. D. Fitzpatrick, L. Watts, G. F. Emerson, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 3254 (1965).

(10) Under these conditions approximately 80% of the tosylate had reacted. The acetates were purified by repeated crystallization from pentane (mp 10–12°).

(11) This table ignores the isotope effect.

(12) Greater than five shifts are indicated.

(13) Concerning the question of possible bridged ion intermediates, it is of interest to note the stereospecificity of these rearrangements together with the enhanced rate of acetolysis found by Schleyer and co-workers.³

clearly indicate that in formolysis, at least, stereochemical leakage can occur.³

Acknowledgment. We thank the National Science Foundation and the Robert A. Welch Foundation for financial support. We also thank Badische Anilin und Soda Fabrik and General Aniline and Film Corporation for generous gifts of cyclooctatetraene and iron carbonyl, respectively.

James C. Barborak, R. Pettit

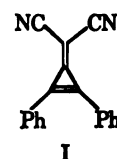
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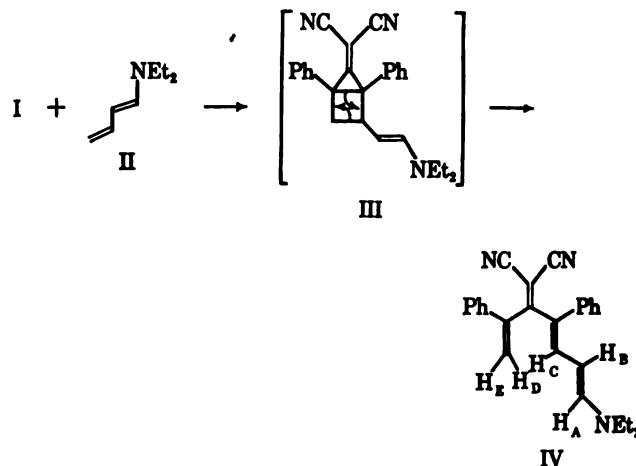
Cycloaddition Reaction of a Triafulvene with Enamines. Intermediacy of a 5-Methylenebicyclo[2.1.0]pentane

Sir:

Our recent study of the reaction of diphenylcyclopropanone with enamines^{1,2} prompted our investigation of the electronically similar triafulvene I.



Addition of 1.03 mmoles of freshly distilled 1-diethylamino-1,3-butadiene (II)³ in 3 ml of anhydrous benzene to 0.928 mmole of 1,2-diphenyl-3,3-dicyanomethylene cyclopropane (I)⁴ in 7 ml of benzene under a nitrogen atmosphere followed by heating at 50–60° for 2 hr produced a deep red color. Dilution with methylene chloride, extraction with aqueous 5% hydrochloric acid and saturated sodium chloride, removal of solvent, and recrystallization from benzene-hexane afforded brilliant orange needles in 82% yield, mp 200.5–201.0°. Structure IV is assigned on the basis of the following data: $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm⁻¹) 2215 (s),



1610 (s), 1555 (m), 1450 (s), 1415 (s), 1350 (m); $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ (m μ) 493 (ϵ 92,500), 247 (13,100), ~290 (5520); nmr (CDCl₃) (ppm from TMS) 1.05 (6 H, triplet, $J = 7$

(1) J. Ciabattini and G. A. Berchtold, *J. Am. Chem. Soc.*, **87**, 1404 (1965).

(2) J. Ciabattini and G. A. Berchtold, *J. Org. Chem.*, **31**, 1336 (1966).

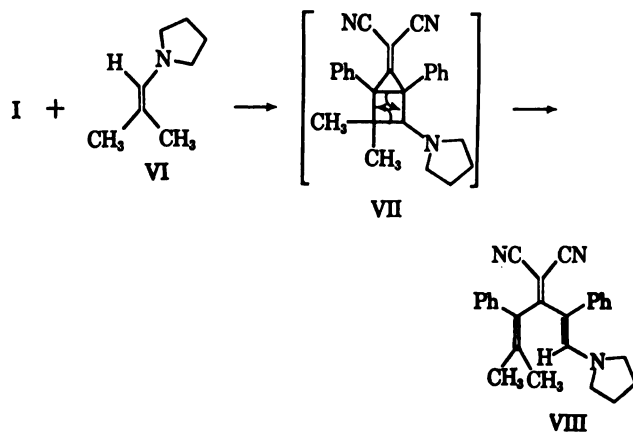
(3) S. Hünig and H. Kahanek, *Chem. Ber.*, **90**, 238 (1957).

(4) (a) S. Andreades, *J. Am. Chem. Soc.*, **87**, 3941 (1965); (b) E. D. Bergmann and I. Agranat, *ibid.*, **86**, 3587 (1964); (c) Y. Kitahara and M. Funamizu, *Bull. Chem. Soc. Japan*, **37**, 1897 (1964).

(cps), 3.11 (4 H, quartet, $J = 7$ cps), 4.97 (H_B , triplet, $J_{AB} = J_{BC} = 12$ cps), 5.43 (H_D or H_E , singlet, $J_{DE} = 0$), 6.00 (H_E or H_D , singlet, $J_{ED} = 0$), 6.76 (H_C , doublet, $J_{CB} = 12$ cps), 7.13–7.60 (11 H, complex multiplet, aromatics and H_A).⁸ *Anal.* Calcd for $C_{26}H_{22}N_2$: C, 82.29; H, 6.64; N, 11.07; mol wt, 379. Found: C, 82.41; H, 6.87; N, 11.04; (mass spectrum) m/e 379.

Tetraene IV⁶ must arise from an initial 1,2 cycloaddition of the 3,4-double bond of II⁷ to the endocyclic double bond of I⁸ and subsequent ring opening of the bicyclic intermediate III.⁹

Reaction of 0.723 mmole of 1-(N-pyrrolidino)-2-methylpropene (VI) with 0.618 mmole of I in benzene under similar conditions produced triene VIII as yellow plates in 92% yield after similar work-up and recrystallization from benzene-hexane: mp 188–189°; $\nu_{\max}^{CHCl_3}$ (cm^{-1}) 2210 (s), 1585 (s), 1455 (s), 1390 (s), 1310 (s);



$\lambda_{\max}^{C_2H_5OH}$ (m μ) 403 (ϵ 43,300), 236 (15,200), 290 (sh) (3600); nmr ($CDCl_3$) (ppm from TMS) 1.5–1.8 (4

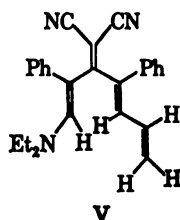
(5) The nmr spectra were recorded with a Varian A-60-A spectrometer. Mass spectral data were recorded on a Hitachi RMU-6D spectrometer. The infrared and ultraviolet data were taken on a Perkin-Elmer Model 337 grating spectrophotometer and a Cary Model 14 spectrophotometer, respectively. The A-60-A and RMU-6D spectrometers were purchased through a National Science Foundation major equipment grant to Brown University.

(6) Examination of Dreiding models reveals that the tetraene probably possesses the more favorable *trans,trans* geometry.

(7) The cycloaddition of sulfene ($CH_2=SO_2$) proceeds by initial attack at the 3,4-double bond of 1-dialkylamino-1,3-butadienes [G. Opitz and F. Schweinsberg, *Angew. Chem.*, 77, 811 (1965); Leo A. Paquette, private communication]. Ketene, on the other hand, undergoes cycloaddition to the 1,2-double bond of 1-(2-ethyl-4-methyl-1,3-pentadien-1-yl)piperidine [R. H. Hasek, P. G. Gott, and J. C. Martin, *J. Org. Chem.*, 31, 1931 (1966)].

(8) The addition of 1-diethylamino-1,3-butadiene to a dibenzocyclohexene derivative proceeds in 1,4 manner [H. Prinzbach, U. Fischer, and R. Cruse, *Angew. Chem.*, 78, 268 (1966)].

(9) The simplicity of the nmr spectrum precludes the alternative possibility of an initial cycloaddition of I to the 1,2-double bond of II to give ultimately, after ring opening, tetraene V.



H, $-CH_2CH_2-$, multiplet), 1.88 (3 H, CH_3 , singlet), 1.98 (3 H, CH_3 , singlet), 2.7–3.3 (4 H, $-CH_2NCH_2-$, broad singlet), 7.05–7.40 (10 H, multiplet, aromatics), 7.56 (vinyl H, singlet). *Anal.* Calcd for $C_{26}H_{22}N_2$: C, 82.29; H, 6.64; N, 11.07; mol wt, 379. Found: C, 82.29; H, 6.86; N, 11.09; (mass spectrum) m/e 379.

The production of compounds IV and VIII necessitates the intermediacy of the substituted 5-methylenebicyclo[2.1.0]pentane derivatives III and VII,¹⁰ respectively. Whether the formation as well as the ring opening of intermediates III and VII proceeds by a concerted or stepwise process is questionable.

Further investigations of these reactions employing other enamines as well as triafulvenes are in progress.

Acknowledgment. We thank the National Institutes of Health (Grant No. GM 14579-01) for generous support of this work.

(10) The reaction of 1,2-diphenyl-3-carbomethoxymethylenecyclopropene with tetracyanoethylene reportedly proceeds across the exocyclic double bond of the triafulvene to give a spirohexene derivative [M. A. Battiste, *J. Am. Chem. Soc.*, 86, 942 (1964)]. On the other hand, 1,2-di-*n*-propyl-3-dicyanomethylenecyclopropene fails to react with tetracyanoethylene under similar conditions [A. S. Kende and P. T. Izzi, *ibid.*, 86, 3587 (1964)].

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Received April 10, 1967

Catalysis of Hydrogen Exchange in *m*-Dinitrobenzene¹

Sir:

In the interaction of aromatic nitro compounds with bases, nuclear hydrogen abstraction is the least well characterized process; the formation of charge-transfer complexes,^{2a} of radical anions,^{2b} and latterly of Meisenheimer adducts³ is well substantiated. Due to the contradictory reports^{4–10} as to the feasibility and significance of such proton abstraction we have undertaken a systematic study of the process. Further, it was hoped that these studies would also provide information on the nature of the catalysis of aromatic hydrogen abstraction. Whereas general-base catalysis of proton abstraction from aliphatic carbon (eq 1) is well documented,^{11a} corresponding evidence for

(1) Hydrogen Exchange Studies. IV.

(2) (a) G. Briegleb, "Electronen-Donator-Acceptor-Komplexe," Springer-Verlag, Berlin, 1961; (b) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, 86, 1807 (1964).

(3) M. R. Crampton and V. Gold, *Chem. Commun.*, 549 (1965); R. Foster and C. A. Fyfe, *Tetrahedron*, 22, 1831 (1966); K. L. Servis, *J. Am. Chem. Soc.*, 89, 1508 (1967); J. H. Fendler, *et al.*, *J. Org. Chem.*, in press.

(4) J. A. A. Ketelaar, A. Bier, and H. T. Vlaar, *Rec. Trav. Chim.*, 73, 37 (1954).

(5) V. Baliah and V. Ramakrishnan, *ibid.*, 78, 783 (1959); 79, 1150 (1960).

(6) R. E. Miller and W. F. K. Wynne-Jones, *J. Chem. Soc.*, 2375 (1959); 4886 (1961).

(7) R. J. Pollitt and B. C. Saunders, *Proc. Chem. Soc.*, 176 (1962).

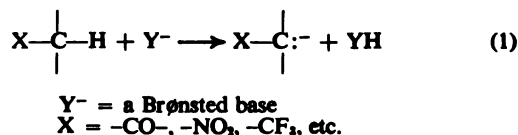
(8) R. Foster and R. K. Mackie, *Tetrahedron*, 19, 691 (1963).

(9) M. R. Crampton and V. Gold, *J. Chem. Soc., Phys. Org.*, 498 (1966).

(10) Part III of series: E. Bunce and E. A. Symons, *Can. J. Chem.*, 44, 771 (1966).

(11) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959: (a) Chapters 9 and 10; (b) Chapter 4.

aromatic hydrogen has not yet been available. The reason is clearly that abstraction of aromatic hydrogen, conveniently measured by isotopic exchange, typically



requires very strongly basic systems such as potassium amide in liquid ammonia¹² or lithium cyclohexylamide in cyclohexylamine;¹³ these systems have afforded valuable information on relative acidities of hydrogens in different environments but have left unanswered the question whether Brønsted bases such as azide ion, amines, etc., can partake in aromatic hydrogen abstraction.

The compound chosen for study was 1,3-dinitrobenzene since this was reported⁷ to exchange the 2-hydrogen under the unusually mild conditions of sodium deuterioxide in DMF-D₂O. We now report some results of the effect of a number of Brønsted bases, and also of reaction medium, on this hydrogen-exchange process. The media examined were dimethylformamide, dimethyl sulfoxide, and dimethoxyethane, containing deuterium oxide. Exchange was allowed to proceed at 30° for the more reactive bases and at 100° for the less reactive ones. The extent of exchange under standard conditions is taken to be a measure of the relative proton abstracting abilities of the bases in the particular media.

The results (Table I) indicate a dependence of reactivity on medium and base. The effect of medium is seen with reference to deuterioxide,¹⁴ acetate, and azide ions. The DMF and DMSO media are about equally facile in base catalysis and are much more effective than DME. In considering a reactivity order with respect to base the anionic and neutral bases must be treated separately to allow for the markedly different medium effects on base strength expected for bases of different charge type;¹⁵ the basicity of the anionic bases will be greatly enhanced by a change to a dipolar aprotic medium, but the basicity of the neutral bases will remain relatively unaffected.¹⁶ Among the anionic bases the reactivity order, for DMF medium, is DO⁻ > PhO⁻ > SO₃²⁻ ≈ AcO⁻ > N₃⁻, which approximates a decreasing order of base strength as given by the pK_a's of the conjugate acids.¹⁷ The

data for the amines do not fall into a definite order, consistent with the known^{11b,18} medium dependence of relative base strengths of primary, secondary, and tertiary amines. Pyridine is seen to be unreactive.

Table I. Exchange of the 2-Hydrogen in 1,3-Dinitrobenzene^a

Y ⁻ ^b (pK _a) ^c	Medium ^d	Temp, °C	% deuteration ^e
OD ⁻ (15.7)	DMF	30	92
	DME	30	29
PhO ⁻ (9.9)	DMF	30	42
SO ₃ ²⁻ (7.1)	DMF	100	83
AcO ⁻ (4.7)	DMF	100	85
	DMSO	100	86
	DME	100	0
N ₃ ⁻ (4.0)	DMF	100	74
	DMSO	100	79
	DME	100	0
Piperidine (11.2)	DMF	100	45
Triethylamine (10.6)	DMF	100	24
n-Hexylamine (10.4)	DMF	100	40
1,4-Diazabicyclo-[2.2.2]octane (8.6)	DMF	100	34
Pyridine (5.4)	DMF	100	0

^a Reaction time was 16 hr throughout. ^b The anions were present as sodium salts. Concentrations were: [Y⁻] = 0.05 M; [1,3-dinitrobenzene] = 0.5 M. In the case of the phenoxide exchange 0.05 M phenol was also present, to repress the deuterioxide ion concentration. ^c The pK_a values refer to water. ^d Contains 10% D₂O by volume. ^e Exchange was measured by infrared and nmr; no evidence was found for exchange of the other hydrogens of the substrate. Maximum theoretical deuteration with the experimental D:H ratio was 95%.

A number of factors are pertinent in consideration of the above results. (1) The apparent parallelism between the extent of exchange and pK is not alone conclusive evidence of Brønsted base catalysis, since lyate ion catalysis as the main cause of exchange is not ruled out thereby. In this respect the significantly lower reactivity of triethylamine, particularly in comparison with the unhindered tertiary amine 1,4-diazabicyclo[2.2.2]octane, which can be ascribed to steric hindrance to proton transfer,¹⁹ argues against lyate ion catalysis as the predominant factor. (2) Evidence has been presented²⁰ that, as a result of hydrogen bonding, internal return in the solvated carbanions may form part of the rate-determining step in certain reaction media. In this connection it is noted that the DMF-D₂O medium was used in a similar study²¹ of kinetic acidities of some carbon acids and that the derived pK_a scale was in good accord with data obtained from other studies.²² Hence the common mechanism for these exchange processes is taken to be rate-determin-

tion for bases of a given charge type.^{11,16} (Sulfite ion should, strictly, not be included in the series for this reason.)

(18) R. G. Pearson and D. C. Vogelsong, *J. Am. Chem. Soc.*, **80**, 1038 (1958).

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(20) J. E. Hofmann, A. Schriesheim, and R. E. Nickols, *Tetrahedron Letters*, 1745 (1965); W. T. Ford, E. W. Graham, and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 690 (1967).

(21) R. E. Dessy, Y. Okuzumi, and A. Chen, *ibid.*, **84**, 2899 (1962).

(22) Summarized in D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 19.

(12) G. E. Hall, R. Piccolini, and J. D. Roberts, *J. Am. Chem. Soc.*, **77**, 4540 (1955); A. I. Shatenshtein, *Tetrahedron*, **18**, 95 (1962); J. A. Zoltewicz and J. F. Bunnett, *J. Am. Chem. Soc.*, **87**, 2640 (1965).

(13) A. Streitwieser, Jr., J. R. Caldwell, R. G. Lawler, and G. R. Ziegler, *ibid.*, **87**, 5399 (1965).

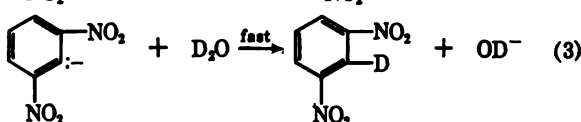
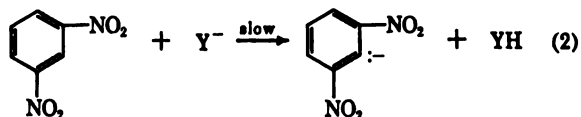
(14) DMSO medium was not used in the case of deuterioxide since DMSO itself undergoes a facile deuterioxide-catalyzed hydrogen exchange.¹⁶ No evidence was found for hydrogen exchange of DMSO in presence of azide or acetate ions.

(15) E. Buncl, E. A. Symons, and A. W. Zabel, *Chem. Commun.*, 173 (1965).

(16) A. J. Parker, *Quart. Rev. (London)*, **16**, 163 (1962); B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Am. Chem. Soc.*, **88**, 1911 (1966); R. G. Pearson, *ibid.*, **85**, 3533 (1963); R. Gompper, *Angew. Chem. Intern. Ed. Engl.*, **3**, 560 (1964).

(17) The pK_a values quoted are for H₂O; they will be affected by a change to D₂O and also to the largely nonaqueous media. Considerations of the pK dependence of hydrogen exchange will be valid as long as the relative order of the pK's remains unaffected by the medium changes. There is good ground for the general validity of this assumption.

ing abstraction of hydrogen by the Brønsted base, followed by fast protonation by solvent of the resulting carbanion (eq 2-4). (3) Since the reaction medium



in some of these exchange processes ($\text{Y}^- = \text{OD}^-$, PhO^- , $\text{S}_2\text{O}_3^{2-}$) was strongly colored (deep red or purple) it is possible that the anion was partly tied up in the form of Meisenheimer adducts; on the other hand the colors may only be indicative of charge-transfer complexing. Detailed equilibrium studies with respect to complex formation, coupled with kinetic studies on the exchange process, will be required to separate these effects. The studies relevant to these factors are under active consideration.

Acknowledgment. This research was supported by a grant (PRF 1841 A-4) from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

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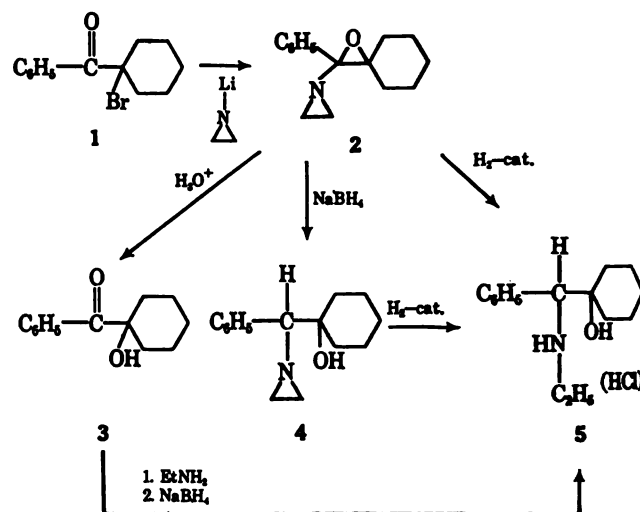
Epoxyamines. A New Functional Group in Organic Chemistry

Sir:

We wish to report the preparation and rearrangement of a new class of organic compounds, the epoxyamines. Although the concept of this unusual functional group has been invoked as an intermediate in several instances,¹⁻³ isolation and complete characterization of an example previously had not been accomplished.⁴ The apparent inaccessibility of these compounds had been attributed to their high reactivity and to the possibility of facile rearrangements.^{1,2}

We have now isolated a stable crystalline epoxyamine, 2-(1-aziridinyl)-2-phenyl-1-oxaspiro[2.5]octane (2), by the action of the lithium salt of ethylenimine⁵

on α -bromocyclohexyl phenyl ketone⁶ (1) in ether at room temperature. Evaporative distillation (bath temperature 90–100° (0.01 mm)) of the crude product gave 70–75% of 2, bp 90–95° (0.001 mm), n_D^{25} 1.5870, which could be crystallized from pentane; mp 20–22°. The infrared spectrum was devoid of any hydroxyl and carbonyl absorptions but had strong peaks at 1025 and 1045 cm^{-1} . The nmr spectrum (CDCl_3) was consistent with structure 2, showing aromatic protons from τ 2.45 to 2.85 and aliphatic protons from τ 7.8 to 9.0 in the ratio 5:14.



Hydrolysis with 2 *N* hydrochloric acid converted 2 into the known α -hydroxycyclohexyl phenyl ketone⁶ (3) in 90% yield. Reduction of 2 with sodium borohydride in methanol gave 1-[α -(1-aziridinyl)benzyl]cyclohexanol (4) (60%), mp 113–114°. Hydrogenation of 4 in ethanol at atmospheric pressure using 10% palladium on carbon as catalyst yielded 1-(α -N-ethylaminobenzyl)cyclohexanol (5), characterized as its hydrochloride (85%), mp 223–224° dec. This amino alcohol 5 was also formed in 80% yield by direct hydrogenation of 2 in methanol using the same catalyst. The structure of 5 was confirmed by its formation from the sodium borohydride reduction of α -hydroxycyclohexyl phenyl ketone *N*-ethylimine, which in turn was made from ethylamine and 3 in the presence of potassium carbonate.

When heated to the reflux temperature in *o*-dichlorobenzene for 15 hr under a nitrogen atmosphere, 2 rearranged with ring expansion to give 2-(1-aziridinyl)-2-phenylcycloheptanone (6) in 35–38% yield, the remainder of the material being an intractable resin. This rearrangement was particularly interesting, since according to a previous postulate⁷ α -(1-aziridinyl)cyclohexyl phenyl ketone (7) would have been the expected product. To show that 7 was not an intermediate in the transformation of 2 to 6, 7 was prepared by the general method⁸ involving the action of ethyl-

aldehydes and ketones suggested that it might impart stability to this class of compounds. Cf. A. Dornow and W. Schacht, *Chem. Ber.*, **82**, 464 (1949).

(6) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 618 (1952).

(7) A. Kirmann, R. Muths, and J.-J. Riehl, *Bull. Soc. Chim. France*, 1469 (1958).

(8) C. L. Stevens and C. H. Chang, *J. Org. Chem.*, **27**, 4392 (1962).

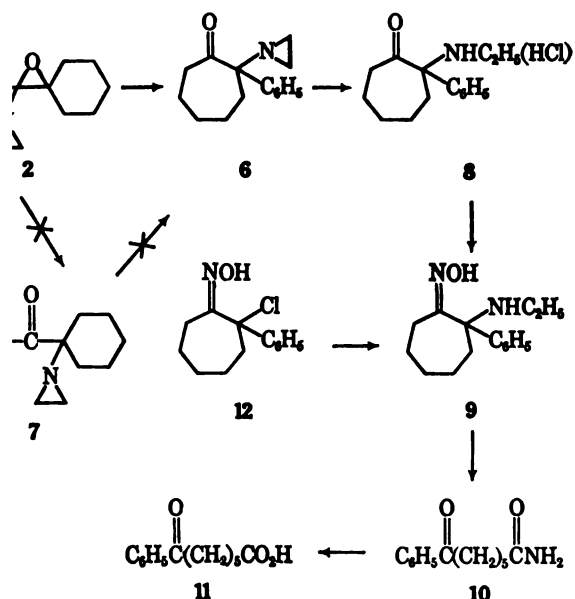
(1) C. L. Stevens, P. Blumbergs, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963), and references cited therein.

(2) A. Kirmann and H. I. Joschek, *Bull. Soc. Chim. France*, 3483 (1963).

(3) A. Hassner and P. Catsolacos, *J. Org. Chem.*, **32**, 549 (1967).

(4) M. Mousseron, J. Jullien, and Y. Jolchine, *Bull. Soc. Chim. France*, 757 (1952), reported the formation of an epoxyamine as a by-product in the reaction of 2-chlorocyclohexanone with aqueous dimethylamine, but they did not fully characterize or establish the structure of the material.

(5) The fact that ethylenimine forms stable addition products with



on an epoxy ether, 2-methoxy-2-phenyl-1-oxaspiro[2.5]octane,⁶ in 84% yield (bp 102–105° mm), n_D^{25} , 1.5502). After 7 was subjected to rearrangement conditions, most of the starting material (55%) was recovered unchanged and an examination of the infrared spectrum of the crude reaction product provided evidence that no detectable amount of 6 was formed.

Upon hydrogenation in ethyl acetate at atmospheric pressure in the presence of 10% palladium on carbon, 6 was selectively reduced to 2-N-ethylamino-2-phenylcycloheptanone (8), characterized as its hydrochloride (85%), mp 233–235° dec, $pK_a' = 7.70$ (50% methanol). Ketone 8 was converted to the corresponding oxime 9 (64%), mp 105–106°, $pK_a' = 8.75$ (50% methanol). Synthesis of 9 was also achieved by the action of ethylamine on the known 2-chloro-2-phenylcycloheptanone oxime⁹ (12). Structure 9 was further confirmed by the formation of 6-benzoylhexanamide (10) (60%), mp 107–108°, when the oxime was subjected to Beckmann degradation conditions using polyphosphoric acid. On treatment with aqueous alcoholic sodium hydroxide 10 was hydrolyzed to the known 6-benzoylhexanoic acid (11) (90%), mp 82–83°. The identity of 11 was established by mixture melting point determination with an authentic sample.

All new numbered compounds have analyses and spectral data consistent with their structures.

Acknowledgment. The authors are grateful to Dr. K. Grant Taylor for helpful suggestions.

(9) D. Ginsberg and R. Pappo, *J. Am. Chem. Soc.*, **75**, 1098 (1953).

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Additions and Corrections

Analysis of α -Hydrogen Exchange. I. The Reaction of n-Butyraldehyde-2-d with Tertiary Amines and Amine Bases [*J. Am. Chem. Soc.*, **87**, 5050 (1965)]. BY JACK HINE, JAMES G. HOUSTON, JAMES H. JENSEN, JULIEN MULDER, School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia.

In this paper an incorrect value for the van der Waals constant of argon was used. The distance 2.45 Å, at which the energy of repulsion is 11.2 kcal/mole, is only 2 times 1.91 Å, the atomic radius for argon given by G. Pannetier, "Nouveau Traité de Chimie Minérale," P. Pascal, Ed., Vol. 1, Masson et Cie., 1956, p 941. With this change, eq 2 becomes

$$E_r = 0.112 \left(\frac{d_0}{d} \right)^{11} - 0.175 \left(\frac{d_0}{d} \right)^7 + 0.06 \quad (2)$$

The energies of repulsion (calculated without allowance for molecular distortion) are only 32% as large as

those calculated originally, but they are still considerably larger than the experimental values. None of the qualitative conclusions is affected by this change.

A Molecular Orbital Theory of Optical Rotatory Strengths of Molecules [*J. Am. Chem. Soc.*, **88**, 4157 (1966)]. BY YOH-HAN PAO and D. P. SANTRY, Bell Telephone Laboratories, Inc., Murray Hill, New Jersey, and Carnegie Institute of Technology, Pittsburgh, Pennsylvania.

On page 4158, eq 1.2 should read

$$\psi_i = \sum_{\mu} \chi_{\mu} C_{\mu i} \quad (1.2)$$

On page 4159, line 10 of column 1 should read M is the magnetic moment operator. Equation 2.9 should read

$$\langle \psi_j | m | \psi_i \rangle = -i \sum_A \{ (C_{sA_j} C_{zA_i} - C_{zA_j} C_{sA_i}) x + (C_{sA_j} C_{yA_i} - C_{yA_j} C_{sA_i}) y + (C_{sA_j} C_{zA_i} - C_{zA_j} C_{sA_i}) z \} \times R_A W_{sp}^A + (C_{yA_j} C_{zA_i} - C_{zA_j} C_{yA_i}) x + (C_{sA_j} C_{zA_i} - C_{zA_j} C_{sA_i}) y + (C_{sA_j} C_{yA_i} - C_{yA_j} C_{sA_i}) z \} \quad (2.9)$$

On page 4161, second column, the first sentence should read: The equatorial proton of carbon atom 2 lies in a negative octant, and almost in the plane *B*. The octant rule predicts a small negative rotation for H₇ in methylcyclohexanone. On page 4162, line 5 of column 1, delete the words "shown in Figure 3."

Stereochemical Consequences of Methoxyl Participation. The Stereochemistry of the Cyclization of 5-Methoxy-2-pentyl Brosylate to 2-Methyltetrahydrofuran [*J. Am. Chem. Soc.*, **89**, 73 (1967)]. By ERNEST R. NOVAK and D. STANLEY TARBELL, Department of Chemistry, University of Rochester, Rochester New York 14627.

Add the following sentence to the last paragraph in the second column on page 74: If this assignment of configuration is correct, the [*+*]-2-chloro-5-methoxypentane is formed from the (*R*)-brosylate **3b** by a process involving *one* inversion. On page 76, revise the last sentence of the first paragraph under Discussion of Results to read as follows: Attack of chloride ion at C-5 of the methoxonium ion yields the 5-chloro-2-methoxypentane, the latter with (*R*) configuration, because removal of the chlorine yields (*R*)-2-methoxypentane.

A New and Convenient Alkylation and Acylation of Pyridine N-Oxides [*J. Am. Chem. Soc.*, **89**, 1537 (1967)]. By R. A. ABRAMOVITCH, MAITREYI SAHA, and ELIZABETH M. SMITH, University of Saskatchewan, Saskatoon, Saskatchewan, Canada, and R. T. COUTTS, University of Alberta, Edmonton, Alberta, Canada.

On page 1538, the structures just above the Acknowledgment should be numbered VII.

Book Reviews

The Chemistry of Technetium and Rhenium. By R. D. PEACOCK, Professor of Inorganic Chemistry, The University of Leicester, Great Britain. American Elsevier Publishing Co., Inc., 52 Vanderbilt Ave., New York, N. Y. 1966. 137 pp. 14 × 22 cm. \$10.00.

Although one book and six review articles on one or the other of the elements technetium and rhenium have appeared during the period 1957-1964, a critical discussion and comparison of the chemistry of these two metals, last published in one volume 10 years ago (in French), is now most welcome. Despite the rarity of these two elements (technetium has only recently become available in weighable quantities at a price of about \$200/g), there have been over 500 citations in the literature about them and interest is increasing. This no doubt is due in part to the chemical novelties discovered through this group such as the first demonstration of Lewis base properties for a transition metal in its complexes (in the reaction $(C_6H_5)_3ReH + H^+ \rightarrow (C_6H_5)_3ReH_2^+$), the unique ions TcH_2^{3-} and ReH_2^{3-} containing only transition metal to hydrogen bonds, the polynuclear halogenometalate $Re_2Cl_8^{4-}$ whose diamagnetism can best be explained by a *quadruple* bond between rhenium atoms, and the first polynuclear carbonyl hydrides, $H_2Tc_2(CO)_{12}$, $H_2Re_2(CO)_{12}$, and $HRe_3(CO)_{14}$. (The latter was characterized too recently to be included in this monograph; another recent discovery in this group is the rare trigonal prismatic coordination for $Re(S_2C_2Ph_2)_2$, the first known molecular complex to display this geometry.)

In the present monograph the literature is well covered through 1963 with some references to later work appearing in scattered portions of the text. A general bibliography and further references (through June 1965) are presented in two appendices which will be useful to the reader. The first two chapters in the text deal with the discovery, isolation, and general properties of the two elements. A systematic survey is presented in the next eight chapters, under the following headings: Oxides; Oxoacids and Oxoalts; Halides and Oxide Halides; Complex Halides, Complex Oxide Halides and Complex Hydrides; Chalcogenides and Compounds with Nonmetals and Metalloids, Alloys; Complex Cyanides and Related Compounds; Carbonyls and Organometallic Derivatives; Compounds with Group V and Group VI Ligands. Seven figures are scattered throughout these chapters summarizing related chemical

reactions in a schematic way; these will also be a help to the reader. A chapter on analytical methods and three appendices (two mentioned above and one containing notes on the laboratory handling of technetium) conclude the text. A subject but no author index is available.

In the area of organometallic chemistry and polynuclear carbonyl hydrides, the coverage of the literature was incomplete, and the cited references suffered from more than the average typographical errors. Furthermore this reviewer takes issue with the heading "*M-C**," first column of infrared frequencies in Table 28 (p 105). These are alleged to have been assigned by the original workers to the M-H frequency. In the first place, no such assignment was proposed by those authors, but even so the substitute chosen for it is little better. In all likelihood the absorptions in question are mixtures of the several characteristic modes, the M-CO and M-H deformation as well as the M-C stretching vibrations, which fall in this range of energy.

The discussions of many subjects are extremely brief, and only a moderate number of tables of data are supplied. I do not believe a specialist would find this book useful as a desk copy. However, for others it should be valuable as an introduction to the literature. In this respect it is only somewhat more up to date than a monograph on precisely the same subject matter (by R. Colton) which was published a short time before (in a competing series on inorganic chemistry from Interscience). Such duplication is wasteful and of no advantage to the scientific community. The present divided and competing efforts are even more regrettable since they come from two former coauthors (R. Colton and R. D. Peacock, "The Chemistry of Technetium," *Quart. Rev.* (London), **16**, 311 (1962)). There ought to be some mechanism either between publishers or between authors to combine such efforts for the benefit of the readers and produce one work of greater scope and usefulness; for the present, at least one of these two monographs should find a place in any library specializing in chemistry.

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Chemicals on Dividing Cells. By BENGT A. KIHLMAN, Dr. Swedish Natural Science Research Council, Research Program of Biochemical Cytogenetics, Institute of Physiological Botany, Uppsala, Sweden. Prentice-Hall, Inc., Englewood Cliffs, N. J. 1966. xi + 260 pp. 16 × 23 cm. \$10.00.

The molecular mechanisms by which genes mutate have come to be fairly well understood in recent years. Since many of the physical and chemical agents that induce gene mutation also cause chromosome breakage and rearrangement, there has been reason to hope that our knowledge of these latter phenomena would advance rapidly. Moreover, in understanding what it takes to break and reorganize chromosomes, one could also expect to learn a good deal about chromosome structure and replication. Unfortunately, however, as this book makes abundantly clear, the problems of chromosome organization and breakage have not led to analysis as swiftly as have the analogous ones of gene structure and mutagenesis. Although a satisfactory explanation of the effects of chemical agents on chromosomes is not yet available, Professor Kihlman has performed a great service in condensing and arranging all of the relevant facts. His book will certainly be read with profit by students of the chromosome for many years to come.

Professor Kihlman has not been afraid to confront experimental facts that are contradictory or difficult to reconcile or out of line with attractively plausible hypotheses. While many knotty questions are left open, the author manages to keep our attention and to avoid confusion. The first part of the book is a brief review of the histology and physiology of the interphase cell, of DNA synthesis, chromosome replication, and mitosis. This review serves as a useful background for the second part, which is devoted to the question of mitosis and the production of chromosomal aberrations by chemical agents. A critical assessment of the experimental findings leaves us with little doubt that most of these agents affect either the structure or synthesis of DNA, but a clear relation between primary action of a chemical agent and a specific aberration cannot be unequivocally discerned. Nevertheless, we may hope that Professor Kihlman that "once fundamental chromosome structure is understood, the damaging effect of chemicals will be more readily comprehensible, and all of the pieces of the puzzle will then fall into place." In the meantime, this book provides a useful summary of what we know and what we need to know.

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Stable Monolayers at Liquid-Gas Interfaces. By GEORGE L. NILES, JR., Research Laboratory, General Electric Co., Schenectady, N. Y. Interscience Division of John Wiley and Sons, Inc., Third Ave., New York, N. Y. 1966. viii + 386 pp. 15.5 × 23 cm. \$14.00.

A half-century ago Irving Langmuir, one of the true geniuses in American chemistry, invented the surface balance and initiated systematic investigations on the properties of insoluble films on aqueous sub-solutions. Not only did he confirm the speculation of Lord Rayleigh and Agnes Pockels that these films were truly molecular, but he also discovered that the molecules in them are oriented with their polar groups immersed in the water and their long, nonpolar chains directed nearly vertically up from the surface. During the first 25 years after Langmuir's first publication, there was much activity in the United States and elsewhere, and the discipline of surface chemistry became firmly established. In the period following World War II, however, there seemed to be a slackening of interest until quite recently when the advance of monolayers to the control of evaporation from water reservoirs and to the understanding of the structures of membranes in living systems was recognized. This renaissance of research activity on insoluble monolayers is accurately reflected by this important new monograph; its appearance is timely and it is likely to stimulate further the realization of the elegance of the experimental method and its promise for understanding intermolecular forces.

The monograph has been written primarily for the researcher who wishes to study unimolecular films either for their own sake or to gain an understanding of natural phenomena involving liquid interfaces and oriented molecules. The tone of the book is essentially descriptive and critical with emphasis on modern

experimental methods and data with a minimum of interpretation. The coverage of laboratory procedures and techniques is comprehensive, and detailed accounts are given of the methods for measuring surface pressures, areas, contact potentials, and viscosities. The applications of optical and related methods, of radioactive tracers, and of measurements of gas transport and evaporation in the elucidation of monolayer behavior are also treated.

The organization and scope of the treatment is revealed by the thoughtfully chosen titles of the nine chapters of the book: Historical Introduction, The Properties of Liquid Surfaces, Experimental Methods: Properties of Liquid Surfaces, Experimental Methods: Properties of Monolayer Films, The Properties of Various Substances in Mono-molecular Films, Mixed Monolayers, Reactions in Monolayers, Transfer of Monolayers to Solids, and Scientific and Technological Applications. The usefulness of the work is augmented by its subject and author indexes and particularly by its index of film-forming compounds. The style of writing is graceful, clear, and concise when appropriate. The author, himself an active research worker on monolayers, is to be congratulated for his scholarly effort in getting out this highly useful, up-to-date summary.

Because of the detailed, almost handbook character of the long discussion (105 pages) on experimental methods, it was surprising that nothing seems to be said about methods for purifying the film-forming compounds themselves or about criteria for their purity. Dramatic examples of the importance of this factor may be found in the discrepancies reported in the literature between experienced investigators. Gas chromatographic techniques in their preparative and analytical applications should do much to ensure that highly accurate measurements will not be performed on impure compounds. Yet, this apparent omission is surely minor compared to the over-all usefulness of the book, which is recommended strongly for the beginner as well as for the experienced investigator.

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Recent Developments in the Chemistry of Natural Carbon Compounds. Volume I. By G. FODOR, D.Sc., Member of the Hungarian Academy of Sciences, Stereochemical Research Laboratory, Hungarian Academy of Sciences, K. NADOR, D.Sc., Institute for Experimental Medicine, Hungarian Academy of Sciences, and I. V. TORGOV, D.Sc., Institute of Organic Natural Compounds, Academy of Sciences of the USSR. Akadémiai Kiadó, Publishing House of the Hungarian Academy of Sciences, Budapest, Hungary. 1965. 319 pp. 17 × 24 cm. \$16.50.

This book is Volume 1 in a series, "Recent Developments in the Chemistry of Natural Carbon Compounds," the individual feature of which will be to collect "for the first time the relevant work of Hungarian chemists which so far has been available only scattered throughout the pages of various journals."

This first volume contains three sections, the first two of which are clearly directed toward the goal of making the results of Hungarian chemical research more readily available. G. Fodor, late of the Stereochemical Research Laboratory of the Hungarian Academy of Sciences and presently of Laval University, Quebec, Canada, writes on "New Methods and Recent Developments of the Stereochemistry of Ephedrine, Pyrrolizidine, Granatane and Tropane Alkaloids," with particular emphasis on work done in Hungary, though the entire field is very extensively reviewed. Most of the Hungarian work has used chemical interrelations between appropriate substances; modern physical techniques have not played a major role. A significant amount of work on biosynthesis of these alkaloids is also reviewed.

The second section, on "Relationships between the Structure and Pharmacological Activity of Tropeines" by K. Nador of the Institute of Experimental Medicine, also of the Hungarian Academy of Sciences, is an appropriate companion to the first. Nador, likewise, stresses the work in Hungary on this problem, particularly his own work and hypotheses. A large number of tables summarize the semiquantitative aspects of work in this area.

I. V. Torgov, of the Institute of Natural Organic Compounds of the Academy of Sciences of the USSR, has contributed the third section on "Achievements in the Total Synthesis of Natural Steroids," which, in a very different vein from the first two sections, reviews very concisely the work from the early synthesis of equilenin by Bachman, Cole, and Wilds in 1939-1940 to the synthesis of the

cardiac aglycone, digitoxigenin, and the steroidal alkaloid, connessine, in 1962. In the 84 pages of this section, Torgov has effectively outlined the many milestones in steroid synthesis. Because the literature is not reviewed beyond 1962, neither Barton's retraction of his first report on the synthesis of connessine nor Stork's synthesis of this substance are mentioned. Much of the material in this section is available already in L. F. Fieser's "Steroids," though the conciseness of Torgov's treatment and the importance of the subject make this the most generally interesting section of the book.

The text contains many instances of grammatical constructions unknown to Fowler, though the meaning is seldom, for this reason, unclear. The present volume can be recommended for those interested in the Hungarian work on stereochemistry and pharmacological activity of a family of alkaloids or in a concise review of steroid synthesis. The book suffers, badly, however, from the absence of either a subject or an author index.

J. H. Richards

*Contribution No. 3495, Gates and Crellin Laboratories of Chemistry
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BOOKS RECEIVED, April 1967

ADRIEN ALBERT. "The Acridines. Their Preparation, Physical, Chemical and Biological Properties and Uses." Second Edition. St. Martin's Press Inc., 175 Fifth Ave., New York, N. Y. 1966. 604 pp. \$32.50.

ALLEN J. BARD, Editor. "Electroanalytical Chemistry, A Series of Advances." Volume 1. Marcel Dekker, Inc., 95 Madison Ave., New York, N. Y. 1966. 426 pp. \$15.75.

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LESLIE E. ORGEL. "An Introduction to Transition-Metal Chemistry Ligand-Field Theory." John Wiley and Sons, Inc., 605 Third Ave., New York, N. Y. 1966. 186 pp. \$5.95.

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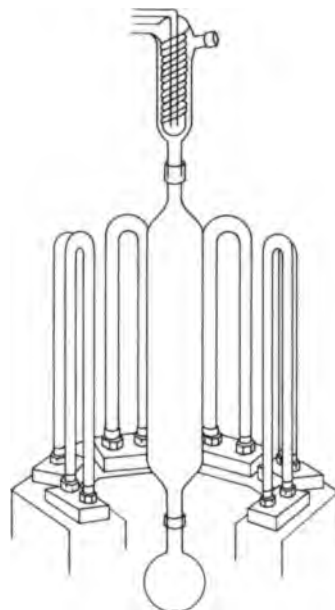
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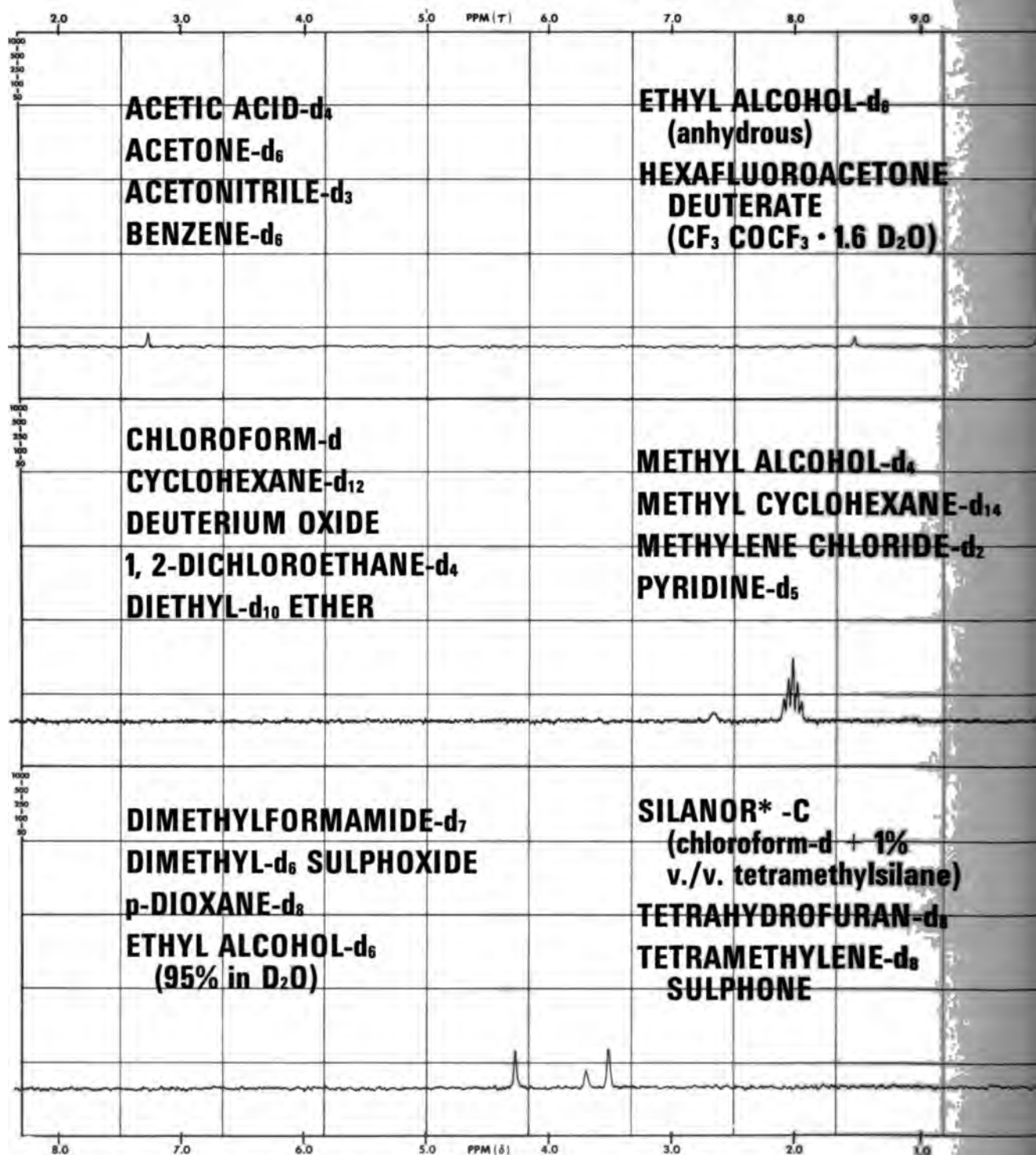
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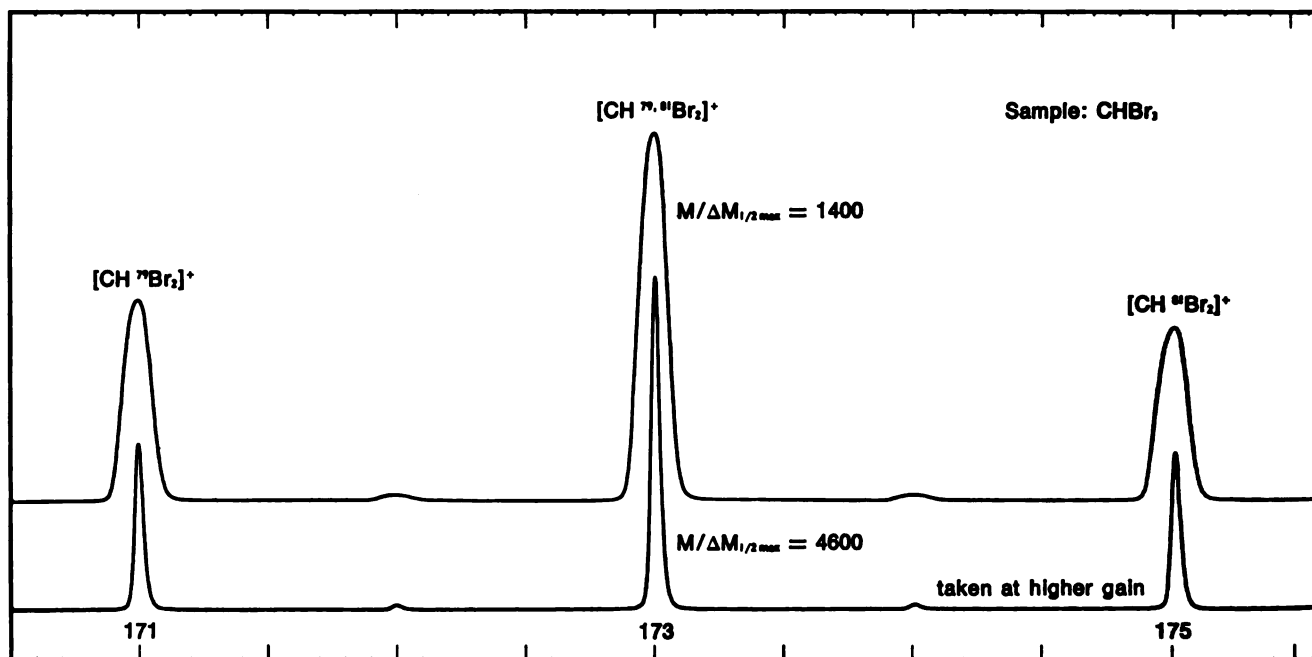
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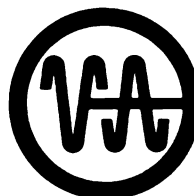


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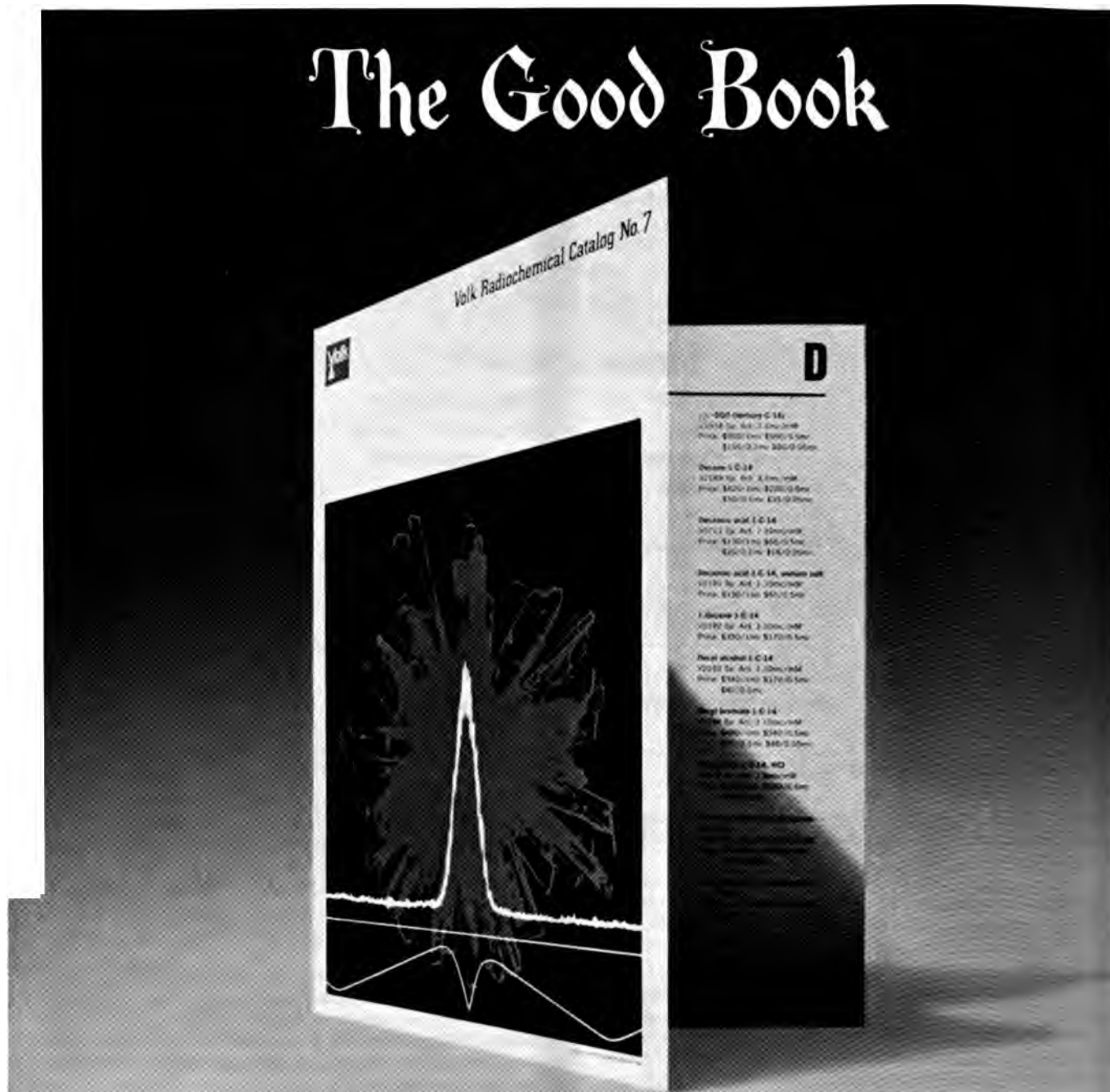
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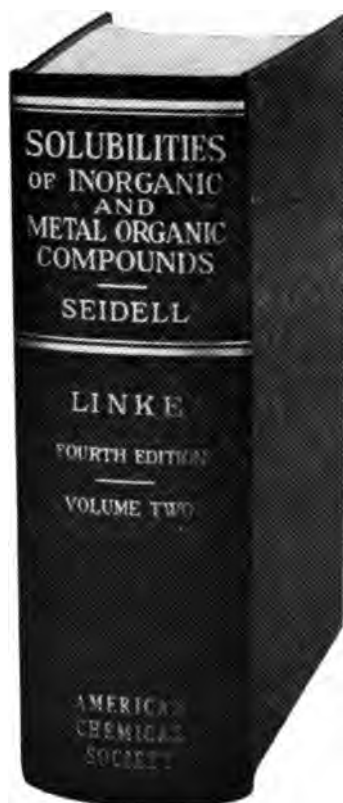
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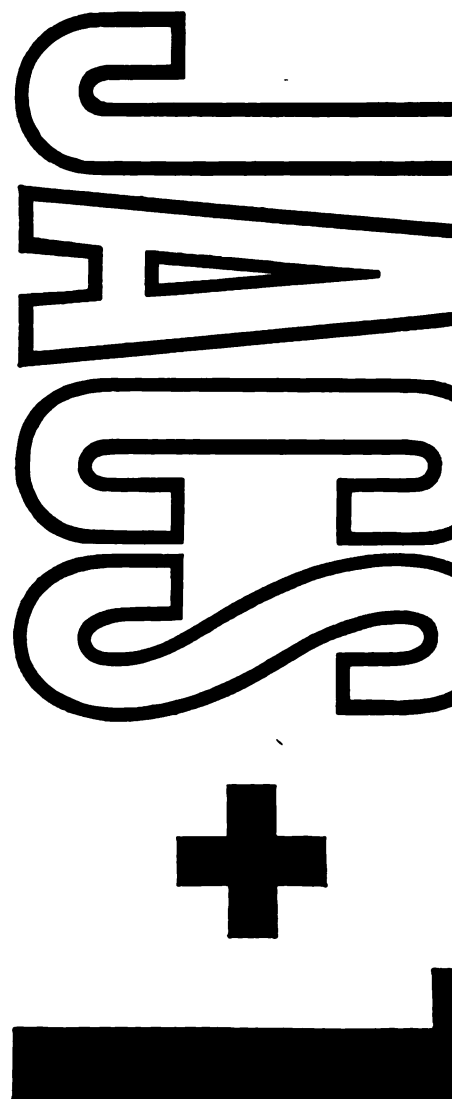
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Physical and Inorganic Chemistry

Ground States of σ -Bonded Molecules. I. A Semiempirical SCF MO Treatment of Hydrocarbons¹

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Abstract: In a recent series of papers³ it was shown that the heats of formation of conjugated molecules can be calculated with surprising accuracy by the Pople SCF MO method, the σ bonds being treated as localized. Here we describe an extension of the method to include all the valence electrons in a molecule, using procedures similar to those suggested by Pople, Santry, and Segal⁴ and by Klopman.⁵ Preliminary calculations for a number of hydrocarbons are reported; the agreement between the calculated and observed heats of formation is already very satisfactory, implying that this approach should ultimately give results of sufficient accuracy to be of value in predicting the structures and reactivities of molecules.

In a recent series of papers³ it was shown that the heats of formation from atoms of conjugated molecules can be calculated with quite unexpected accuracy ($\pm 0.1\%$), using the localized bond model for the σ bonds and calculating the π binding energy by the Pople method. However, although this approach represents a very considerable advance over anything previously reported, it is still of limited chemical value; it cannot be applied to reactions even of conjugated molecules since transition states do not normally have the symmetry necessary for the π approximation to be applicable, nor can it be applied to many problems concerning the behavior of unconjugated molecules, *e.g.*, conformational equilibria and steric hindrance.

However, in view of the unexpected success of the π calculations, it seems reasonable to hope that an

analogous treatment of σ bonds might prove equally successful; if so, we would have a complete solution of the basic problems of chemistry. Preliminary calculations of this kind for diatomic molecules have indeed proved very promising,⁵ and Pople, Santry, and Segal⁴ have reported preliminary calculations for larger molecules. Here we describe our own initial efforts in this direction, which already seem to have achieved a degree of accuracy almost in the "chemical" zone.

Theoretical Approach

The Pople SCF MO method is now familiar, and the problems involved in its extension to σ -bonded systems have been discussed in a formal manner by Pople, Santry, and Segal. The following pictorial representation has the advantage of clarifying these problems and will also help to illustrate our own approach.

In the original Pople treatment of conjugated systems, the π MOs ψ_μ are written as linear combinations of p AO's ϕ_i of the participating atoms (eq 1). The choice of

$$\psi_\mu = \sum_i a_{\mu i} \phi_i \quad (1)$$

basis set functions ϕ_i is unambiguous, since the orientation of each ϕ_i is determined by the geometry of the π system. In calculations for a three-dimensional, σ -bonded system, the situation is more complicated.

(1) This work was supported by the Air Force Office of Scientific Research through Grant No. AF-AFOSR-1050-67.

(2) Robert A. Welch Postdoctoral Fellow.

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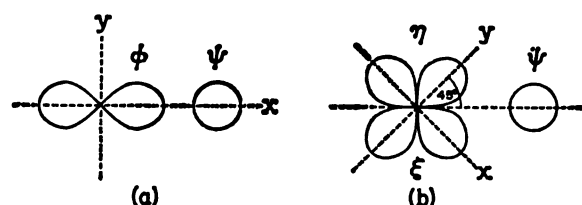


Figure 1. Illustrating the interactions between an electron in an s AO (ψ) of atom N, and an electron in a p AO (ϕ) of atom M.

Each atom other than hydrogen will contribute at least three p AOs; the orientation of these orbitals is arbitrary, since there will normally be no reference frame to fix the choice of coordinate axes. Since the choice of axes is arbitrary, the results of the calculation must be independent of it. While this condition is automatically met in a complete Roothaan SCF MO treatment, the same is not necessarily the case in the simplified version of Pople. The following example illustrates the difficulty.

Consider the interactions between two electrons, one occupying an s AO (ϕ) of atom M, and the other, a p AO (ψ) of atom N, ψ having its axis along the line joining the two nuclei (Figure 1a). In a coordinate system where this line is one of the coordinate axes, ψ will be represented as a single p AO. The terms in the total energy that represent the interactions between the two electrons are of two kinds; first there will be a one-electron resonance integral β , given by

$$\beta = \int \phi H^C \psi d\tau \quad (2)$$

where H^C is the core operator; secondly there will be an electron repulsion term γ , given by

$$\gamma = \iint \phi^2(1) \frac{e^2}{r_{12}} \psi^2(2) d\tau_1 d\tau_2 \equiv (\phi\phi, \psi\psi) \quad (3)$$

in the usual notation for such integrals.

Suppose now that we calculate these interactions in a coordinate system rotated through 45° about the z axis (Figure 1b). The AO ϕ must now be written as a linear combination of the p_x AO (ξ) and the p_y AO (η); i.e.

$$\phi = \frac{1}{\sqrt{2}}(\xi + \eta) \quad (4)$$

The corresponding one- and two-electron interaction terms, β' and γ' , are then given by eq 5 and 6. If our

$$\beta' = \int \phi H^C \psi d\tau = \frac{1}{\sqrt{2}} (\int \xi H^C \psi d\tau + \int \eta H^C \psi d\tau) \quad (5)$$

$$\begin{aligned} \gamma' = \iint \phi^2(1) \frac{e^2}{r_{12}} \psi^2(2) d\tau_1 d\tau_2 = \\ \frac{1}{2} \iint \xi^2(1) \frac{e^2}{r_{12}} \psi^2(2) d\tau_1 d\tau_2 + \frac{1}{2} \iint \eta^2(1) \frac{e^2}{r_{12}} \psi^2(2) d\tau_1 d\tau_2 + \\ \iint \xi(1)\eta(1) \frac{e^2}{r_{12}} \psi^2(2) d\tau_1 d\tau_2 \equiv \frac{1}{2} [(\xi\xi, \psi\psi) + (\eta\eta, \psi\psi) + \\ 2(\xi\eta, \psi\psi)] \quad (6) \end{aligned}$$

calculation is to be independent of the choice of coordinate axes, it is necessary that

$$\beta \equiv \beta' \quad (7)$$

$$\gamma \equiv \gamma' \quad (8)$$

Equation 7 will be automatically satisfied if we make the usual assumption that one-electron resonance integrals are proportional to overlap integrals. The second condition will be met in a full Roothaan treatment where all electron repulsion integrals are included; however, in the standard Pople treatment, where integrals involving overlap between different AOs are neglected, complications will arise, since the final integral in eq 6 will be set equal to zero. Since the remaining integrals in eq 6 are equal, from symmetry, eq 8 will be satisfied only if

$$(\phi\phi, \psi\psi) = (\xi\xi, \psi\psi) = (\eta\eta, \psi\psi) \quad (9)$$

Since these integrals represent the mutual repulsions of two clouds of charge, one representing the distribution of an electron occupying a p AO, the other the distribution of an electron occupying an s AO, the condition implied in eq 8 is equivalent to the assumption that such clouds of charge are spherically symmetrical. This is the CNDO approximation of Pople, *et al.*⁴ (complete neglect of differential overlap). In it one assumes that electron repulsion integrals of the type $(\chi\chi, \omega\omega)$ depend on the nature of the orbitals χ and ω and on their distance apart, but not on their orientation.

Our experience indicates, however, that this approximation is too severe. In spite of very extensive trials, we have been unable to devise any satisfactory scheme for calculating heats of formation of molecules based on the CNDO approximation. This is not surprising, for the directivity of valence probably depends at least partly on the variation with orbital orientation of repulsion integrals involving p AOs. If so, one would not expect to be able to calculate heats of formation accurately, using an approximation in which these variations are neglected.

If such variations in the repulsion integrals are to be included in our treatment, we must then include three- and four-orbital repulsion integrals, involving overlap of orbitals on a common center. In other words, *all* two-center repulsion integrals must be included. We can still, of course, neglect three- and four-center integrals, involving overlap between AOs of different atoms, for neglect of these does not affect the invariance of our calculations to choice of coordinate axes. Thus in the notation of Figure 1, and with χ representing an AO of a third atom, we can set

$$(\chi\phi, \psi\psi) = (\chi\xi, \psi\psi) = (\chi\eta, \psi\psi) = 0 \quad (10)$$

without affecting the invariance to rotation, for the contribution of such integrals will be zero no matter what axes we choose.

This is the NDDO approximation of Pople, *et al.*⁴ (neglect of diatomic differential overlap); it involves obvious technical difficulties, and no calculations have as yet been reported in which the full NDDO scheme has been adopted. Not only are there a large number of additional integrals to be evaluated, but it is also difficult to estimate them by the kind of semiempirical approach we have used for the two-orbital integrals.^{1,3} While the NDDO approximation may prove essential, and while we are at present developing an appropriate program for applying it, we decided first to try the following intermediate approximation in the hope that it might combine simplicity with adequate accuracy.

Consider the integrals (km,ln) between AO's of two atoms M and N. First we transform the AO's of the atoms into the coordinate system of Figure 2. The repulsion integrals between the original AO's can also be expressed in terms of corresponding integrals between the transformed AO's. In this new system, three-orbital integrals involving overlap between any of p AO's vanish through symmetry, as also do the corresponding four-orbital integrals. We assume that the remaining three- and four-orbital integrals can be neglected. The neglect of integrals involving overlap between an s AO and p AO of a given atom can be shown to have no effect on the invariance of the calculations to choice of coordinate axes. The neglect of integrals involving four distinct p AO's can in principle affect this invariance; however, various experiments indicate that such effects are negligible (see ref. 10). With these assumptions our problem is greatly simplified, for the remaining two-center integrals are now of the standard two-orbital type, i.e., (kk,ll) . This approach might be termed the PNDDO approximation (partial neglect of diatomic differential overlap). There are ten distinct integrals of this kind to be considered for the orbitals indicated in Figure 2, viz.

$$\begin{aligned} & s\sigma_N, s\sigma_M-p\sigma_N, p\sigma_M-s\sigma_N, p\sigma_M-p\sigma_N, s\sigma_M-p\pi_N, \\ & -s\sigma_N, p\pi_M-p\pi_N, p\sigma_M-p\pi_N, p\pi_M-p\sigma_N, p\pi_M-p\pi_N^* \end{aligned} \quad (11)$$

the last integral, $p\pi_M-p\pi_N^*$, is one between the p_y AO of M and the p_z AO of N, or conversely. For n atoms, there are therefore $5n(n-1)$ different integrals; in our computer program, each set of integrals is stored in half of an $n \times n$ matrix, five such matrices being required.

Our treatment also involves repulsion integrals between orbitals of a single center; here the three- and four-orbital integrals vanish through symmetry, only two-orbital integrals of the type (kk,mm) and (km,km) remain. Integrals of the latter type must be retained; otherwise we could not distinguish between singlet and triplet states of atoms; thus the difference in energy between the singlet and triplet configurations $(1s)^2(2p)^2$ of carbon arises from an integral of this type where ϕ_k and ϕ_m are different 2p AO's.

We neglect inner electrons, e.g., the 1s electrons in carbon; we treat the valence electrons as moving in the field of a set of cores, each composed of a nucleus and a pair of occupied inner AO's. Thus the core of carbon is a C^{4+} , consisting of the nucleus and a pair of electrons.

The one-center repulsion integrals (kk,mm) and (km,km) are estimated from spectroscopic data for the corresponding atom by a procedure considered in detail elsewhere. In this it is assumed that the repulsion between two electrons in the valence shell of a given atom has a value independent of the orbitals occupied by the electrons and depending only on their relative spins,

$$\text{repulsion between electrons of like spin} = A_M^+ \quad (12)$$

$$\text{repulsion between electrons of opposite spin} = A_M^- \quad (13)$$

These repulsion integrals can be expressed in terms of

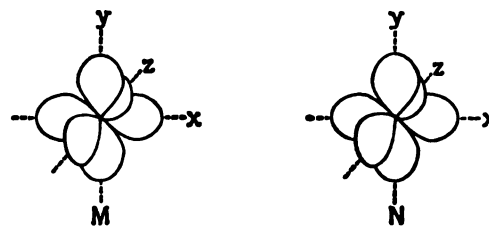


Figure 2. Illustrating calculation of electron repulsion integrals.

these quantities as

$$(kk,mm) = A_M^- \quad (k = m \text{ or } k \neq m) \quad (14)$$

$$(km,km) = A_M^- - A_M^+ \quad (k \neq m) \quad (15)$$

In order to make the treatment as general as possible, we derived an expression for the total electronic energy (E_{el}) for an open-shell SCF MO treatment. Here q_i^α, q_j^β are respectively the densities of α -spin and β -spin electrons in the AO's ϕ_i and ϕ_j given by

$$q_i^\alpha = \sum_\mu n_\mu^\alpha a_{\mu i}^2 \quad q_j^\beta = \sum_\nu n_\nu^\beta a_{\nu j}^2 \quad (16)$$

where n_μ^α and n_ν^β are the numbers of electrons (zero or unity) occupying the corresponding MO's ψ_μ^α and ψ_ν^β . Likewise p_{ij}^α and p_{ij}^β are the corresponding bond orders, defined by eq 17. In the case of a closed-shell

$$\begin{aligned} p_{ij}^\alpha &= \sum_\mu n_\mu^\alpha a_{\mu i} a_{\mu j} \\ p_{ij}^\beta &= \sum_\nu n_\nu^\beta a_{\nu i} a_{\nu j} \end{aligned} \quad (17)$$

molecule, the net charge densities q_i and bond orders p_{ij} are given by

$$q_i = 2q_i^\alpha = 2q_i^\beta \quad p_{ij} = 2p_{ij}^\alpha = 2p_{ij}^\beta \quad (18)$$

The expression for E_{el} is shown in eq 19. Here

$$\begin{aligned} E_{el} = & \sum_k^{(M)} \left\{ (q_k^\alpha + q_k^\beta) W_k + \sum_m^{(M)} \left\{ \sum_{N \neq M} \left[k_{zN} m_z V_{kN}^\pi + \right. \right. \right. \\ & \left. \left. \left. (k_y m_y + k_z m_z) V_{kN}^\pi \right] (p_{km}^\alpha + p_{km}^\beta) + \frac{1}{2} [q_k^\alpha q_m^\alpha - (p_{km}^\alpha)^2 + \right. \right. \\ & \left. \left. q_k^\beta q_m^\beta - (p_{km}^\beta)^2] A_M^+ + \frac{1}{2} (q_k^\alpha q_m^\beta + q_k^\beta q_m^\alpha) A_M^- \right\} \right\} + \\ & \sum_k^{(M)} \sum_{l>k}^{(N)} \left\{ 2(p_{kl}^\alpha + p_{kl}^\beta) \left[k_z l_z \beta_{kl}^\alpha + (k_y l_y + k_z l_z) \beta_{kl}^\pi \right] \right\} + \\ & \sum_m^{(M)} \sum_n^{(N)} \left\{ (p_{km}^\alpha p_{ln}^\alpha + p_{km}^\beta p_{ln}^\beta + p_{km}^\alpha p_{ln}^\beta + p_{km}^\beta p_{ln}^\alpha - \right. \\ & \left. p_{kn}^\alpha p_{lm}^\alpha - p_{kn}^\beta p_{lm}^\beta) \left[k_z l_z m_z n_z \gamma_{kl}^{\alpha\alpha} + (k_y l_y m_y n_y + \right. \right. \\ & \left. \left. k_z l_z m_z n_z) \gamma_{kl}^{\pi\pi} + k_z m_z (l_y n_y + l_z n_z) \gamma_{kl}^{\pi\alpha} + (k_y m_y + \right. \right. \\ & \left. \left. k_z m_z) l_z n_z \gamma_{kl}^{\alpha\pi} + (k_y m_y l_z n_z + k_z m_z l_y n_y) \gamma_{kl}^{\pi\pi} \right] \right\} \quad (19) \end{aligned}$$

ϕ_k and ϕ_m are AO's of one atom M, while ϕ_l and ϕ_n are AO's of some other atom N; the summations are labeled accordingly to avoid confusion.

The integral W_k represents a sum of the kinetic energy of an electron occupying the AO ϕ_k and its potential energy due to attractions by the core of the corresponding atom (M). The integrals V_{kN}^π and V_{kN}^σ represent respectively the attractions between an electron in a σ -type AO (s or $p\sigma$) or a π -type AO, ϕ_k , and the core of

atom N. The quantities A^+ and A^- have already been defined (eq 14 and 15). The remaining one-electron integrals β_{ki}^r and β_{ki}^r are resonance integrals between AO's of atoms M and N in the local coordinate system of Figure 2. There are five nonvanishing combinations of this type, *i.e.*

$$s\sigma-s\sigma, s\sigma-p\sigma, p\sigma-s\sigma, p\pi-p\pi, p\sigma-p\sigma \quad (20)$$

where the first symbol designates the orbital ϕ_k , the second ϕ_i .

The quantities γ_{ki} are two-orbital repulsion integrals for orbitals of atoms M and N, again in the local coordinate system of Figure 2; *i.e.*

$$\gamma_{ki} \equiv (kk, ll) \quad (21)$$

The integrals are labeled with superscripts to indicate the types of orbital involved; the distinction between $s\sigma$ and $p\sigma$ types follows automatically from the nature of the AO's. Thus if ϕ_k and ϕ_m are p AO's, the integral γ_{ki}^{rr} is of the $p\sigma-p\pi$ type, while if $k = m$ and ϕ_k is a σ AO, the integral is of the $s\sigma-p\pi$ type. (Note that in our scheme γ_{ki}^{rr} vanishes if ϕ_k is an s AO and $k \neq m$, since three- and four-orbital integrals involving s-p overlap are neglected.)

The quantities k_x, k_y, \dots, n_z are involved in the transformation of the original basis set of AO's into the locally oriented sets of Figure 2. They are defined in (22), where $i = k, l, m$, or n , and other terms are defined

	Type of orbital ϕ_i			
	s	p_x	p_y	p_z
$i_x =$	1	X	Y	Z
$i_y =$	0	$-rY/R$	rX/R	0
$i_z =$	0	$-rXZ/R$	$-rYZ/R$	R/r

(22)

$$X = |X_M - X_N|/r; Y = |Y_M - Y_N|/r; Z = |Z_M - Z_N|/r; r = (X^2 + Y^2 + Z^2)^{1/2}; R = (X^2 + Y^2)^{1/2} \quad (23)$$

in eq 23. X_p, Y_p , and Z_p are the coordinates of atom P in the original coordinate system used to specify the positions of the atoms in the molecule.

The elements of the F matrix for the α -spin electrons are given in eq 24-26. Equation 25 refers to off-

$$F_{kk} = W_k^{(M)} + \sum_{N \neq M} [k_x^2 V_{kN}^{\sigma} + (k_y^2 + k_z^2) V_{kN}^{\tau}] + q_k^{\beta} A_M^{-} + \sum_{m \neq k}^{(M)} (q_m^{\alpha} A_M^{+} + q_m^{\beta} A_M^{-}) + \sum_i^{(N)} \sum_n^{(N)} (p_{in}^{\alpha} + p_{in}^{\beta})(kk, ln) \quad (24)$$

$$F_{km}^{(M)} = \sum_{N \neq M} [k_x m_x V_{kN}^{\sigma} + (k_y m_y + k_z m_z) V_{kN}^{\tau}] - p_{km}^{\alpha} A_M^{+} + \sum_i^{(N)} \sum_n^{(N)} (p_{in}^{\alpha} + p_{in}^{\beta})(lm, ln) \quad (25)$$

$$F_{ki}^{(M,N)} = k_x l_x \beta_{ki}^{\sigma} + (k_y l_y + k_z l_z) \beta_{ki}^{\tau} - \sum_m^{(M)} \sum_n^{(N)} p_{mn}(km, ln) \quad (26)$$

diagonal matrix elements between AO's ϕ_k and ϕ_m of the same atom M, while eq 26 refers to corresponding elements between AO's of two different atoms M and N. Here the electron repulsion integrals have been

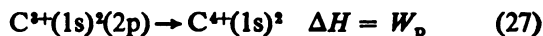
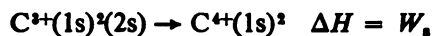
left in their original form, over AO's set up in the original coordinate system; in order to evaluate them, the AO's ϕ_k, ϕ_l, ϕ_m , and ϕ_n for each pair of atoms M and N are transformed into the local coordinate system of Figure 2.

The calculations were carried out at the Computation Center of The University of Texas, using first a CDC 1604 digital computer, and later a CDC 6600. The program, while somewhat complex, followed a fairly conventional path. The integrals β_{km} and γ_{km} , and the quantities k_x etc. of eq 22, are first computed and stored. An initial F matrix is then set up, using assumed values for the q 's and p 's; in the case of hydrocarbons, we set the charge density (q) equal to unity for each valence orbital, and each bond order (p) equal to zero. The F matrix is then diagonalized, new q 's and p 's are computed, and the process is continued until the sum of the energies of the occupied orbitals converges to within a predetermined limit. The total electronic energy is then computed (eq 19) and the total bonding energy found from it by adding the core repulsion and subtracting the total energy of the isolated atoms. The following section indicates the procedure we have followed in estimating the various integrals and other quantities appearing in the treatment.

Calculations of Integrals Etc.

The quantities appearing in this treatment are of five types: (a) valence-shell ionization potentials, W_k ; (b) one-center repulsion integrals, (kk, mm) and (km, km) ; (c) one-electron resonance integrals, β_{ki} ; (d) two-center repulsion integrals, γ_{ki} ; (e) the core repulsion and core-electron attraction. For reasons indicated above, we are prepared if necessary to treat any or all of these quantities as parameters, our sole purpose being to develop a reliable and general method for calculating heats of formation of molecules of all kinds (including transition states) with "chemical" accuracy. However, one must obviously try to minimize the number of arbitrary parameters in a treatment such as this; we have accordingly adopted the course of introducing parametric functions for the calculation of the various quantities, these functions containing the minimum number of parameters and being chosen on the basis of physical intuition. In this connection, empirical data for atoms can be regarded as free information, for we are concerned only with the heats of formation of molecules, not with their total binding energies. The true parameters in our treatment are those whose values must be fixed by reference to properties of specific molecules; the number of such "molecular" parameters must be kept as small as possible if the method is to be useful and convincing. The procedure we followed in the calculations reported here was as follows.

(a and b) **Valence-Shell Ionization Potentials and One-Center Repulsion Integrals.** These were estimated for carbon from spectroscopic data by the following⁴ procedure. We represent the core of the carbon atom as the ion C^{4+} , consisting of the nucleus and two 1s electrons. The quantities W_s or W_p should then represent the energy of a 2s or 2p electron, respectively, moving in the field of this core, and one might therefore try to equate them to the appropriate fourth ionization potentials of carbon, *i.e.*



ever, the orbitals in C^{2+} are smaller than those in neutral carbon and their binding energies correspondingly greater; the quantities W_s and W_p were therefore chosen to give a best fit to the energies of various states of neutral and singly ionized carbon.

We assume that the repulsion between two valence electrons has the same value, regardless of the orbitals occupied by the electrons; for electrons of like spin, the repulsion is A^+ , and for electrons of opposite spin, A^- . Thus the energy (E^1 or E^3) of a carbon atom in the singlet or triplet states $(1s)^2(2s)^2$, represented by single determinants with $S_z = \pm \frac{1}{2}$, respectively, are given in eq 28 and 29. The

singlet $(1s)(\bar{1}s)(2s)(\bar{2}s)(2p)(\bar{2}p)$

$$E^1 = 2W_s + 2W_p + 2A^+ + 4A^- \quad (28)$$

triplet $(1s)(\bar{1}s)(2s)(\bar{2}s)(2p_x)(2p_y)$

$$E^3 = 2W_s + 2W_p + 3A^+ + 3A^- \quad (29)$$

quantities A^+ and A^- are related to the one-center resonance integrals by eq 14 and 15.

In order to estimate A^+ and A^- it is necessary to determine E^1 and E^3 from spectroscopic data. The single determinants in eq 28 and 29 do not of course correspond to true states of carbon. There are 15 possible configurations, corresponding to the possible partitions of two electrons between the three 2p AO's; these are listed in (30) and (31). In our approximation, all states with $S_z = 0$

$$\begin{aligned} & \left(\uparrow \downarrow \right) \rightarrow \left(\uparrow \uparrow \right) \rightarrow \left(\uparrow \downarrow \right) \left(\downarrow \uparrow \right) \rightarrow \left(\downarrow \downarrow \right) \\ & \left(-\uparrow \downarrow \right) \rightarrow \left(-\uparrow \uparrow \right) \rightarrow \left(-\uparrow \downarrow \right) \left(-\downarrow \uparrow \right) \rightarrow \left(-\downarrow \downarrow \right) \end{aligned} \quad (30)$$

states with $S_z = \pm \frac{1}{2}$

$$\left(\uparrow \uparrow \right) \rightarrow \left(\uparrow \downarrow \right) \rightarrow \left(\downarrow \uparrow \right) \rightarrow \left(\downarrow \downarrow \right) \rightarrow \left(\uparrow \downarrow \right) \rightarrow \left(\downarrow \uparrow \right) \quad (31)$$

"singlet" configurations of (30) have the same energy while all those of (31) have energy E^3 . In practice the 15 configurations correspond to the following 15 states of carbon.

one state

five substates ($M = 2, 1, 0, -1, -2$)

nine substates ($M = 1, 0, -1; S = 1, 0, -1$) (32)

In order to obtain correct representations of these states, we should construct appropriate linear combinations of the configurations indicated in (30) and (31). The configurations of different multiplicity do not have the same energy. The six triplet states of (31) lead only to six substates of 3P (those with $S_z = \frac{1}{2}$ or $-\frac{1}{2}$). Since these states have the same energy (that of the state 3P), we equate this energy to A^+ . The remaining states are the 1S and 1D states, and the three substates of 3P with $S_z = 0$. These are represented by a set of nine orthogonal linear combinations of the configurations in (30) and (31). Now it is easily shown that the total energy of such a set of linear combinations is the same as the sum of the individual energies of the original configurations; the total energy of the nine configura-

tions is of course $9E^1$, while that of the nine real states and substates is $[(^1S) + 5(^1D) + 3(^3P)]$, where (^1S) , (^1D) , and (^3P) are the energies of the corresponding states. Hence

$$E^1 = \frac{1}{9}[(^1S) + 5(^1D) + 3(^3P)] \quad (33)$$

The configuration thus appears as a weighted mean or *barycenter*⁵ of the appropriate states. The energies of barycenters can thus be calculated from spectroscopic data, and the results can then be used to determine the various one-center integrals A^+ , A^- , W_s , and W_p .

This treatment of atoms may seem rather primitive, but it is fully justified by its practical success.⁵ The number of appropriate barycenters for a given atom is usually greater than the number of parameters; the energies of all the barycenters are given well by this approach for a wide variety of different atoms.

In calculating the binding energy of a molecule, we naturally compare its calculated total energy with a sum of the energies of ground-state barycenters of the component atoms, for, since we use a single Slater determinant to describe the molecule, it would be inconsistent not to use a similar description for its component atoms.

(c) The one-electron resonance integral β_{ki} can be interpreted physically as the energy of an electron occupying the overlap cloud between the AO's ϕ_k and ϕ_i , and moving in the field of the core and remaining electrons. We would therefore expect β_{ki} to be proportional (a) to the magnitude of the overlap cloud, i.e., to the overlap integral S_{ki} ; (b) to some mean of the binding energies of the AO's ϕ_k and ϕ_i ; (c) and to the distance between the overlap cloud and the nuclei of the atoms of which ϕ_k and ϕ_i are AO's. The last two conditions follow since the potential field in the overlap region arises mainly from the two atoms. We therefore adopted the following expression for β_{ki} .

$$\beta_{ki} = (\beta_{ki})_0 S_{ki} (I_k + I_i) [r_{ki}^2 + (\rho_k + \rho_i)]^{-1/2} \quad (34)$$

Here I_k and I_i are the valence-state ionization potentials of the AO's ϕ_k and ϕ_i , calculated for the appropriate barycenters by the method of ref 5; r_{ki} is the internuclear distance between the atoms of which ϕ_k , ϕ_i are AO's; ρ_k and ρ_i are quantities appearing in the expressions for two-center repulsion integrals (see below); $(\beta_{ki})_0$ is a parameter to be determined empirically, being the same for all valence orbitals of a given atom. The overlap integrals S_{ki} were calculated in the usual way using Slater-Zener orbitals ($Z = 3.25$ for carbon). In order to reduce the number of parameters in the treatment, we assumed that β_0 has a common value β_{xy} for orbitals of two atoms x and y , regardless of the type of orbitals (s or p) and mode of overlap (σ or π), and that

$$\beta_{xy} = \sqrt{\beta_{xx}\beta_{yy}} \quad (35)$$

Equation 34 is more complicated than the corresponding expressions used by other authors; we have tried a number of such simpler expressions, but with less success. Thus omission of the terms I_k and I_i leads to results for unsaturated molecules such as ethylene in which the orbitals appear in the wrong order of energy; it is essential to use different values of β for s and p AO's. Again, omission of the term in r gave heats

of formation for acetylene that were much too low; it is apparently necessary to use for β an expression that increases more rapidly with decreasing bond length than does the corresponding overlap integral.

(d) The two-center integrals $(\phi\phi, \psi\psi)$ were estimated in two different ways, one for the CNDO calculations and one for the PNDDO approximation. The integral $(\phi\phi, \psi\psi)$ must in each case obey two boundary conditions. As the internuclear distance r tends to zero, the integral should approximate to a one-center repulsion integral, while, when $r \rightarrow \infty$, the integral should approximate to e^2/r .

In the CNDO calculations, we adopted expression 36, one which has been used successfully in previous work.^{4,5} Here ρ_k and ρ_l are constants characteristic

$$\gamma_{kl} = e^2[r_{kl}^2 + (\rho_k + \rho_l)^2]^{-1/2} \quad (36)$$

of the two atoms, chosen to make γ_{kl} approach the corresponding one-center integral as $r_{kl} \rightarrow 0$; i.e.

$$2\rho_k = e^2/A_k^- \quad 2\rho_l = e^2/A_l^- \quad (37)$$

In the second approach, different values were assumed for the integral γ_{kl} , depending on the nature of the orbitals involved and their mode of overlap. Two arguments guided us in choosing a suitable expression for the integrals. First, an analysis of the role of electron correlation, using a model⁶ similar to that invoked in the SPO approach,⁶ suggested that the integrals should fall into three distinct groups, i.e., (38)–(40).

$$\text{I. correlation large: } s\sigma:s\sigma; p\pi:p\pi; s\sigma:p\pi \quad (38)$$

$$\text{II. correlation medium: } s\sigma:p\sigma; p\sigma:p\pi \quad (39)$$

$$\text{III. correlation small: } p\sigma:p\sigma \quad (40)$$

Secondly, this subdivision of the integrals also appears in the values estimated theoretically, using Slater–Zener orbitals;⁷ these are shown in Table I.

Table I. Values for Carbon–Carbon Two-Center Repulsion Integrals

Class	Type	Value of integral, ev	
		Calcd using Slater–Zener AO's	Calcd from (41)–(43)
1	$s\sigma:s\sigma$	9.28	
	$s\sigma:p\pi$	9.12	7.13
	$p\pi:p\pi$	8.98	
	$p\pi(x):p\pi(y)$	8.98	
2	$s\sigma:p\sigma$	9.61	7.81
	$p\pi:p\sigma$	9.41	
3	$p\sigma:p\sigma$	9.99	8.45

Our object was to duplicate this pattern, subject to the condition that the integral (ii, kk) between orbitals of two identical atoms should converge to the corresponding one-center integral (ii, ii) at zero internuclear separation. The expressions we adopted are given in eq 41–43, where in class II, the orbital ϕ_k is the one of

Class I

$$(ii, kk) = e^2[r_{ik}^2 + (\rho_i + \rho_k)^2]^{-1/2} \quad (41)$$

Class II

$$(ii, kk) = e^2[r_{ik}^2 + (\rho_i + \rho_k T_{ik})^2]^{-1/2} \quad (42)$$

Class III

$$(ii, kk) = e^2[r_{ik}^2 + (\rho_i T_{ik} + \rho_k T_{ik})^2]^{-1/2} \quad (43)$$

the $p\sigma$ type, and where

$$T_{ik} = e^{-r_{ik}/2(\rho_i + \rho_k)} \quad (44)$$

The values calculated in this way for carbon atoms at an internuclear distance of 1.55 Å are listed in the last column of Table I.

(e) **Core Repulsion.** Having calculated the total electronic energy (E_{el}), we can then find the total energy of a molecule by adding to this the core repulsion. Our last problem is to decide how to calculate this.

In the π calculations, the repulsion between two cores M and N was set equal to the corresponding two-center repulsion integral; however, if we try to do this in the present case, we find that the molecule collapses to a point. The repulsion between point charges (i.e., the nuclear repulsion) is much greater at short distances than is the corresponding repulsion between clouds of charge representing occupied orbitals; this enhanced repulsion is one of the factors that keeps the atoms in a molecule at bond's length. In the π calculations, this difficulty did not arise since we assumed Morse functions for the σ components of bonds; here our calculations include all the valence electrons, so there is no escape.

Nor is it satisfactory to set the core repulsion equal to a point charge potential, i.e., to $Z_M Z_N e^2/R$, where Z_M and Z_N are the nuclear charges, for in this case the calculated binding energy is too small. The reason for this is implied in the literature. Consider for example H_2 . The potential field in which the electrons move is greater than that in an isolated hydrogen atom; consequently, the orbitals of H_2 are more compact than one would expect for a combination of ordinary 1s hydrogen AO's. Indeed, if we carry out an orbital treatment, regarding the nuclear charges (Z) as variation parameters, we find the best agreement with experiment given by a value of Z considerably greater than unity. In our treatment, where the "atomic" parameters are fixed from spectroscopic data for isolated atoms, we assume in effect that the effective nuclear charge is the same for each atom in isolation as it is when the atom forms part of a molecule. In order to get realistic binding energies, either we must abandon this assumption or we must make some allowance for it by compensating changes in the other parameters. In this case the changes are best made in the nuclear repulsion, because this does not affect calculations of the electron distribution or orbital energies.

We therefore calculated the core repulsion from an appropriate parametric function. The function chosen must satisfy two boundary conditions. For large r_{ik} , it must approach the corresponding interelectronic repulsion between neutral atoms in order that the net potential due to a neutral atom should vanish at large distances, while for small r_{ik} it must have a value between this and that calculated for point charges. We

(6) See M. J. S. Dewar and N. L. Sabelli, *J. Phys. Chem.*, **66**, 2310 (1962).

(7) We are grateful to Dr. F. A. Matsen for these values.

ried a large number of possible one-parameter ons of this type; the most successful was that of

$$V = E_{MN} + [Z_M Z_N e^2 / r_{MN} - E_{MN}] e^{-\alpha_{MN} r_{MN}} \quad (45)$$

Here C_{MN} is the core repulsion between atoms l N; E_{MN} is the corresponding electronic repul- between neutral atoms M and N (*i.e.*, (kk,mm) ed over the valence orbitals); Z_M and Z_N are the core charges in units of e (*i.e.*, the number of e electrons) of the two atoms; α_{MN} is a parameter. ler to reduce the number of parameters in the ent, we assumed (*cf.* eq 35) that the value of α_{MN} o dissimilar atoms M and N is given in terms of rameters α_{MM} and α_{NN} for pairs of similar atoms

$$\alpha_{MN} = \sqrt{\alpha_{MM}\alpha_{NN}} \quad (46)$$

treatment contains very few "molecular" param- *i.e.*, parameters whose value has to be deter- from data for molecules rather than atoms. are just two molecular parameters for each kind m X, *i.e.*, the parameter β_{XX} that appears in the sion for one-electron resonance integrals involv- bitals of X, and the parameter α_{XX} that appears expressions for corresponding core repulsion.

attraction between an electron in an AO i of one M and the core of atom N, was set equal to the sum of repulsions between the electron and lence electron of N (*cf.* the corresponding ap- ation in the π treatment³).

ation to Hydrocarbons

method outlined above has been applied to a of hydrocarbons. The general procedure was ows: (a) the parameters β_{HH} and α_{HH} were chosen the correct internuclear distance and bond energy

(b) assuming various values for β_{CC} , α_{CC} was to give the correct heat of formation for CH_4 ; ats of formation were then calculated for ne, ethane, and propane, using the values of d α_{HH} from step a, and with the various pairs of for β_{CC} and α_{CC} from step b; (d) having thus shed optimum values for the parameters, calcula- vere carried out for a number of other saturated isaturated hydrocarbons.

order to apply this treatment, it is necessary to the Cartesian coordinates of the atoms in a ile; these must be calculated from the known sumed) bond lengths and bond angles. In our he positions of the atoms are specified by the lengths, bond angles, and dihedral angles of the in the molecule; we have written a program y the coordinates of the atoms are calculated hese data. In the calculations reported below, umed tetrahedral geometry for sp^3 carbon and al geometry for sp^2 carbon (bond angles, 120°). ssumed bond lengths are shown in Table II.

values for the parameters in the treatment are in Table III, while Table IV compares calculated bserved heats of formation for the various com- s. Except when otherwise stated, saturated C_2 vere assumed to have the conformation observed opene (*i.e.*, one sp^3 CH bond eclipsing the $C=C$

Other calculated quantities will be found below isscussion).

Table II. Bond Lengths for CC and CH Bonds

Bond	Hybridization	Length, nm
C—C	sp^3-sp^3	0.1534
	sp^2-sp^2	0.1520
	sp^3-sp	0.1459
	sp^2-sp^2	0.1483
	(Aromatic)	0.1397
C=C	...	0.1337
C≡C	...	0.1205
C—H	sp^3	0.1093
	sp^2	0.1083
	(Benzene)	0.1084
	sp	0.1059

Table III. Parameters for Carbon and Hydrogen

Atom	β_{XX} , pm	α_{XX} , nm ⁻¹
C	45.84	47.08
H	27.87	14.8

Table IV. Comparison of Calculated and Observed Heats of Formation (ΔH_f) of Hydrocarbons from Atoms in the Gas Phase at 25°

Compound	ΔH_f , kcal/mole		$\delta\Delta H_f^b$
	Obsd ^a	Calcd	
Ethane	674.6	677.3	2.7
Ethane (eclipsed)	671.7 ^c	676.5	4.8
Propane	954.3	957.3	3.0
<i>n</i> -Butane	1234.7	1237.5	2.8
<i>n</i> -Pentane	1514.7	1517.6	2.9
Isobutane	1236.7	1236.8	0.1
Isopentane	1516.6	1516.3	-0.3
Cyclopropane ^d	812.6	809.1	-3.5
Cyclohexane (chair)	1680.0	1680.2	0.2
Cyclohexane (boat)	1678.0 ^e	1674.9	3.1
Ethylene	537.7	540.1	2.4
Propene	820.4	822.6	2.2
<i>cis</i> -2-Butene	1102.0	1101.4	-0.6
<i>trans</i> -2-Butene	1103.0	1103.4	0.4
<i>trans</i> -1,3-Butadiene	969.8	971.6	1.8
<i>cis</i> -1,3-Butadiene	967.5 ^f	971.3	3.8
Benzene	1318.1	1314.0	-4.1
Allene	675.2	697.2	22.0
Acetylene	391.8	414.0	22.2
Methylacetylene	676.8	704.4	27.6

^a The thermochemical data are taken from Rossini except where otherwise stated. ^b Difference between calculated and observed heats of formation in kcal/mole. ^c Calculated from the value for staggered ethane, using the experimentally determined height (2.9 kcal/mole) of the rotational barrier; see D. R. Lide, *J. Chem. Phys.*, **29**, 1426 (1958). ^d Heat of formation calculated for structure with D_{3h} symmetry; see H. A. Skinner and G. Pilcher, *Quart. Rev.* (London), **20**, 264 (1966). ^e Calculated from the value for chair conformation, using the experimental value (5.2 kcal/mole) for the heat of conversion to the boat conformation; see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962. ^f Calculated from the observed difference in energy between the *cis* and *trans* isomers; see Table V.

Invariance to Rotation

As has been pointed out, the treatment used here is not strictly invariant to choice of coordinate axes, due to the neglect of repulsion integrals involving four p AO's of two different atoms. Four lines of argument suggested, however, that variations of this kind should be small. Firstly, integrals of this type represent quadrupole-quadrupole repulsions and are consequently much smaller than the charge-charge repulsions

corresponding to "normal" repulsion integrals; even in the case of adjacent carbon atoms, the integrals have values⁷ of only about 0.1 ev. Secondly, the effect of changing the coordinate axes appears only as secondary changes in the values of these integrals, and the net effect in the sum of the integrals between a given pair of atoms should consequently be small. Thirdly, the integrals between a given pair of atoms do not all have the same sign; the resulting cancellations will further reduce their net contribution to the total energy and so likewise to its variation with choice of axes. And finally, the integrals in question, representing as they do higher multipole repulsions, decrease very rapidly with distance; integrals between nonadjacent atoms are essentially negligible.

Obviously, however, these arguments needed to be checked experimentally. We therefore repeated the calculations for a number of molecules in various orientations relative to the coordinate axes; in each case the eigenvalues, total energies, charge densities, and bond orders were identical with the accuracy with which they are printed (seven significant figures in the total energy, four in the other quantities). As a further check, we carried out calculations for carbon monoxide and hydrogen cyanide in various orientations; here again the results were quite unaffected by choice of coordinate axes, although these molecules contain heteroatoms and the neglected quadrupole-quadrupole integrals should be greatest for triple bonds since these are so short. It seems clear from these results that our procedure is for all practical purposes invariant to rotation of the coordinate axes, any variations being entirely negligible.

Discussion

The agreement between the calculated and observed heats of formation in Table IV is rather remarkable, the differences in most cases being less than 4 kcal/mole (0.15 ev). The only serious discrepancies (~1 ev) occur in the case of allene and the acetylenes; these are probably due to our use of a nuclear potential which does not increase sufficiently rapidly at short distances. Thus our method correctly predicts the heat of formation (and so by implication the strain energy) of cyclopropane, in which the bonds are single; on the other hand, attempts to calculate bond lengths, by minimizing the total energy of a molecule with respect to them, have given values which are much too small.

Several other qualitative checks also seem satisfactory. Thus ethane is correctly predicted to be most stable in the staggered conformation, cyclohexane in the chair conformation, and 2-butene and 1,3-butadiene in *trans* configurations; previous SCF MO calculations for 1,3-butadiene had incorrectly predicted the *cis* form to be more stable.⁸

Admittedly the differences in energy are not predicted exactly; this is clear from the data listed in Table V. In one case our procedure even leads to a qualitatively incorrect prediction, *i.e.*, that normal paraffins should be more stable than their branched isomers, while the predicted barrier to rotation in ethane is too small. Nevertheless, the over-all picture is very encouraging, given that the work described here represents only a preliminary approach to the problem and given

(8) R. G. Parr and R. S. Mulliken, *J. Chem. Phys.*, **18**, 1338 (1950).

that the errors in the calculated heats of formation are less by two orders of magnitude than those derived from other recent SCF MO calculations.^{4,9}

Table V. Comparisons of Energies of Isomeric Hydrocarbons

Reaction	Energy change, kcal/mole	
	Calcd	Obsd
Ethane (staggered → eclipsed)	0.8	2.9
1,3-Butadiene (<i>trans</i> → <i>cis</i>)	0.3	2.2*
2-Butene (<i>trans</i> → <i>cis</i>)	2.0	1.0
Cyclohexane (chair → boat)	2.0	5.3
<i>n</i> -Butane → isobutane	-2.0	0.7
<i>n</i> -Pentane → isopentane	-1.9	1.3

* J. G. Aston, *Discussions Faraday Soc.*, **10**, 73 (1951).

The objective of these calculations was admittedly different from ours. Both Pople and Segal⁴ and Lipscomb, *et al.*,⁹ were trying to devise some simple semiempirical MO procedure that would reproduce the results to be expected from an *a priori* Roothaan-type approach. The parameters were therefore chosen in such a way as to make the results of the two calculations agree for small molecules where *a priori* calculations have, or could, be made. This procedure of course ensured that the semiempirical treatments would give poor estimates of heats of formation, seeing that heats of formation calculated by the Hartree-Fock method are known to be very inaccurate.

Another check on our work is provided by the photoionization potentials measured for various hydrocarbons by Al-Joboury and Turner.¹⁰ The ionization potentials of a molecule should, according to Koopman's theorem, be approximately equal to the calculated orbital energies; Table VI shows that this parallel exists in a remarkable way for a variety of hydrocarbons and for all measured ionization potentials up to about 19 ev. The photoionization spectra show numerous peaks in this region, due to the possibility of producing ions in vibrationally excited states; our calculations suggest that in several cases Turner, *et al.*,¹⁰ may have mistaken multiple peaks as being due to different vibrational states of a single ion, rather than to two or more different ions of similar energy. Similar difficulties arise in attempts to correlate observed electronic spectra of molecules with calculated excitation energies.

The last column of Table VI shows orbital energies calculated by Palke and Lipscomb^{9b} by an *a priori* SCF LCAO MO method, using the POLYATOM program. It will be seen that their orbital energies run parallel to ours but are in general greater; the correlation with measured photoionization potentials is clearly poor. Another comparison of this kind is provided by the population analyses shown in Table VII; here again our values run parallel to those given by the *a priori* procedure and also to those reported by Pople and Segal.

Our method predicts small dipole moments for several of the compounds studied; values are listed in Table VIII. The available experimental evidence (last column

(9) M. D. Newton, F. P. Boer, and W. N. Lipscomb, *J. Am. Chem. Soc.*, **88**, 2353, 2361, 2367 (1966); (b) W. E. Palke and W. N. Lipscomb, *ibid.*, **88**, 2384 (1966).

(10) M. I. Al-Joboury and D. W. Turner, *J. Chem. Soc.*, 5141 (1963); 4434 (1964); 616 (1965).

Table VI. Comparisons of Ionization Potentials with Orbital Energies

Compound	Ionization potential, ev	Orbital energy, ev This paper	Ref 9b
Methane	12.99	13.88	14.74
Ethane	11.49	12.51	13.08
		13.04	13.38
	14.74	14.98	16.15
	19.18	20.80	22.51
Ethylene	10.48	10.86	10.09
		12.76	13.77
	12.50	12.94	15.28
	14.39	15.25	17.51
	15.63		
	19.13	19.18	21.28
Acetylene	11.36	11.06	11.03
	16.27	13.63	17.85
	18.33	18.08	20.44
Propane	11.07	12.01	
		12.49	
		12.85	
	13.17	13.73	
		13.90	
	15.17	14.68	
	15.70	15.46	
	18.57	19.67	
n-Butane	10.50	11.63	
		12.39	
	12.36	12.78	
		13.07	
		13.21	
		14.13	
	14.13	14.36	
		14.47	
	15.69	15.79	
Isobutane	10.78	11.88	
		12.54	
	12.54	13.48	
		13.79	
	14.51	14.59	
		15.40	
	18.63	18.68	
Cyclohexane	9.79	11.51	
	11.33	12.23	
		12.59	
	12.22	12.69	
		13.48	
	14.37	15.10	
		15.51	
Benzene	9.25	10.15	
	11.49	11.54	
	12.19	12.72	
		12.86	
	13.67	13.45	
	14.44	15.67	
	16.73	16.07	
	18.75	18.98	
1,3-Butadiene (trans)	9.08	10.16	
		11.70	
	11.25	11.83	
	12.14	12.58	
		13.09	
	13.23	14.39	
		14.71	
	18.78	17.99	
		19.24	

Table VIII) suggests that the calculated moments are the right order of magnitude.

Summary

While the results reported here are preliminary in nature,¹¹ they are sufficient to suggest that this kind of

Table VII. Population Analyses for Hydrocarbons

Compound	Orbital	Population		
		This paper	Ref 9b	Ref 3
Methane	H	1.077	0.876	0.965
	C2s	1.136	1.274	1.081
	C2p	0.852	1.088	1.020
Ethane	H	1.064	0.876	0.967
	C2s	1.199	1.248	1.042
	C2p σ	0.872	0.981	1.007
Ethylene	C2p π	0.865	1.074	1.044
	H	1.033	0.860	0.954
	C2s	1.243	1.197	...
Acetylene	C2p σ	0.844	1.013	...
	C2p π	0.845	1.072	...
	C2p $\pi^*(a)$	1.000	1.000	...
	H	0.941	0.812	0.893
	C2s	1.263	1.105	...
	C2p σ	0.797	1.086	...
	C2p π	1.000	1.000	...

Table VIII. Calculated and Observed Dipole Moments of Hydrocarbons

Compound	Dipole moment, D.	
	Calcd	Obsd
Propane	0.03	0.08 ^a
Isobutane	0.05	0.13 ^b
cis-2-Butene	0.08	...
Propyne	0.24	0.75 ^c
cis-1,3-Butadiene	0.04	...

^a D. R. Lide, *J. Chem. Phys.*, **33**, 1879 (1960). ^b A. A. Maryott and G. Birnbaum, *ibid.*, **24**, 1022 (1956); D. R. Lide and D. E. Mann, *ibid.*, **29**, 914 (1958). ^c F. J. Krieger and H. H. Wenzek, *J. Am. Chem. Soc.*, **60**, 2115 (1938).

approach has exciting possibilities. It seems very likely that it may be improved to a point where heats of formation, etc., of molecules of all kinds may be predicted with an accuracy comparable with that already achieved for conjugated hydrocarbons, using the Hückel approximation. If so, the impact on chemistry would be considerable, for not only would one be able to calculate heats of formation and reaction with "chemical" accuracy, but it would also be possible to predict reaction mechanisms and rates of reaction.

Our results represent a considerable improvement over those of previously reported investigations. The main factors responsible for this seem to be the following: (a) our treatment of the internuclear repulsion as a parameter to allow for the effects of orbital contraction (if the repulsion is treated as one between point charges, the calculated heats of formation must inevitably be too small); (b) our use of different integrals for s and p AO's of a given center, together with a sufficient inclusion of integrals involving one-center differential overlap to make the calculations effectively invariant to choice of coordinate axes; (c) our use of thermochemical data to fix the parameters in our treatment, rather than the results of *a priori* calculations.

There are several obvious ways in which this general approach could be modified and extended, in particular the use of Hartree-Fock AO's in the calculation of over-

(11) For this reason we have not reported the results (e.g., eigenvalues, eigenvectors, bond orders, etc.) in detail; we will be happy to communicate them to anyone interested.

lap integrals and the use of separate parameters for different types of bonds in place of the approximations of eq 35 and 46. We are studying these and other analogous possibilities, and we are also extending our

treatment to include all integrals involving one-center differential overlap (NDDO approximation⁵) in case this should prove necessary in treating molecules containing heteroatoms.

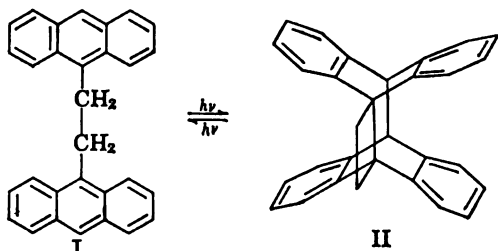
Reversible Photoisomerization of 1,2-Bis(9-anthryl)ethane¹

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Contribution from the Division of Physical Chemistry, University of Minnesota, Minneapolis, Minnesota. Received January 21, 1967

Abstract: The hydrocarbon 1,2-bis(9-anthryl)ethane (I) is photoisomerized efficiently and reversibly. The isomeric product (II) does not absorb appreciably at wavelengths longer than 260 m μ . The quantum yields of the forward and back reactions (0.19 and 0.42, respectively) are independent of the concentration of the reactant. Compound I is strongly fluorescent with maxima at 408, 436, and 460 m μ , and a fluorescent quantum yield of about 0.37. Flash illumination of its deoxygenated solutions produces an absorption transient, similar to but not identical with the lowest triplet of anthracene. No attempt was made to observe the fluorescence or triplet formation of the isomer (II).

The hydrocarbon 1,2-bis(9-anthryl)ethane (I) is efficiently and reversibly photoisomerized.³ The detailed structure of the photoproduct (II) has not been



established definitely. However, as was clearly stated by Roitt and Waters,^{3a} its ultraviolet absorption spectrum is in general similar to that of dianthracene,⁴ demonstrating that in II the conjugation of the anthracene rings is interrupted. It was postulated^{3a} that II is a dimer of I, but molecular weight determinations (with a Mechrolab osmometer^{3b}) prove that it is an isomer rather than a dimer of I. Our present finding, that the quantum yields of the photochemical reactions are independent of the concentrations of the reactants, confirms this conclusion unambiguously. Physical evidence (nmr, infrared, and mass spectrographic measurements⁵) is consistent with formula II.

Compound II is stable at room temperature (in the absence of ultraviolet radiation) but isomerizes at its melting point, re-forming I.

Since the product II does not absorb appreciably at wavelengths longer than 260 m μ , the quantum yield of the forward reaction was measured directly, using light

of 365 m μ . The quantum yield of the reverse reaction was estimated from the extinction coefficients, the quantum yield of the forward reaction, and the composition of a steady-state mixture, prepared by prolonged exposure to 254 m μ .

Experimental Section

Methods and Materials. Materials. The 1,2-bis(9-anthryl)ethane was furnished by Dr. S. Fenton (University of Minnesota). It was recrystallized from *n*-hexane before use. The cyclohexane was Fisher Spectro Grade and was used without further purification.

Determination of Quantum Yields. The intensity of the absorbed light was determined by the use of a ferrioxalate actinometer, following the procedure outlined by Parker.⁶ The absorption of the incident light was practically complete, except for those experiments made with the most dilute solutions; for these, the percent absorption was calculated from the extinction coefficients. Light of the required wavelengths was isolated from the radiation of a Hanovia S-100 mercury arc, using combinations of glass, solution, and Cl₂ gas filters.⁷

Optical Measurements. The absorption spectra were measured with a Cary 15 spectrophotometer. The fluorescence spectrum was measured by T. Bednar of this department, using a deaerated, 5×10^{-5} M solution of I in cyclohexane and exciting light of 370 m μ . The fluorescence was observed at right angles to the exciting beam. The spectral resolution of the fluorimeter was estimated to be 10 Å. The spectrum was corrected for variation of the sensitivity of the apparatus with wavelength but not for reabsorption, which probably seriously distorted the curve at wavelengths shorter than 400 m μ . Qualitatively similar results were obtained by K. S. W., using a manually operated spectrofluorimeter.⁷

Results

The absorption and fluorescence spectra of I are shown on Figure 1; the absorption spectrum of its isomer (II) is shown on Figure 2. The quantum yield of fluorescence of I was estimated to be 0.37, by comparing its total emission to that from anthracene, for which the fluorescence yield (measured under similar conditions) is 0.31.⁸

Carefully deoxygenated, 10^{-5} M solutions of I exhibited large transient changes in absorption, when

(1) This work was sponsored by the U. S. Army Research Office (Durham). K. S. Wei wishes also to express his gratitude for a fellowship from E. I. du Pont de Nemours & Co.

(2) Author to whom inquiries should be sent.

(3) (a) I. Roitt and W. Waters, *J. Chem. Soc.*, 2695 (1952); (b) W. Henderson, Doctoral Thesis, University of Minnesota, 1962.

(4) (a) C. Coulsen, L. Orgel, W. Taylor, and J. Weiss, *J. Chem. Soc.*, 2961 (1955); (b) K. S. Wei and R. Livingston, *Photochem. Photobiol.*, in press.

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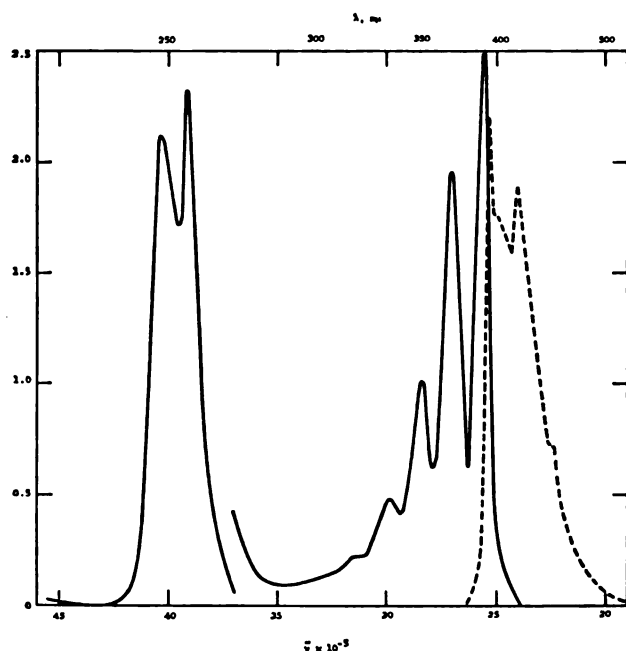


Figure 1. Absorption and emission spectra of 1,2-bis(9-anthryl)ethane in cyclohexane. The scale for absorption between 220 and 70 $m\mu$ is reduced by a factor of 10. The emission spectrum is plotted as intensity in arbitrary units. It is corrected for variation of instrumental sensitivity with wavelength but not for reabsorption, which seriously distorts the curve at wavelengths shorter than 400 $m\mu$. Absorption is indicated by a solid line, emission by a dash line.

subjected to flash illumination, under conditions which have been described elsewhere.⁹ The maximum of this transient occurred at 445 $m\mu$, about 15 $m\mu$ longer than the wavelength of the maximum of the anthracene triplet. The half-life of the transient was approximately 1.5×10^{-8} sec. An anthracene solution, prepared in a similar way, showed a half-life of 3.0×10^{-8} sec. These half-lives are minimum values and are probably much shorter than the values which correspond to the spontaneous unimolecular decay of the triplet state.¹⁰ The observed difference between the values of the half-lives for anthracene and I is probably due to differences in the residual oxygen concentration in the two solutions.

Quantum yields of isomerization of I, in cyclohexane, are summarized in Table I. Generally similar results

Table I. Quantum Yields of Isomerization of 1,2-Bis(9-anthryl)ethane^a

[A], M	[O ₂], M	Temp, °C	ϕ
5.0×10^{-4}	2.0×10^{-4}	25	0.18
1.0×10^{-3}	2.0×10^{-4}	25	0.18
2.0×10^{-3}	2.0×10^{-4}	25	0.21
6.0×10^{-3}	2.0×10^{-4}	25	0.19
1.0×10^{-4}	2.0×10^{-4}	25	0.19
1.0×10^{-4}	2.0×10^{-4}	10	0.18
1.0×10^{-4}	2.0×10^{-4}	35	0.19
1.0×10^{-4}	2.0×10^{-4}	70	0.21
1.0×10^{-4}	$<10^{-4}$	25	0.26
1.0×10^{-4}	1.0×10^{-3}	25	0.17

^a Solvent, cyclohexane, λ 365 $m\mu$.

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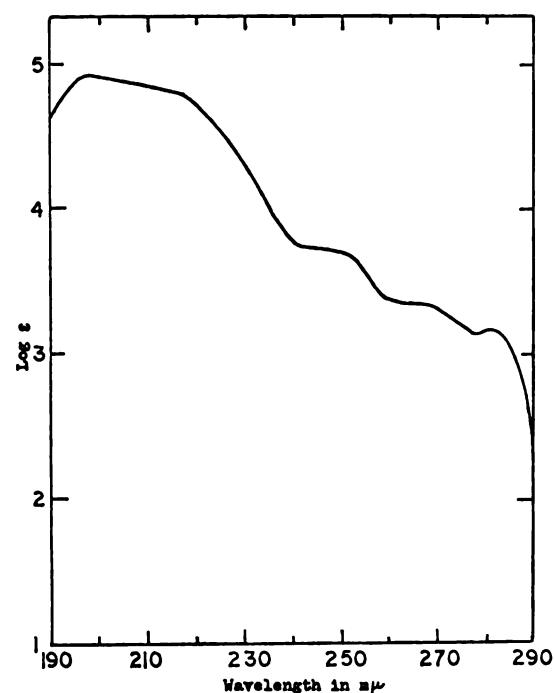


Figure 2. Absorption spectrum of the isomer (II) of 1,2-bis(9-anthryl)ethane in *n*-hexane.

were obtained using benzene as the solvent. Over a 20-fold range the yield is independent of the concentration of the reactant. The apparent dependence on temperature is of doubtful significance but, if real, corresponds to an energy of activation of about 400 cal/mole. Oxygen has a small but definite inhibiting effect. This effect cannot be explained as due to peroxide formation, since its occurrence would increase the apparent quantum yield of dimerization.

Quantum yields for the back reaction, which are listed in Table II, were calculated from the steady-state compositions; they depend on the measured values of the extinction coefficients, the quantum yield of the forward reaction, and the assumption that this yield is the same for 365 and 254 $m\mu$. Light of 254 $m\mu$ was used to produce the steady state. Effects of the reactant concentration, oxygen, and temperature are similar to those observed for the forward reaction.

Table II. Steady-State Composition and Quantum Yields of the Reverse Isomerization^a

[A], M	[O ₂], M	Temp, °C	Steady-state mole % of I	Quantum yield
1.0×10^{-4}	2.0×10^{-4}	25	4.5	0.42
5.0×10^{-4}	2.0×10^{-4}	25	4.1	0.37
1.0×10^{-3}	2.0×10^{-4}	25	4.5	0.41
1.0×10^{-3}	2.0×10^{-4}	10	4.8	0.44
1.0×10^{-3}	2.0×10^{-4}	35	4.8	0.45
1.0×10^{-3}	2.0×10^{-4}	70	5.3	0.49
1.0×10^{-3}	$<10^{-4}$	25	5.4	0.51

^a Solvent, cyclohexane; λ 254 $m\mu$.

Discussion

The observation that the quantum yield of isomerization is not affected by a 20-fold change in the concentration of the reactant indicates that the reaction is a

unimolecular rearrangement of the electronically excited molecule. This unimolecular reaction must compete with the spontaneous (radiative and nonradiative) decay of the excited state and with its quenching by oxygen. Measurements, made by M. Walker of this department with a phase shift apparatus¹¹ using a deaerated $5 \times 10^{-5} M$ solution of I in cyclohexane, indicate a mean lifetime of fluorescence of 2.5×10^{-9} sec. The rate constants for the spontaneous decay of the triplet and for the oxygen quenching of the first excited singlet and the lowest triplet have not been determined for I. It is plausible that they are in general similar to the corresponding values for anthracene, which are as follows: first-order decay of the triplet, 30 sec^{-1} ; ¹² second-order (oxygen) quenching of the excited singlet,⁸ $2.3 \times 10^{10} \text{ l./mole sec}$; second-order quenching of the triplet,¹² $2.3 \times 10^9 \text{ l./mole sec}$.

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Values of these orders of magnitude preclude the possibility that the active intermediate for isomerization is exclusively the triplet state. The postulate that the observed reaction is the result of a spontaneous rearrangement of the fluorescent state is consistent with the observed values for air- and oxygen-saturated solutions. However, the relatively high value obtained for deoxygenated solutions is incompatible with this mechanism. This value, if correct, suggests that both the excited singlet and the triplet states can isomerize, but that the triplet state contributes significantly to the reaction only in deoxygenated solutions.

Acknowledgment. We wish to express our gratitude to Dr. S. Fenton (Minnesota) for suggesting this problem and providing the sample of 1,2-bis(9-anthryl)ethane, and to Dr. R. Lumry (Minnesota) and his colleagues, Dr. T. Bednar and Dr. M. Walker, for determining the fluorescence spectrum and mean lifetime.

Electron Spin Resonance Studies on Ion Pairing in Semiquinone-Alkali Metal Systems

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Abstract: ESR spectra from semiquinone anion radicals produced by alkali metal reduction of parent quinones in ether solvents have been investigated. The results reveal large changes in the spin density distribution in the semiquinone rings as a consequence of association of the anion with alkali metal cations. Ion pairs with different amounts of solvation have been detected, and the results have been interpreted in terms of an ion-pair equilibrium model. Alternating line-width effects have also been observed in the semiquinone-alkali metal system. This arises from the time-dependent modulations of the isotropic ring proton splitting constants resulting from an equilibrium between "solvated" and "intimate" ion pairs in which the metal cation does not drift away from the radical anion.

There has been considerable interest in the experimental and theoretical investigations of the electron spin resonance (esr) of semiquinones in the recent past. The semiquinones form a convenient system for such investigations for various reasons, like ease of producing radicals using different methods and the simplicity of their esr spectra. *p*-Benzosemiquinone (PBSQ), which forms the simplest member of the semiquinone type of radicals, has been investigated extensively, and accurate data are available for hyperfine splittings from protons¹⁻¹² and carbon-13¹²⁻²⁰ and oxygen-17^{21,22} nuclei.

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From these data a good deal of information is available^{14,19,20,22} as regards the unpaired electron density distribution in the molecule and the solvent-induced perturbations on the distribution of the π density.

In the past, semiquinone ion radicals have been produced by air oxidation of the hydroquinone in alkaline solvents,^{1-11,12-17} by electrolytic methods¹⁸⁻²² and by ultraviolet irradiation methods.²³ However, a very

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Hyperfine Splitting Constants (gauss) in *p*-Benzosemiquinone Anion in DME^a

Na				K			
A species ^b a_H	B species ^b		a_{Na}	A species ^b a_H	B species ^b		a_K
	a_1^H	a_2^H			a_1^H	a_2^H	
...	2.35 ± 0.03
2.40 ± 0.02	2.06 ± 0.02	2.74 ± 0.02	1.09	2.41 ± 0.01
2.36 ± 0.02	2.05 ± 0.04	2.66 ± 0.04	1.07
2.42 ± 0.01	2.38 ± 0.01
2.32 ± 0.09	2.16 ± 0.01	2.66 ± 0.01	...

ext for definition of "A" and "B" species. ^b No metal splitting observed in the spectra.

ful technique in producing aromatic radicals has been the reduction of the parent material in a polyether alkali metals; the method has been described previously.²⁴⁻²⁷ A variety of interesting results have been obtained on the alkali metal-aromatic radical ion obtained in this manner. The interest centered around the structure of ion pairs,²⁸⁻³⁰ the differences of ionic equilibria existing in the radical-metal system,^{28,30,39-42} and the effect of intramolecular and intermolecular interactions on the esr spectrum.^{30,34,39-42} The observation of an alternation in the esr spectra resulting from an intermolecular exchange of a cation first observed by Mackor^{41,42} and supported by later studies^{22,34} has been of particular interest.

The present work was undertaken with a view to investigate the ion-pairing phenomenon in the semiquinone-alkali metal system in detail using the alkali reduction technique in ether solvents. From experimental observations^{10-12,18-20,22} one expects large perturbations in the unpaired electron in the semiquinone ring systems as a consequence of ion pairing. The expectations have been substantiated by esr results. The results obtained on semiquinones with different alkali metals using 1,2-dioxethane (DME) and tetrahydrofuran (THF) are reported together with the temperature dependence of splittings in section III. These results and the mechanism of the alternation in line intensities that we have observed in the present system

are discussed on the basis of an ion-pair equilibrium model in section V.

II. Experimental Section

p-Benzoquinone was prepared from hydroquinone (May & Baker Ltd.) according to the method of Gilman and Blatt⁴⁴ and was purified by sublimation (mp 116°). Duroquinone was synthesized starting from durene (Fluka, Switzerland) using known methods.⁴⁵ The product was crystallized from ethanol and purified by vacuum sublimation (mp 111°). 2,6-Dichloroquinone was obtained from Eastman Organic Chemicals and was purified by vacuum sublimation before use. DME and THF were obtained commercially. The solvents were purified according to methods described previously.^{27,46}

The semiquinone radicals were made *in vacuo* by reducing the corresponding quinones with alkali metals using known techniques.²⁴⁻²⁷

The X-band esr spectrometer used has been described previously.¹² The temperature studies were made using a Varian V-4540 temperature-control unit. The details of field calibration have been described elsewhere.⁴⁷

III. Experimental Results

p-Benzosemiquinone Ion (PBSQ). The results obtained on PBSQ with sodium and potassium as gegenions using DME as solvent are given in Table I.

The PBSQ-K sample in DME was bluish green in color and was stable for 36-48 hr. Afterwards the radicals gradually decayed. At room temperature the esr spectrum from this sample was qualitatively similar to those observed for PBSQ by air oxidation of hydroquinone or by the electrolytic reduction of *p*-benzoquinone, and the hyperfine splitting arises from the interaction of the unpaired electron with four equivalent protons. However, on cooling the sample, the spectrum gradually changed its shape. At -20°, lines with total *z* component of the proton nuclear spin angular momentum $M_H = \pm 1$ were broadened and were comparable in intensity to lines with $M_H = \pm 2$. At -60°, a nine-line esr spectrum was observed, and it has been reported in a preliminary communication.¹² This spectrum has been attributed to a radical species which has two sets of two equivalent protons.

In Table I, the radical species in which the four ring protons are equivalent is referred to as the "A" species, and the one in which they form two sets of equivalent groups is referred to as the "B" species. The same terminology will be used in discussing the results from durosemiquinone (2,3,5,6-tetramethyl-*p*-benzosemiquinone) also. Radical species in which all the four

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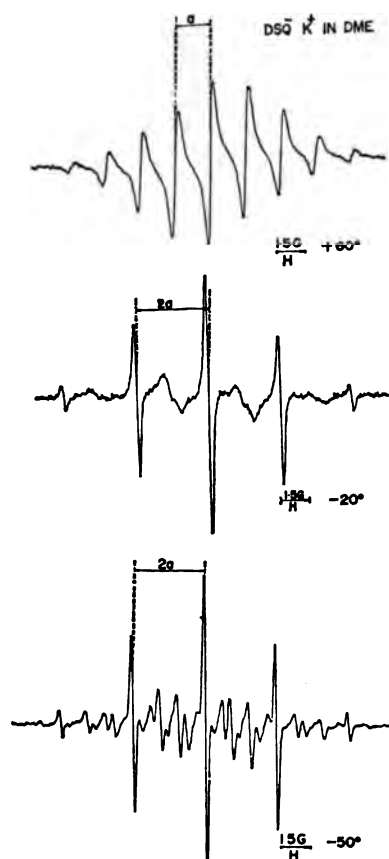


Figure 1. First derivatives of the esr spectra from durosemiquinone ion in DME with potassium as counterion.

methyl groups are equivalent will be designated as the "A" species, and the one in which they fall into two groups of equivalent protons will be referred to as the "B" species.

The PBSQ-Na sample in DME was also bluish green in color, but it was less stable, and it was necessary to complete the esr measurements within 10–12 hr after the sample was prepared. The room-temperature spectrum was a superposition of two spectra, one from the A species with one proton splitting constant and another from the B species with two proton splitting constants. The spectrum from the B species shows additional structure due to ^{23}Na ($I = 3/2$) hyperfine interaction (see Table I). However, the relative concentration of the two species could not be correctly determined as a result of the highly overlapped nature of the experimental spectrum. At -20° the lines were considerably broadened, and it was not possible to obtain accurate data from the spectrum. The sample showed the same behavior even on further cooling.

Attempts to record esr spectra from PBSQ-Li in DME and PBSQ-M ($M = \text{Li, Na, K}$) in THF were not successful as the radicals were found to be unstable.

Durosemiquinone Ion (DSQ). Unlike PBSQ, samples of DSQ with lithium, sodium, and potassium as counterions were quite stable in both DME and THF. The results obtained from these samples are reported in Tables II and III.

DSQ-K Samples. When the radical was prepared with potassium metal in DME, the sample exhibited esr spectra with equally spaced components at room temperature and at 60° . These could readily be in-

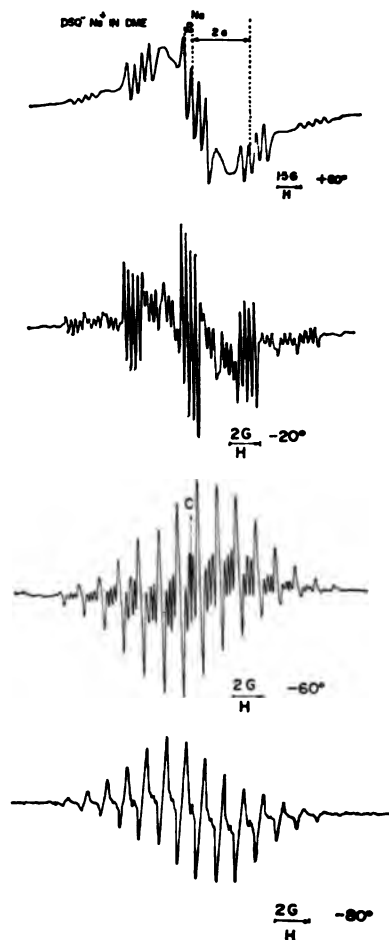


Figure 2. First derivatives of the esr spectra from durosemiquinone ion in DME with sodium as counterion.

terpreted as arising from 12 equivalent methyl protons (A species). However, the room-temperature spectrum showed dormant alternating line-width effects. At -20° the alternating line-width effect was considerably enhanced (Figure 1), and as the temperature was further lowered lines arising from the B species started appearing. At -80° , the spectrum could be interpreted in terms of two groups of equivalent protons, each consisting of six protons and arising from pure B species. A sample of DSQ-K in THF solution behaved essentially in the same manner. However, at room temperature there was larger alternation in the width of the lines in the esr spectrum from this sample as compared to the spectrum from DSQ-K in DME. No potassium splittings were observed in either case.

DSQ-Na Samples. The spectra from this sample in DME at different temperatures are shown in Figure 2. Except at -80° , at all other temperatures reported in Table II, the individual figures arise from both A and B species of DSQ. Both species show hyperfine splittings arising from ^{23}Na hyperfine interaction (see assignments of splitting constants below). A different extent of alternation in the line broadening at different temperatures is also evident in Figure 2.

In interpreting the spectra from DSQ-Na samples, the equally spaced four-line pattern arising from the A species could be easily picked out. The problem was then reduced to assigning the rest of the lines to B species. In order to do this, spectra were reconstructed

Table II. Hyperfine Splitting Constants (gauss) in Durosemiquinone Anion in DME^a

Temp, °C	Li ^a		Na ^a		K ^a		A species ^b		B species ^b	
	a_1^H	a_2^H	a^H	a^{Na}	a_1^H	a_2^H	a^{Na}	a^H	a_1^H	a_2^H
80	1.920 ± 0.004	0.504 ± 0.011
60	0.768 ± 0.094	3.125 ± 0.009	1.901 ± 0.005
25	0.863 ± 0.005	2.981 ± 0.004	1.926 ± 0.003	0.387 ± 0.008	1.916 ± 0.008
-20	0.964 ± 0.003	2.887 ± 0.003	1.898 ± 0.006	0.299 ± 0.014	1.280 ± 0.007	2.565 ± 0.006	2.331 ± 0.008
-50	1.017 ± 0.005	2.825 ± 0.005	1.915 ± 0.002	1.415 ± 0.008	2.413 ± 0.006
-60	1.940 ± 0.007	0.264 ± 0.015	1.280 ± 0.002	2.562 ± 0.003	1.789 ± 0.003
-70	1.033 ± 0.012	2.796 ± 0.013	1.434 ± 0.009	2.407 ± 0.009
-80	1.434 ± 0.009	2.402 ± 0.012

^a See text for definition of "A" and "B" species. ^b No metal splitting observed in the spectra. ^c No A species observed for the sample.

Table III. Hyperfine Splitting Constants (gauss) in Durosemiquinone Anion in THF^a

Temp, °C	Li ^a		Na ^a			K		
	B species ^b		B species ^b			A species ^b <i>a</i> ^H	B species ^b	
	<i>a</i> ₁ ^H	<i>a</i> ₂ ^H	<i>a</i> ₁ ^H	<i>a</i> ₂ ^H	<i>a</i> ^{Na}		<i>a</i> ₁ ^H	<i>a</i> ₂ ^H
25	0.815 ± 0.004	3.039 ± 0.003	1.056 ± 0.017	2.739 ± 0.006	0.346 ± 0.007	1.913 ± 0.003
−20	0.860 ± 0.007	2.955 ± 0.008	1.198 ± 0.002	2.653 ± 0.001	0.257 ± 0.002	...	1.313 ± 0.014	2.534 ± 0.010
−40	0.892 ± 0.009	2.952 ± 0.008	1.208 ± 0.002	2.623 ± 0.001	0.208 ± 0.002	...	1.312 ± 0.006	2.485 ± 0.004
−60	0.955 ± 0.016	2.936 ± 0.013	1.350 ± 0.004	2.458 ± 0.002
−80	1.381 ± 0.004	2.505 ± 0.002

^a See text for definition of "A" and "B" species. ^b No metal splitting observed in the spectra. ^c No A species observed for the sample.

and compared with the experimental one. In doing so, it was assumed that the sum of the two proton splitting constants, a_1^H and a_2^H , for the B species is twice the proton splitting constant, a^H , for the A species. This is justifiable as it holds true for all other spectra from B species. Consequently, the individual values of a_1^H and a_2^H were varied keeping their sum constant. Different values of a^{Na} were then used for computing each spectrum.

Taking the -60° case as a typical representative of the group, stick plots were constructed and were compared with the experimental spectrum. After successfully interpreting the -60° spectrum, it was possible to pick out typical patterns arising from the B species in the overlapped spectra at other temperatures, and an intelligent guess regarding the splitting constants from the B species could be made. Stick diagrams were then reconstructed which explained all the observed lines in the experimental spectrum.

The splitting constants for the B species at 80° and at room temperature could not be calculated because of the broadening of the lines in the region where lines from the B species were expected. Consequently, no assignments of proton splitting constants for the B species could be made at these temperatures. The values of the splitting constants in DME are reported in Table II.

The DSQ-Na sample in THF behaved in a slightly different fashion. At all the temperatures at which

investigations were carried out, only the B-type of spectra were observed. They exhibited ²³Na hyperfine splittings. No alternation in the widths of hyperfine components were observed in this case. The splitting constants are reported in Table III.

DSQ-Li Samples. Samples of DSQ-Li in both DME and THF behaved essentially in the same manner. The spectra at different temperatures could be explained in terms of B species spectra with two splitting constants, each arising from six equivalent protons. There was no observable Li metal splitting unlike the experiments in *t*-pentyl alcohol,²³ and no alternating line-width effects were present. A typical spectrum from the DSQ-Li sample is given in Figure 3. The splitting constants are reported in Tables II and III.

In all instances where the presence of a B species with two splitting constants could be detected, the larger splitting constant, a_2^H , increases with temperature and the smaller one, a_1^H , decreases with temperature. The variation depends on the solvent and the counterion used, and this will be discussed later. The proton splitting constant, a^H , for the A species does not show any measurable temperature variation, although the ²³Na splittings in both the A and B species increase with temperature (Tables II and III).

2,6-Dichlorosemiquinone Ion (2,6-DCSQ). Solutions of 2,6-DCSQ in DME and THF were green in color. The radicals were unstable and they decayed completely in 1-1.5 hr. The expected⁶ three-line spec-

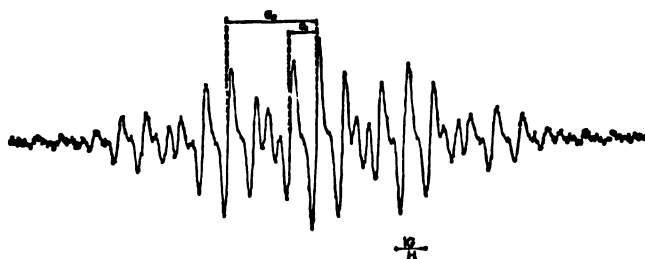


Figure 3. First derivative of the esr spectrum from durosemiquinone ion in DME with lithium as counterion.

trum, with approximate intensity distribution 1:2:1, arising from two equivalent protons was observed from all the samples from which signals could be recorded. However, except for 2,6-DCSQ-K in DME, all the other samples in DME as well as in THF gave spurious esr signals which could not be attributed to any simple radical species arising from 2,6-dichloroquinone. The correct lines from 2,6-DCSQ could be easily identified from intensity considerations and spacings of the hyperfine components. There was no change in the number of lines with temperature, and no alkali metal splittings were present either. Consequently, little information could be obtained by making extensive temperature studies. The results obtained at room temperature and at -75° are given in Table IV. For all the samples, careful measurements have shown a difference in the proton hyperfine splitting with temperature, contrary to a preliminary report.¹² The proton splitting constant increases with temperature for all samples, and at the same temperature the DME samples show a larger splitting as compared to THF samples.

Table IV. Proton Splitting Constants (gauss) for 2,6-Dichlorosemiquinone Anion

Temp, °C	DME ^a		THF ^a	
	Na	K	Li	K
25	2.869	2.989	1.471	...
-75	2.139	2.943	...	3.124

^a No metal splitting observed in the spectra.

IV. Assignments of Splitting Constants

1. Assignments of Proton Splittings in B Species. There is no ambiguity in the assignment of proton splittings for the A species radicals. Once the proton splittings are assigned, it is not difficult to make assignments for the alkali metal splittings also. However, the spectra from the B species result from two equivalent groups of protons as a consequence of ion-pair association. The positions 2, 3, 5, and 6 (see Figure 4) in a *p*-benzosemiquinone ring can be divided into two equivalent groups in any one of three ways, (a) 2,5 and 3,6; (b) 2,3 and 5,6; or (c) 2,6 and 3,5. However, it is possible to make a satisfactory choice in the following manner. Previous experimental investigations^{10-12, 18-20} on the semiquinone radicals indicate that most interactions with the surroundings take place through the oxygen atoms in the semiquinone ring. Consequently, the most probable position of the alkali metal counterion also is near one of the oxygens which has maximum charge density.²⁰ If this assumption is

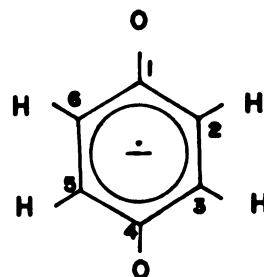


Figure 4. *p*-Benzosemiquinone anion.

made, the best possible division will be to have the 2 and 6 positions in one group and the 3 and 5 positions in the other. There is experimental evidence to support this view. For 2,6-DCSQ one expects association with the counterion at least to the same extent as in the case of either PBSQ or DSQ owing to the presence of two electronegative chlorine atoms in the ring. When there is strong association, one expects a four-line spectrum from 2,6-DCSQ if either of the groupings a or b were correct. On the other hand, the spectra from 2,6-DCSQ showed only three hyperfine components at all conditions, irrespective of the difference in the temperature of the experiment, the metal cations, and the solvents used, although the magnitude of the splittings changed considerably under different experimental conditions.

2. Position of Counterion and Magnitude of Ring Proton Splittings. From the experimental data alone it is difficult to assign the splittings, a_1^H and a_2^H , in PBSQ and DSQ to specific positions in the molecule. The problem arises, in the case of the B species, whether the larger splitting constant, a_2^H , should be assigned to the group of protons that are nearer to the oxygen atom complexed with the alkali metal or to those farther away from it. A satisfactory assignment is, however, possible by comparing the temperature dependence of the splittings in PBSQ and DSQ with that of 2,6-DCSQ (see section V2).

It is reasonable to assume that in the "intimate" species of 2,6-DCSQ the metal cation is near the oxygen atom having two chlorine atoms as neighbors because of the higher electronegativity of the chlorines as compared to protons.⁴⁸ It is experimentally observed that the proton splitting constant for 2,6-DCSQ increases with temperature. It may therefore be assumed that the splitting from protons away from the metal cation increases with temperature. On this basis the larger splitting constant, a_2^H , in *p*-benzo- and durosemiquinones, which shows a positive temperature coefficient, can be assigned to protons farther away from the metal cation and the smaller splitting constant, which decreases with temperature, to protons nearer to the metal cation. It may also be noticed that the effect of association at an oxygen site in the semiquinone is to increase the electronegativity of the oxygen atom, which results in the use of a larger numerical value for the Coulomb integral parameter for the complexed oxygen.²⁰

(48) It may be noticed that Lücken¹¹ has reported the existence of two types of "intimate" ion pairs for 2,6-DCSQ in anhydrous *t*-butyl alcohol, the major fraction having the alkali metal complexed to the oxygen atom flanked by the chlorine atoms and a small fraction with the alkali metal complexed to the oxygen flanked by protons. It has also been observed that simple MO theory predicts larger association at the oxygen flanked by chlorine atoms.

Lücken¹¹ has shown that simple MO theory predicts an increase in the splitting constant of one pair of protons with a simultaneous decrease in the splitting constant of the other pair as a result of complex formation involving one of the oxygen atoms. Lücken¹¹ has noticed further that the pair *ortho* to the complexed oxygen atom has a lower coupling constant.

V. Discussion

1. The Ion-Pair Equilibrium Model. The additional hyperfine structure arising from ²³Na nuclei in the esr spectra from PBSQ-Na and DSQ-Na in DME and THF suggests the formation of ion pairs in these systems. Even in the absence of alkali metal hyperfine splitting, the observation of esr spectra from the B species, when potassium and lithium are used as counterions, supports ion-pair formation. Further, experimental evidence from both PBSQ and DSQ reveals the presence of more than one type of ion pair which are interconvertible. The best evidence for the simultaneous existence of two types of ion pairs is obtained from DSQ-Na in DME. ESR lines from both A and B types of radical with different ²³Na splittings have been observed in this case. Presumably, the ion pairs differ from each other in their different extents of solvation. The formation of ion pairs with different amounts of solvation has been observed by other workers also.^{39,40-54} Hirota³⁹ has observed different distinct solvated species in the naphthalene negative ion, where the radical species have different ²³Na splittings, although the magnitude of the proton splittings remains unchanged. In the present instance, as a consequence of stronger association between the alkali metal and the radical, we do observe changes in both proton splittings and alkali metal splittings in species that are solvated to different extents. In fact, the results reported in section IV can be satisfactorily explained on the basis of an ion-pair equilibrium model in which an "intimate" or "contact" ion pair is in equilibrium with a "loose" or "solvated" ion pair. The different possible equilibria for a species with a given nuclear spin state are indicated below (Figure 5). Species of the type M⁺||R⁻ represent the solvated ion pair, and the ones of the type M⁺R⁻ represent the intimate pairs.

In the intimate pairs, the alkali metal cation is close to one of the oxygens, and this perturbs the unpaired electron distribution in the semiquinone ring. Two sets of equivalent ring positions are formed resulting in the B type of radical exhibiting two proton splitting constants, a_1^H and a_2^H . In the solvated pair, which corresponds to the A type of radicals, the equivalence of the four ring positions is retained as the alkali metal is farther separated from the oxygen atom by the solvent layer.

If the metal ion does not leave the vicinity of the radical anion, equilibria 1 and 2 (Figure 5) can be considered to be intramolecular processes insofar as the preservation of the spin state of the metal nucleus during the conversion is concerned. Equilibria 3 and 4 are intermolecular processes in which the metal cation

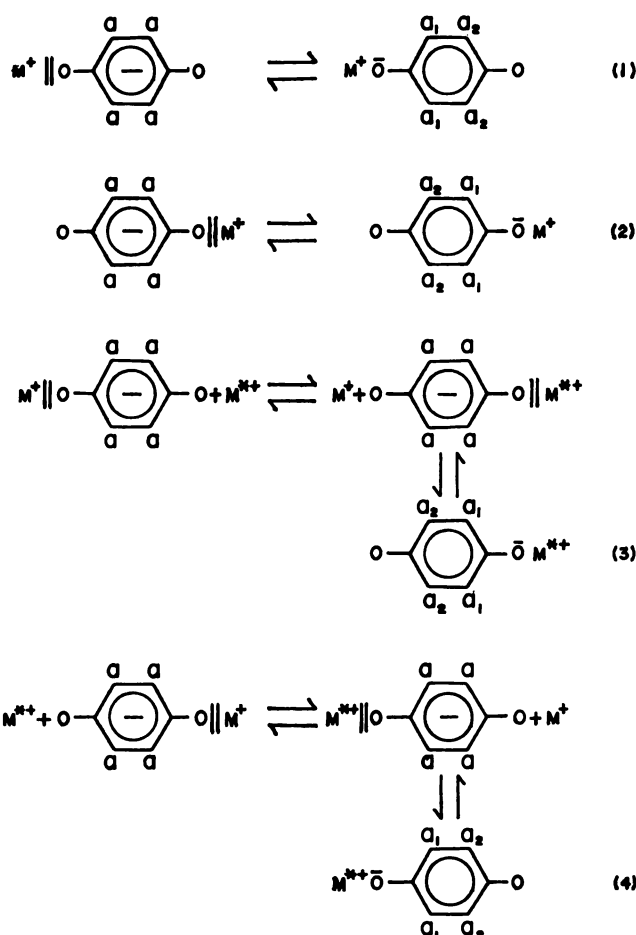
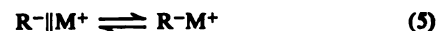


Figure 5. Different possible ion-pair equilibria for *p*-benzosemiquinone ion with a given nuclear spin state.

from the oxygen at one end of the molecule gets detached from the anion, and another cation from the surroundings gets associated with the anion at the other end. However, owing to the presence of sharp alkali metal lines even in spectra exhibiting alternating line widths, it may be argued⁴² that intermolecular processes are absent in the system. The preservation of the spin state of the alkali nucleus during the exchange process, which is fulfilled by the intramolecular processes 1 and 2, can then explain all the observed effects satisfactorily. Thus equilibria 1 and 2 which can be simply represented by



need only be considered. This assumes that each alkali metal, to begin with, is associated with a radical ion in the form of either a solvated or an intimate ion pair.

2. Temperature Dependence of Splitting Constants and Structure of Ion Pairs. de Boer⁵⁵ has noticed that, although two splitting constants are observed for the aliphatic protons (which are equivalent in the absence of association) in pyracene anion, their values remain unchanged with any variation in temperature. However, in the durosemiquinone-alkali metal system (Tables II and III), it has been observed that the smaller splitting constant, a_1^H , decreases with temperature and the larger splitting, a_2^H , increases with temperature. Table V gives the difference in the two splitting constants ($a_2^H - a_1^H$) at various temperatures for durosemi-

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quinone with different counterions in DME and THF. Table V shows several interesting features. The values of $(a_2^H - a_1^H)$ increase as the temperature of a given sample is increased. The increase is more for a THF solution as compared to a DME sample at a given temperature, and for different alkali metals the value increases in the order $\text{Li} > \text{Na} > \text{K}$. From Tables II and III it is also clear that just like $(a_2^H - a_1^H)$, the sodium splitting, a^{Na} , also has a positive temperature coefficient.

Table V. Temperature Variation of $(a_2^H - a_1^H)$ in B Species of Durosemiquinone Anion (gauss)

Temp, °C	Li		Na		K	
	DME	THF	DME	THF	DME	THF
60	2.351
25	2.118	2.224	...	1.683
-20	1.923	2.095	1.285	1.455	...	1.221
-40	...	2.060	...	1.415	...	1.173
-50	1.808	0.998	...
-60	...	1.981	1.282	1.108
-70	1.763	0.973	...
-80	0.968	1.124

These results are understandable if we assume the position of the alkali metal ion to be near one of the oxygen atoms in the semiquinone and close to the plane containing the atoms in the ring, which forms a nodal plane for the π molecular orbital containing the unpaired electron.^{37,42,55} The alkali metal may further be assumed to undergo oscillations⁵⁵ in a potential well at this position. In such a model, the effect of increasing the temperature or of decreasing the mass of the counterion will be to enhance the amplitude of the oscillations. Enhanced oscillation should result in the counterions spending more time away from the nodal plane, causing larger perturbation in the π molecular orbital. As the difference in ring proton splittings is caused by the perturbation induced by the counterion situated near one of the oxygen atoms, it is reasonable to expect the value of $(a_2^H - a_1^H)$ to increase with a larger amount of perturbation (see also section IV2).

A change in $(a_2^H - a_1^H)$ can also arise from a change in equilibrium constants.⁵⁶ However, in cases where only the B-type radical is present at all the temperatures, as in the case of Li-DSQ in DME and THF and Na-DSQ in THF, the variation in $(a_2^H - a_1^H)$ may be arising from the oscillational mechanism.

3. Alternating Line Widths in Semiquinone Anions. Several instances of alternation in line broadening in the esr spectra of free radicals have been reported in the literature,^{23,34,37,42,57-61} and this phenomenon is

(56) We are thankful to the reviewer for pointing this out.

understood in a satisfactory fashion. However, it has been shown by de Boer and Mackor^{41,42} that a novel mechanism, viz., an intramolecular migration of the alkali metal cation between two equivalent sites in a radical, can give rise to alternation in line broadening. The alternation in the width of hyperfine components in the esr spectra from pyrazine³⁴ and durosemiquinone anions²³ has also been explained on the basis of this phenomenon. The alternating line-width effects observed in the present case can be satisfactorily explained on the basis of the ion-pair equilibrium model discussed in section VI. When either the lifetime τ_A of the A species or τ_B of the B species is large compared to the other, an esr spectrum corresponding to the species with the larger lifetime is observed, and in cases where both τ_A and τ_B are large compared to $1/\gamma(a_2^H - a_1^H)$, where γ is the gyromagnetic ratio of the electron, distinct lines from the two different species can be observed. In situation corresponding to $\tau_A \sim \tau_B = 1/\gamma(a_2^H - a_1^H)$ alternation in the widths of the lines can be observed.⁶² Figures 1-3 show spectra corresponding to all these conditions. It is, in fact, possible to calculate the line shapes using this model, and this can be compared with experimental spectra. The result in kinetic data obtained on the system in this manner will be published later.⁶²

Although most of our results also could be interpreted in terms of a jumping model, we favor the ion-pair equilibrium model in the present system. In the semiquinone system any intramolecular exchange of the cation should be less favored compared to hydrocarbon anions owing to the strong electrostatic attraction between the oxygen atom and the counterion. Further, our results show that the association between the ion pairs decreases in the order $\text{Li} > \text{Na} > \text{K}$ for different cations. However, on the basis of an intramolecular exchange model, one should expect the association to be minimum for the lighter Li ion, and the association should increase in the order $\text{Li} < \text{Na} < \text{K}$. But it is not possible to lay too much emphasis on this argument to rule out the possibility of the jumping model as a decrease in ionic radius in going from K to Li favors association.

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Chemical Shift Nonequivalence in Proton Magnetic Resonance Spectra of Glycyl Peptides¹

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Abstract: Glycyl methylene splitting due to chemical shift nonequivalence occurs in the proton magnetic resonance spectra of a dozen amino acid-glycyl dipeptides. The magnitude of the splitting does not appear to be correlated with any single structural element and is reduced by the addition of salt or urea and by an increase in temperature. The chemical shift of the high-field glycyl methylene hydrogen in phenylalanylglycine actually moves downfield upon loss of a proton from the ammonium group. Glycyl methylene splitting also occurs in the central glycyl residue of aminoacylglycylglycines, but not in aminoacylglycinamides. Despite the almost exclusive appearance of chemical shift nonequivalence in the dipolar ion form of di- and tripeptides, it is argued that head-to-tail folding is not implied but rather that the oppositely charged termini of the molecules provide a field gradient which acts upon nonequivalent atoms or groups of atoms. Nonbonded interactions of the amino acid side chains with atoms of planar, *trans* amide bonds restrict the number of allowed rotamers about single bonds in the peptide backbone, reducing the averaging effect and resulting in possible augmentation of field gradients at nonequivalent atoms. Examples of chemical shift nonequivalence of methyl group resonances in some derivatives of valine are also reported.

A recent survey of proton magnetic resonance spectra of amino acids and peptides reported splitting of the methylene hydrogens in leucylglycine and in the middle residue of leucylglycylglycine.² This splitting was ascribed to preferences for certain unspecified rotamers. Because of the importance of this conclusion for protein conformation and the efficacy of proton magnetic resonance spectroscopy in describing these apparent rotamers, we undertook a pmr study of amino acid-glycine dipeptides for 19 of the 20 (all except asparaginyl) amino acid residues commonly occurring in proteins and for others as well. We find methylene splitting in at least 12 dipeptides and also confirm its existence in tripeptides.

Experimental Section

The peptides used in this study were the best grade commercially available from Cyclo Chemical Corp., Mann Research Laboratories, and Calbiochem Corp. N-Benzylbutyramide was synthesized from *n*-butyric anhydride and benzylamine following the standard procedure, mp 49–49.5°, lit.³ 41–44°. The infrared and pmr spectra are consistent for the product. D-Phenylalanyl-L-valine was synthesized from N-carbobenzoxycarboxy-D-phenylalanine and L-valine methyl ester hydrochloride, purchased from Cyclo Chemical Corp. The synthesis was carried out in the usual way with N,N-dicyclohexylcarbodiimide.⁴ N-Carbobenzoxycarboxy-D-phenylalanyl-L-valine methyl ester was prepared in methylene chloride,⁵ followed by basic hydrolysis⁶ at room temperature and hydrogenolysis in a Parr hydrogenation apparatus. The infrared and pmr spectra are consistent with the products of each step. Carbon, hydrogen, and nitrogen analyses are in excellent agreement with the intermediate and final products.

Proton magnetic resonance spectra were recorded on a Varian A-60 nmr spectrometer equipped with variable-temperature probe.

All spectra were run at room temperature (about 25°) except where noted for leucylglycine. Chemical shifts were generally calculated from the spectra recorded on the 50-cycle sweep width. Sweep widths were frequently calibrated with the Model 200 CD wide-range oscillator and 5512 A electronic counter manufactured by the Hewlett-Packard Co.

In general, 0.3 to 0.5 mmole of the compound was dissolved in 0.5 ml of D₂O. In cases where the compound failed to dissolve completely, NaOD was added dropwise until the sample was completely dissolved. The pH was measured with a Beckman Model G pH meter equipped with a Beckman No. 40316 one-drop glass electrode. Observed pH meter readings are reported. After the spectrum was recorded at this pH, either NaOD or DCl, depending on the initial pH, was added. The pH was again measured and the spectrum recorded. In all dipeptides, spectra were recorded at high and low pH and at or near to the isoelectric pH. Where possible excess acid or base was added to suppress ionizations. Some peptide spectra were recorded at intermediate pH values. The pH dependence of the chemical shifts of phenylalanylglycine was determined by titrating a 0.9 M, pH 0.5 solution with 3.2 M NaOD and a 0.8 M, pH 11.5 solution with 3.3 M DCl using a Manostat microburet. All chemical shifts are reported in ppm downfield from sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) as an internal standard.

Results

In acidic or basic solutions, the glycyl methylene absorption appears as a single resonance line for most of the aminoacylglycines studied in this research. Frequently this resonance peak is broadened or split into an AB quartet in the dipolar ion form of the dipeptide. In the last case a $\Delta\nu$ and J_{AB} may be calculated from the spectrum. For these dipeptides the high-field, ν_B , and low-field, ν_A , chemical shifts in ppm downfield from DSS as an internal standard are recorded in Table I. The dipeptides are listed in approximate order of increasing $\Delta\nu$. Values of J_{AB} vary only slightly from 17.0 to 17.6 cps with a tendency for the greater values to appear in more acidic solutions. The pH values for the solutions recorded in Table I were carefully regulated so that a single charged species predominated. Charges are indicated by beginning with the N terminal ammonium group and ending with the carboxylic acid charge of the glycyl residue. For example, the three charge signs for α -glutamylglycine refer successively to the N terminal ammonium group,

(1) This research was supported by grants from the National Science Foundation and the National Institutes of Health. Similar results have been obtained by O. Jardetzky and A. Nakamura, private communication.

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the γ -carboxylic acid group, and the glycyl carboxylic acid group. In the leucylglycine spectra of the earlier study,² one of the peaks designated as an impurity resonance is actually the highest field component of an AB quartet, while the lowest field component occurs at the same field strength as the CH triplet.

Table I. Chemical Shifts (ppm) of Glycyl Methylene Protons in L-Aminoacylglycines^a

L-Amino-acylglycine		ν_A	ν_B
Glutamyl	+0	4.10	
	+—	3.85	3.76
	0—		3.78
α -Glutamyl	+00	3.99 ^b	
	+—	3.88	3.73
	0—		3.76
α -Aspartyl	+00	4.08	
	+—	3.84	3.71
	0—		3.78
Histidyl	+00	4.09	
	+—	3.98	3.83
	0—		3.82 ^c
Norvalyl	00—	3.73	
	+0	4.04	
	+—	3.88	3.71
Valyl	0—		3.75
	+0	4.08	
	+—	3.90	3.71
Norleucyl	0—		3.76
	+0	3.99 ^b	
	+—	3.88	3.71
Leucyl	0—		3.75
	+0	4.06	
	+—	3.89	3.70
Isoleucyl	0—		3.74
	+0	4.07	
	+—	3.90	3.70
Tyrosyl	0—		3.76
	+00	4.02	
	+0—	3.95	3.75
Phenylalanyl	00—	3.82	3.71
	0—		3.70
	+0	4.00	
Tryptophanyl	+—	3.89	3.60
	0—	3.80	3.67
	+0	4.00	
	+—	3.97	3.64
	0—	3.79	

^a In ppm downfield from DSS as internal standard in D₂O.

^b Solution insufficiently acid so that this value is a minimum one.

^c Indication of splitting.

Using a peak width at a half-height of 2 cps or less on the 50-sweep width as the criterion, as well as no indication of the low-intensity outer components of the AB pattern, we observed no splitting of methylene hydrogens in neutral solutions of the following dipeptides and related compounds: glycylglycine, D,L-alanylglycine, β -alanylglycine, L-serylglycine, L-threonylglycine, L-prolylglycine, hydroxy-L-prolylglycine, L-arginylglycine, L-methionylglycine, L-cystinyl-bisglycine, glutathione, acetylglycine, benzoylglycine (basic solution), N-benzylbutyramide (in CDCl₃ where it exhibited a *cis-trans* mixture), sarcosylglycine, glycylsarcosine (exhibits a *cis-trans* mixture), glycyl-L-tyrosine, glycyl-L-leucine, L-valylglycinamide, and L-tyrosylglycinamide. L-Lysylglycine exhibited a peak width of 2.5 cps which was unresolvable. Chemical shift differences of less than about 0.1 ppm would be detected only with difficulty on our instrument. Consideration of these

results and those reported in Table I indicates that no simple single factor, such as electronegativity or the number of substituents on the β -carbon atom, appears to account for the magnitude of splitting.

The magnitude of the methylene splitting in dipolar ion leucylglycine was observed under a variety of solution conditions. The increment of splitting with a decrease in concentration is about 0.017 ppm/mole. Solutions of this dipeptide in 8 M urea or 2.5 M KCl exhibited a decrease in $\Delta\nu$ of about 0.04 ppm or 20%. Increasing concentrations of MgCl₂ are more effective on a molar basis than KCl in causing decreases in $\Delta\nu$. A solution of dipolar ion leucylglycine in D₂O at 100 or 120° exhibits a decrease in $\Delta\nu$ of 0.04 ppm compared to the same solution at room temperature.

Several miscellaneous features of the spectra of the dipeptides recorded in Table I are worth mentioning. Splitting of the glycyl methylene hydrogens in tryptophanylglycine persists into quite acid solutions but finally becomes unanalyzable on our instrument with a peak width at half-height of 4 cps near zero pH. The phenylalanyl part of phenylalanylglycine exhibits an ABX spectrum in basic solutions with $J_{AX} = 5.1$, $J_{BX} = 8.4$ cps, and $\Delta\nu_{AB} = 0.125$ ppm. In neutral and acid solutions only an A₂X type spectrum is obtained. The results are similar to those reported for phenylalanine⁷ and other amino acids.^{8,9} Upon ionization of the phenolic group in tyrosylglycine, the high-field hydrogens of the A₂B₂ system of the aromatic ring undergo an upfield shift greater than do the low-field hydrogens, confirming the assignment of the high-field pair as those *ortho* to the hydroxyl group.¹⁰

The interesting case of phenylalanylglycine, where the methylene resonance is split even in basic solutions, was carefully studied over a range of pH. Individual variations of the low- and high-field proton resonances, A and B, respectively, are shown in Figure 1. A sufficient number of pH values were studied in order to establish that the curves in Figure 1 do not cross. Plateaus occur where one kind of charged species predominates. Upon removal of protons from the carboxylic acid or ammonium groups, the resonance frequency changes in a manner typical of a titration curve. The midpoint of the change in basic solution where the ammonium group is undergoing deprotonation occurs at an observed pH in D₂O of 7.8 for both A and B hydrogens. A similar analysis is not possible for the region of carboxylic acid ionization because the spectra collapse into a single average line before the extreme acid limit frequencies of the A and B protons may be established. The average value of the chemical shifts of A and B protons moves upfield markedly with deprotonation of the carboxylic acid group and slightly with deprotonation of the ammonium group. These average shifts are similar to those observed for the other dipeptides and for the single peak of the C terminal residue of glycylglycine¹¹ upon

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equivalent ionizations. In all dipeptides where splitting is observed, the greatest value of $\Delta\nu$ occurs in solutions of the dipolar ion.

Unequal chemical shift changes are exhibited by the A and B protons as the observed pH is varied in Figure 1. Even more noteworthy is the downfield shift of the high-field B hydrogen on loss of a proton from the ammonium group leaving a negatively charged molecule. This downfield shift of the B hydrogen is just compensated by an upfield shift of the A hydrogen so that the average shift of both hydrogens taken together is slightly upfield by 0.01 ppm on ammonium ionization.

The pronounced difference in behavior between the A and B protons of phenylalanylglycine upon ammonium ionization, along with their continued separate resonances in basic solutions, suggested that a comparison of the resonances of L-phenylalanyl-L-valine with its diastereomeric L,D or D,L dipeptide would be informative. Valine was chosen for the carboxyl terminal residue because there is only one asymmetric carbon atom, and its α -CH hydrogen resonance is only a doublet and is not split more extensively. Unfortunately after synthesizing the D,L compound, we found the dipolar ion form insufficiently soluble in water. The results are presented in Table II.

Table II. Valyl Resonances of Phenylalanylvalines^a

Charge	L,L		D,L	
	α -CH	Methyls	α -CH	Methyls
+0	4.23	0.97, 0.88	4.18	0.78, 0.67
+—	4.05	0.97, 0.95, 0.86, 0.84	Insoluble	
0—	4.03	0.91, 0.79	3.97	0.71, 0.59

^a In ppm downfield from DSS as an internal standard in D₂O.

In the cationic and anionic forms, the valyl methyl groups of phenylalanylvaline appear as a doublet split by the β -CH hydrogen with coupling constants of about 6.8 cps. In the dipolar ion form four peaks appear in the methyl region: β -CH splitting yields a similar coupling constant, and there is a second splitting of 0.018 ppm due to chemical shift nonequivalence. The double doublet for methyl resonances also occurs in all three ionic forms of the amino acid valine.⁹ The splittings due to chemical shift nonequivalence are 0.017, 0.053, and 0.072 ppm for the cationic, dipolar ion, and anionic forms, respectively, with the high-field methyl group undergoing the largest shift with pH. With no β -CH hydrogen present, the appearance of two peaks in the methyl region of penicillamine (β -mercaptovaline) must be due to chemical shift nonequivalence. The chemical shift differences are 0.06, 0.08, 0.25, and 0.24 ppm for the +1, 0, -1, and -2 charged forms, respectively. Again the high-field methyl peak undergoes the greater shift with pH. Unlike the dipeptides, where the greatest chemical shift nonequivalence for either methyl group or hydrogen splitting occurs in the dipolar ion form, the splitting due to this cause is greater in the most negatively charged species of amino acids.⁹ The tripeptide valylglycylglycine exhibits a double doublet for the methyl groups only in basic solution with a splitting due to chemical shift nonequivalence of about 0.02 ppm.

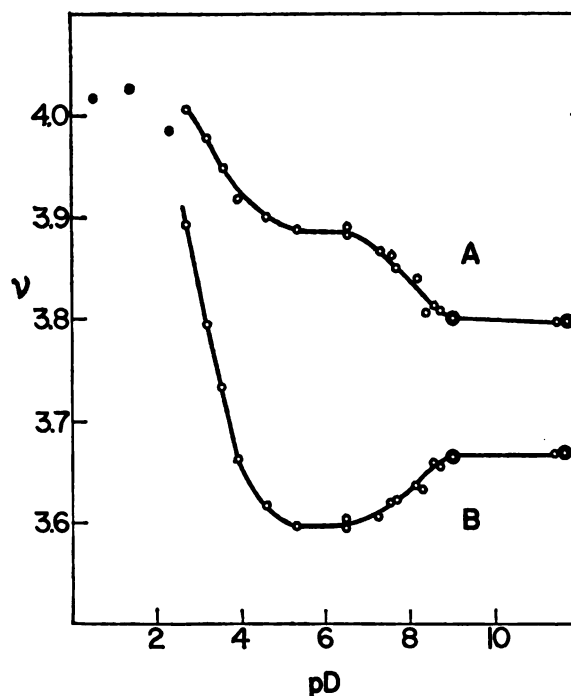


Figure 1. Chemical shift in ppm downfield from DSS as internal standard vs. observed pH meter readings for glycyl methylene protons A and B of 0.75 M phenylalanylglycine in D₂O. Bullseyes represent two points. Solid points in most acid solutions are average values for unresolved peaks.

A select sample of aminoacylglycylglycine tripeptides was also examined for glycyl methylene splitting in neutral solutions. Consistent with the behavior of the corresponding dipeptides, no splitting was observed in alanylglycylglycine and prolylglycylglycine. A small splitting in the central glycyl residue was observed in valylglycylglycine. Sufficient splitting of the methylene hydrogens in the central glycyl residue to permit analysis was observed in leucylglycylglycine and phenylalanylglycylglycine. Though no splitting of the terminal glycine appeared, the methylene hydrogens of the central glycyl residue exhibited an AB quartet in leucylglycylglycine ($\nu_A = 4.06$, $\nu_B = 3.98$ ppm) and phenylalanylglycylglycine ($\nu_A = 3.98$, $\nu_B = 3.88$ ppm). No splitting was observed in either glycyl residue of glycyl-L-leucylglycine.

Discussion

In order to exhibit chemical shift nonequivalence in nuclear magnetic resonance spectra, two conditions must be met. To be chemical shift nonequivalent, atoms or groups may not be related by a symmetry operation taking into consideration internal motions that are rapid compared to the time scale of an nmr experiment. Secondly, there must exist a sufficient field gradient so that the nonequivalent atoms or groups exhibit chemical shifts resolvable on the instrument employed.

For the L-amino acid-glycine dipeptides of this study, no symmetry element exists along the N-CH₂ bond axis. Even if rotation about the planar and *trans* amide bond were rapid, the methylene hydrogens would still be nonequivalent in these optically active dipeptides and their racemic mixtures. Only if inversion at the asymmetric carbon atom were rapid compared to the nmr

chemical shift would a plane of symmetry include the N-CH₂ bond axis. This explanation for chemical shift nonequivalence arising from molecular dissymmetry does not invoke rotamer preferences about the N-CH₂ or C-CO bonds. If such favored rotamers do exist, they might serve to enhance dissymmetry and hence nonequivalence. The main question posed by the results reported here is, "To what extent are the observed chemical shift differences in glycyl methylene hydrogens augmented or due solely to rotamer preferences?"

Since rotations about all single bonds except the C-N bond in the peptide backbone are rapid, proton magnetic resonance spectra represent weighted average spectra over all rotamers present. Each kind of rotamer gives rise in general to unique shielding at each hydrogen or other atom. If rotamers are equally represented about the whole 360°, then parts of their individual contributions probably cancel and observed chemical shifts represent highly averaged values. In this case contributions to chemical shifts from rotamer preferences are considered insignificant, and any splitting is ascribed to field effects operating on an asymmetric environment.

One of the problems in assessing the importance of rotamer preferences is that potential barriers about C_α-N and C_α-CO single bonds in the peptide backbone are not well defined, but appear to be very low, with the result that large numbers of rotamers may be significant. Primarily because of the *trans* conformation of the planar amide group, rotations about single bonds within a given amino acid residue are nearly independent of rotations about neighboring residues in the peptide chain.¹² However, nonbonded interactions of the amino acid side chains with atoms of *trans*, planar amide bonds restrict the number of allowed rotamers even in the case of glycine and markedly more so for larger side chains.¹³ In the aminoacylglycines certain rotamers are disadvantaged because of nonbonded interactions, but there remains a considerable arc over which rotamers can occur, especially about the N-CH₂ single bond. There does not seem to be a good correlation between the extent of methylene splitting and the permissible arc over which rotamers can occur. Though large groups with restricted rotamers show chemical shift nonequivalence and appear in Table I, side-chain groups with equally restricted rotamers appear in the list where any splitting was too small to be observed.

Several studies of the physical properties of di-, tri-, tetra-, and pentapeptides have been interpreted to indicate a lesser end-to-end distance in those peptides that contain some D amino acid residues than in those that contain only L residues. This conclusion has been drawn from comparisons of acid ionization constants,¹⁴ transition metal ion interactions,¹⁵ dielectric increments,^{16,17} rates of ring closure,^{17,18} and proton

magnetic resonance spectra.¹⁹ Not all of these experiments were performed on the dipolar ion form of the peptide; in the last two kinds of measurements the carboxylic acid groups were uncharged.

Examination of nonbonded interactions by use of Courtauld's molecular models indicates that the amino and carboxylic acid groups are brought closer together in L,D than in L,L dipeptides. This result is independent of pH or charge on the terminal groups; the conclusion is forced by consideration of nonbonded interactions alone. Thus the results referred to in the previous paragraph receive a natural explanation so that it is not necessary or desirable to invoke interactions between opposite charges inducing preferred rotamers. Nearly the same rotamer preferences exist in the presence and absence of the dipolar ion charge distribution. No special folded conformation is produced by attraction of oppositely charged ends of the molecule. In an independent study, the chemical shifts produced upon proton ionization in glycine, alanine, and their di- and tripeptides are correlated with the separation along the chain of the measured hydrogen from the protonic center, indicating that head-to-tail folding does not occur to an observable extent in these compounds.²⁰

The same nonbonded interactions that force the amino and carboxylate groups to be closer together in the D,L dipeptide also force the side chains to be closer together than in the L,L diastereomer. When one of the side chains is aromatic, the other appears in its shielding cone in the D,L dipeptide with the result that all valyl resonances in Table II for phenylalanylvalines appear at higher field in this diastereomer than in the L,L compound. An identical explanation accounts for the observed higher field resonances in the nonaromatic side chain of the D,L diastereomers of leucyltyrosine¹⁹ and alanyltyrosine²¹ compared to the L,L dipeptides.

Counting separately individual charged forms, nearly 100 compounds were examined in this study of chemical shift nonequivalence, yet methylene hydrogen or methyl group nonequivalence was observed only in dipolar ion forms or with aromatic amino acid residues. The lack of correlation between the magnitude of nonequivalence and the allowed rotamers as derived from peptide maps, along with the dependence of rotamer preferences on nonbonded interactions and their independence of charge distribution, suggests that rotamer preferences are not the primary cause for nonequivalence in the di- and tripeptides of this study. Rather the asymmetric carbon provides the potential for chemical shift nonequivalence which is realized by the field gradients produced in dipolar ion forms and by aromatic groups. Any rotamer preferences that occur as a result of nonbonded interactions might serve to heighten nonequivalence.

Methylene splitting also occurs in the central glycyl residues of the dipolar ion forms of the tripeptides leucylglycylglycine and phenylalanylglycylglycine where the charge separation is almost 50% greater than in

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dipeptides. The splitting in these two tripeptides is about 40% of that observed in the corresponding dipeptides. Lack of observed methylene splitting in the terminal glycyl residues of tripeptides and either glycyl residue in glycyl-L-leucylglycine is evidently due to their being out of a region of sufficient field gradient.

Temperature dependence of the extent of methylene splitting may in principle distinguish field from rotamer effects since all rotamers should be nearly equally populated at high temperatures, leaving only the averaged field effect to contribute to chemical shift nonequivalence. In the case of leucylglycine an increase in temperature from 25 to 120° reduced the methylene splitting by about 20%. Not even this degree of splitting may be ascribed to rotamer preferences about C-C single bonds because collapse of amide spectra has been observed at less than 100° owing to the onset of rapid rotation about the C-N bond. Because of the small energy differences between potential minima, a very wide temperature range would have to be studied in order to assess quantitatively the importance of rotamers about C-C single bonds. It does not seem possible to separate rotamer from field effects on the basis of the ionic strength dependence of $\Delta\nu$. We are unable to determine precisely the extent to which rotamer preferences due to nonbonded interactions contribute to chemical shift nonequivalence, which is due primarily to field effects in the compounds reported in this study.

Methylene or methyl group splitting has also been observed in many compounds that contain no charged groups. Chemical shift nonequivalence has been observed in the nitrogen substituents of uncharged amides with an asymmetric center in the carbonyl substituent.²²

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The presence of an AB quartet of the methylene hydrogens of neopentyl O-methylmandelate²³ demonstrates that nonequivalence may occur across ester as well as amide bonds. Methyl group nonequivalence has been observed in several isopropyl esters.²⁴ In these compounds polar and aromatic groups may produce field gradients and nonequivalence as do charged and aromatic groups in peptides. The important role of solvent in contributing to the magnitude of chemical shift nonequivalence of solutes has been stressed. In cases where rotamer preferences appear unable to account for the results, greater magnitudes of methylene splitting are observed in media of lower dielectric constants.²⁵

Two arguments suggest that the high-field resonance in the aminoacylglycine dipeptides is the one that would remain if the glycyl residue were stereoselectively deuterated so that the deuterium atom appears in the position of the side chain in an L,D or D,L dipeptide. Table II shows that the high-field α -CH hydrogen resonance of phenylalanylvalines occurs in the D,L diastereomer. In addition, selective deuteration of the methylene group in neopentyl O-methylmandelate such that the product might be considered analogous to a D,L compound results in retention of the high-field resonance.²³ Since both of these examples contain phenyl groups, the conclusion is valid for the compounds with nonaromatic side chains in Table I only if the additional effect of an aromatic group is simply to augment and not to reverse the sign of the chemical shift difference found with aliphatic groups.

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A New Evaluation of Platt's Model for Diatomic Hydrides¹

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Contribution from the W. A. Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61801. Received January 30, 1967

Abstract: Platt's model for diatomic hydrides has been reevaluated using Clementi's Roothaan-Hartree-Fock atomic wave functions. The diatomic hydrides from H₂ through HBr have been treated. The calculated equilibrium internuclear distances are in excellent agreement with experimental values for the united-atom model, $(Z + 1)^0 \rightarrow (ZH)^0$, but are too large for the separated-ion model, $(Z)^-, H^+ \rightarrow (ZH)^0$. The calculated force constants are also in better agreement with experiment for the united-atom model.

The united-atom model for diatomic hydrides has been the subject of a considerable literature since the initial formulation by Platt in 1950.²⁻¹⁰ In the

model one begins with a neutral atom of atomic number $Z + 1$. The wave function is assumed to have averaged spherical symmetry. A proton is removed from the nucleus and allowed to move out through the fixed

(1) This research was supported by a grant from the National Science Foundation.

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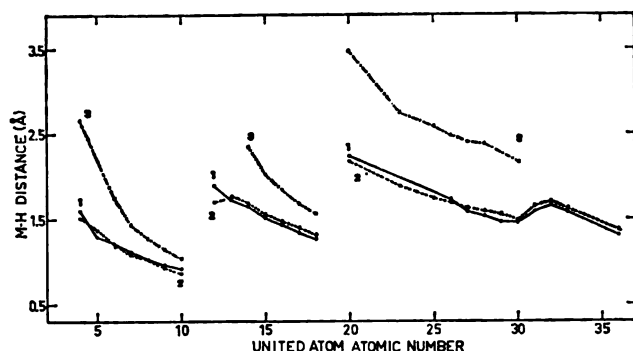


Figure 1. Comparison of experimental internuclear distances (1) with those calculated by the united-atom model (2) and by the separated-ion model (3).

electron distribution. At any distance r from the nucleus it experiences a force

$$F_H = \frac{-Z + \int_0^r \Psi^* \Psi r^2 dr}{r^2} \quad (1)$$

where Ψ is the normalized radial function for the initial neutral atom of atomic number $Z + 1$. Zero force is achieved when the numerator on the right-hand side is zero. Thus r_e , the equilibrium internuclear distance, is determined by the relation

$$Z = \int_0^{r_e} \Psi^* \Psi r^2 dr \quad (2)$$

Differentiation of eq 1 gives

$$\frac{\partial F_H}{\partial r} = + \frac{2}{r^3} \left(Z - \int_0^r \Psi^* \Psi r^2 dr \right) + \frac{1}{r^2} \frac{\partial}{\partial r} \left(\int_0^r \Psi^* \Psi r^2 dr \right) \quad (3)$$

This derivative at the equilibrium distance $r = r_e$ gives the force constant k for M-H stretching. At $r = r_e$, the first term on the right is zero, so

$$k = \left(\frac{\partial F_H}{\partial r} \right)_{r=r_e} = \frac{1}{r_e^2} \frac{\partial}{\partial r} \int_0^{r_e} \Psi^* \Psi r^2 dr = (\Psi^* \Psi)_{r=r_e} \quad (4)$$

Thus, both the equilibrium internuclear distance and stretching force constant are obtainable from a knowledge of the united-atom wave function. Alternatively, one might begin with the separated-ion wave function for M^- and bring the proton in through the fixed wave function until a point of zero force is reached. Since the model itself is not exact, the two procedures will not in general lead to the same values for r_e and k , even if the exact united-atom and separated-ion wave functions were employed.

It has been pointed out that Platt's model violates the quantum mechanical virial theorem, by requiring $\partial \Psi^* \Psi / \partial r$ to be zero.⁵

This deficiency can be remedied⁷ by an appropriate scaling factor η_0 , given by

$$\eta_0 = 1 - \frac{1}{U} \int_0^{r_e} \Psi^* \Psi r dr \quad (5)$$

where U is the united-atom potential energy, and ρ_0 is determined by the condition

$$Z = \int_0^{r_e} \Psi^* \Psi r^2 dr \quad (6)$$

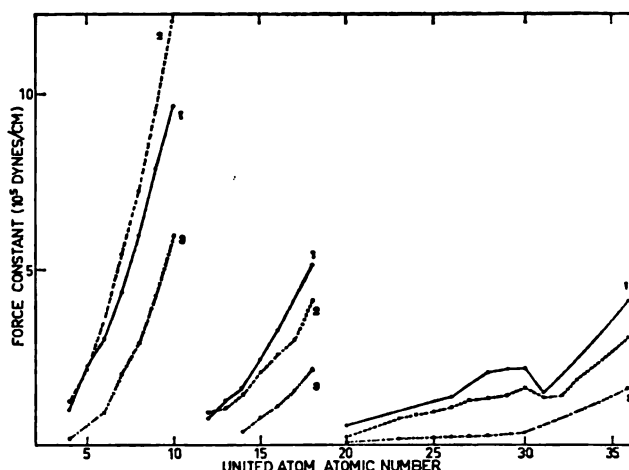


Figure 2. Comparison of experimental force constants (1) with those calculated by the united-atom model (2) and by the separated-ion model (3).

The equilibrium internuclear distance is then given by $r_e = \rho_0 / \eta_0$. The scaled force constant is given by the relationship

$$k = \eta_0^4 \Psi^* \Psi (\eta_0 - \rho_0^2 \Psi^* \Psi / U)^{-1} \quad (7)$$

In this expression it is assumed that the united-atom wave function satisfies the atomic virial theorem, which is in fact the case in the results presented here. Equation 7 approaches Platt's expression (eq 4) as $\eta_0 \rightarrow 1$. Equation 5 requires amendment for the separated-ion model; the correct expressions are given by Hall and Rees.⁷

Despite a perennial interest in Platt's model, and numerous considerations of its significance and limitations, it has not as yet been thoroughly tested in terms of an extensive set of accurate atomic and ionic wave functions. The recent appearance of such wave functions makes adequate testing feasible. We present herein the application of Platt's model for both united-atom and separated-ion wave functions to the extensive set of atomic and ionic wave functions of Clementi¹¹ for the elements He through Kr, both with and without scaling. In the following paper,¹² the model is extended to a consideration of the transition metal carbonyl hydrides.

Computation

The atomic and ionic wave functions employed in our calculations are the analytical Hartree-Fock functions developed by Clementi.¹¹ The total wave functions are expressed as sums of several Slater determinants which are in turn antisymmetrized products of one-electron spin orbitals. The orbital functions are obtained by solving the Roothaan-Hartree-Fock equations.¹³ The orbitals which make up the Slater determinants are of the form

$$\vartheta_{i\lambda\alpha} = \sum_p \chi_{p\lambda\alpha} C_{i\lambda p}$$

in which λ is a symmetry index (quantum number l)

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Table I. Observed Data for Diatomic Hydrides and Calculated Values Using the United-Atom and Separated-Ion Approximations

	Z ^a	k, exptl ^b	r ₀ , exptl ^c	United-atom approximation			Separated-ion approximation		
				Scale factor	k ^b (calcd unscaled)	k ^b (calcd scaled)	r _e ^c (calcd scaled)	k ^b (calcd)	r _e ^c (calcd)
HH	2	5.71	0.74 ^a	0.761	36.3	24.8	0.56		
HeH	3	0.805	1.36	0.73	1.01		
LiH	4	1.03	1.60	0.853	1.91	1.22	1.52	0.18	2.66
BeH	5	2.26	1.30 ^a	0.881	3.06	2.16	1.37		
BH (³ P)	6	3.04	1.23 ^a	0.900	4.75	3.56	1.22	0.93	1.75
BH (¹ D)				0.900	4.54	3.37	1.23	0.72	1.82
BH (¹ S)				0.899	4.05	3.00	1.26	0.91	1.77
CH (⁴ S)	7	4.37	1.12 ^a	0.913	7.03	5.44	1.09	2.04	1.43
CH (³ D)				0.913	6.55	5.07	1.11	1.70	1.48
CH (³ P)				0.913	6.25	4.84	1.12	1.50	1.52
NH (³ P)	8	5.98 ^b	1.04 ^a	0.923	9.05	7.23	1.03	2.92	1.28
NH (¹ D)				0.923	8.80	7.0	1.01	2.73	1.30
NH (¹ S)				0.923	8.28	6.62	1.02	2.35	1.33
OH	9	7.76	0.97 ^a	0.931	11.6	9.50	0.93	4.27	1.15
FH	10	9.66	0.92 ^a	0.937	14.6	12.1	0.86	5.97	1.04
NeH	11	0.943	1.29	1.08	1.21		
NaH	12	0.78	1.89 ^a	0.947	1.09	0.93	1.70		
MgH	13	1.27	1.73 ^a	0.952	1.24	1.07	1.77		
AlH (³ P)	14	1.61	1.65 ^a	0.946	1.70	1.45	1.69	0.40	2.35
AlH (¹ S)					1.42	1.25	1.74	0.16	2.75
SiH	15	2.46 ^b	1.52 ^a	0.958	2.34	2.08	1.56	0.80	2.03
PH	16	3.26 ^b	1.44 ^a	0.961	2.89	2.59	1.48	1.12	1.85
SH	17		1.35 ^{d,e}	0.963	3.34	3.00	1.40	1.57	1.69
ClH	18	5.15	1.27 ^a	0.965	4.57	4.13	1.31	2.16	1.56
KH	20	0.56	2.24 ^a	0.969	0.27	0.24	2.18	0.09	3.47
TiH	23	0.973	0.85	0.79	1.89	0.19	2.75
VH	24	0.974	0.96	0.89	1.82		
CrH	25	0.975	1.05	0.98	1.75	0.22	2.59
MnH	26	1.38	1.73 ^a	0.976	1.19	1.09	1.70	0.25	2.48
FeH	27	...	1.59 ^{d,f}	0.977	1.34	1.26	1.62	0.27	2.41
CoH	28	2.09 ⁱ	1.54 ^d	0.977	1.42	1.33	1.59	0.28	2.38
NiH(4s ² 3d ⁹)	29	2.17 ⁱ	1.47 ^a	0.978	1.52	1.43	1.55		
NiH(4s ¹ 3d ¹⁰)				0.978	2.24	2.11	1.33	1.2	1.46
CuH	30	2.18	1.46 ^a	0.979	1.74	1.64	1.49	0.36	2.17
ZnH	31	1.50	1.59 ^a	0.980	1.44	1.36	1.65		
GaH	32	...	1.66 ^j	0.980	1.49	1.41	1.70	0.39	2.33
GeH	33	...	1.59 ^k	0.981	2.07	1.97	1.62		
BrH	36	4.12	1.41 ^a	0.982	3.25	3.09	1.47	1.64	1.72

^a Atomic number of corresponding united atom. ^b In units of 10⁴ dynes/cm. ^c k is calculated from ω_e values^g (i.e., it is corrected for anharmonicity) except where noted. ^d In angstroms. ^e The equilibrium values given here are r_0 as defined in footnote g. The r_0 values differ very little from the r_e values. For example, r_0 for NiH is 1.47 Å, whereas r_e is 1.49 Å. ^f Data taken from Tables de Constantes et Données Numériques, Vol. 4, B. Rosen, Ed., Hermann & Cie, Depositaires, Paris, 1951. ^g Value estimated by J. L. Margrave, *J. Phys. Chem.*, **58**, 258 (1954). ^h G. Herzberg, "Molecular Spectra and Molecular Structure. 1. Spectra of Diatomic Molecules," D. Van Nostrand Co., Inc., Princeton, N. J., 1950. ⁱ B. Kleman and E. Werhagen, *Arkiv Fysik*, **6**, 359 (1953). ^j Calculated from $\Delta G^\circ_{1/2}$ values as defined in footnote g. These values are uncorrected for anharmonicity in the vibrations. The correction is usually small and results in a 2% error at most in k . ^k There are two observed states. In the other, $r_0 = 1.48$ Å. ^l The force constants are calculated from ω_e values which are not well known.

and α is the subspecies index which labels the individual members of the degenerate set transforming according to the λ representation. The subscript p refers to the p th basis function of symmetry λ . The χ 's are Slater-type orbitals with integral quantum numbers

$$\chi_{p\lambda\alpha}(r, v, \varphi) = R_{\lambda p}(r) Y_{\lambda\alpha}(v, \varphi)$$

We are concerned with the radial part of the orbitals

$$R_{\lambda p} = [(2n_{\lambda p})!]^{-1/2} (2\xi_{\lambda p})^{n_{\lambda p}} + 1/2 r^{n_{\lambda p}-1} \exp(-\xi_{\lambda p} r) \quad (8)$$

The size of the basis set employed in obtaining each $\vartheta_{\lambda\alpha}$ varies. In all cases, however, the resulting atomic wave functions are very good approximations to the Hartree-Fock limit and represent the most accurate extensive set of wave functions presently available.

The solutions to eq 2 or 6 and 5 are found by numerical integration of the appropriate expansions at various values for r . The values for k , from eq 2 or 7, are readily computed once η_0 , ρ_0 , and r_e are known (U is given by Clementi). The results for the binary hydrides are

given in Table I for the united-atom and separated-ion models. (Scaling was not included in the separated-ion calculations because the scale factor is essentially unity in all cases.)

The internuclear M-H distances calculated by the two methods are compared with the experimental results in Figure 1.

Discussion

It is quite evident from Table I and Figure 1 that the united-atom model yields very good values for the internuclear distance. Discounting the results for the first two or three elements, to which the model can hardly be expected to apply, the error seldom exceeds 5%. This is a particularly pleasing result, since Platt was unable to obtain satisfactory values for r_e with the atomic wave functions available to him. It is also noteworthy that the united-atom model gives much better results for r_e than the separated-ion model. It has not been obvious until now that this would prove

to be the case, and, in fact, arguments have been advanced⁷ for the superiority of the latter model. The united-atom model is also clearly more successful in calculating the force constants (Figure 2). The general trend of force constant within each horizontal row is reproduced quite well. The errors in the calculated values for this observable are relatively much larger than for the internuclear distance. The reasons for this are perhaps most evident when the problem is viewed in terms of the Hellmann-Feynman theorem. The expectation value for internuclear distance is dependent on the equilibrium wave function, for which the Hartree-Fock atomic wave function for the neutral atom of $Z + 1$ nuclear charge is apparently a good approximation. The stretching-force constant, however, involves an expression of the form⁸

$$k = \frac{2Z}{r^3} + \int \Psi^* \Psi \frac{\partial^2 V_{ne}}{\partial r^2} d\tau + \int \frac{\partial(\Psi^* \Psi)}{\partial r} \frac{\partial V_{ne}}{\partial r} d\tau \quad (9)$$

where V_{ne} is the nuclear-electronic attraction operator, $V_{ne} = \sum_{\alpha} -1/r_{\alpha H}$, where the sum is over all electrons. The last term in this equation is a measure of relaxation in the electron distribution accompanying nuclear motion. In the Platt model this term is assumed to be zero. Only a fortunate cancellation with another large term of opposite sign can yield a satisfactory value for k . Such a cancellation does apparently exist, but k is nevertheless not as accurately predicted as r_e .

Acknowledgment. Calculations were performed at the University of Illinois Digital Computer Laboratory.

Application of Platt's Model for Diatomic Hydrides to Metal Carbonyl Hydrides¹

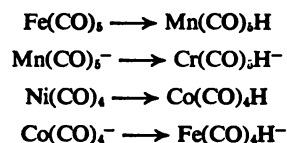
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Contribution from the W. A. Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61801. Received January 30, 1967

Abstract: Platt's united-atom model for diatomic hydrides is extended to metal carbonyl hydrides. The equations are the same as for the diatomic case, except that a classical approximation is employed to take account of net charge which may be present on the CO groups. The model provides a simple picture for metal-hydrogen bonding and accounts nicely for the similarity in M-H stretching frequency with the corresponding diatomic metal hydride. The following values are estimated for equilibrium M-H distances: $\text{Mn}(\text{CO})_5\text{H}$, 1.60 Å; $\text{Co}(\text{CO})_4\text{H}$, 1.40 Å; $\text{Fe}(\text{CO})_4\text{H}^-$, 1.40 Å; $\text{Cr}(\text{CO})_5\text{H}^-$, 1.50 Å.

The transition metal carbonyl hydrides are an interesting and varied group of compounds.^{2,3} The purpose of the present contribution is to consider the metal-hydrogen bond in terms of an extension of Platt's model for diatomic hydrides.^{4,5}

The metal carbonyl hydrides can be considered to derive in principle from a parent metal carbonyl molecule or ion by abstraction of a proton from the nucleus of the central metal atom.⁶ The abstracted proton is allowed to move out through an electronic environment which is forced to remain unchanged, except for relatively minor C-M-C bond angle changes. When the nuclear-electronic attractive forces on the proton equal the proton-nuclear repulsive forces, the proton comes to rest. Some examples of the process envisaged are



If it is assumed that the proton exerts a slight net repulsive effect on the CO groups, it may then be expected to occupy somewhat less space than the surrounding CO groups. Thus in $\text{Mn}(\text{CO})_5\text{H}$ the axial-radial C-Mn-C angle is 97°;⁷ the average CO-CO distance is only slightly less than in the parent $\text{Fe}(\text{CO})_5$.

The carbonyl hydride formation described above is an isoelectronic process and may be considered in terms of the Hellmann-Feynman theorem. Employing the integral form of this theorem,⁸ we label the parent carbonyl compounds as the X state and the carbonyl hydride in its equilibrium configuration as the Y state. Then the difference in energy, ΔW , exclusive of the change in nuclear energy, is given by

$$W = \Delta V_{nn} + \frac{N}{S} \int \Psi_X H'(1) \Psi_Y d\tau \quad (1)$$

$$W = \Delta V_{nn} + \frac{N}{S} \int \rho_{XY}(1) H'(1) d\tau(1)$$

The first term on the right represents the difference in the classical nuclear-nuclear potential, $\sum_{jk} Z_j Z_k / r_{jk}$, where Z_j and Z_k are the charges on nuclei j and k , and r_{jk} is the internuclear distance. The normalized transi-

(1) The research is supported by a grant from the National Science Foundation, NSF GP 6369X.

(2) R. B. King, *Advan. Organometal. Chem.*, **2**, 157 (1964).

(3) J. A. Ibers, *Ann. Rev. Phys. Chem.*, **16**, 389 (1965).

(4) J. R. Platt, *J. Chem. Phys.*, **18**, 932 (1950).

(5) W. G. McDugle, Jr., and T. L. Brown, *J. Am. Chem. Soc.*, **89**, 3111 (1967).

(6) A related idea was expressed 25 years ago by W. Hieber, *Die Chemie*, **55**, 24 (1942).

(7) S. J. LaPlaca, W. C. Hamilton, and J. A. Ibers, *Inorg. Chem.*, **3**, 1491 (1964).

(8) H. J. Kim and R. G. Parr, *J. Chem. Phys.*, **41**, 2892 (1964).

tion density $\rho_{XY}(1)$ is given by

$$\rho_{XY}(1) = \frac{N}{S} \int \Psi_X(1) \Psi_Y(1) d\tau(2) d\tau(3) \dots d\tau(N)$$

$$S = \int \Psi_X(1, 2, \dots, N) \Psi_Y(1, 2, \dots, N) d\tau(1) \dots d\tau(N)$$

The perturbation Hamiltonian H' is given by

$$H'(1) = V_{ne}^Y(1) - V_{ne}^X(1)$$

The elucidation of these expressions is greatly simplified if it is assumed that all interactions of the CO groups with one another and with the central metal are unchanged in the process $X \rightarrow Y$. This means that only the term $\sum Z_{jH}/r_{jH}$ remains in ΔV_{nn} , and that $H'(1) = \sum_{\alpha} (-1/r_{H\alpha})$, where α runs over all electrons. Although this assumption may seem a bit drastic, it is quite reasonable in terms of what data are available. The CO stretching frequencies in the infrared-active modes, for example, are not changed drastically, as the comparisons in Table I show. The CO frequencies in the hydride are very little different from those in the parent carbonyl, whereas they are much lower in the anion corresponding to complete removal of the proton.

Table I. Comparative CO Stretching Frequencies of Metal Carbonyl Derivatives

Compound	Infrared CO frequencies, cm^{-1}	Ref
$\text{Ni}(\text{CO})_4$	2057	<i>a</i>
$\text{Co}(\text{CO})_4\text{H}$	2062, 2043	<i>a</i>
$\text{Co}(\text{CO})_4^-$	1886	<i>a</i>
$\text{Fe}(\text{CO})_5$	2034, 2014	<i>a</i>
$\text{Mn}(\text{CO})_5\text{H}$	2007, 2014, 2117	<i>b</i>
$\text{Mn}(\text{CO})_5^-$	1898, 1863	<i>a</i>
$\text{Co}(\text{CO})_4^-$	1886	<i>a</i>
$\text{Fe}(\text{CO})_4\text{H}^-$	1897, 1937	<i>a</i>
$\text{Fe}(\text{CO})_4^{2-}$	1786	<i>a</i>

^a W. F. Edgell, J. Huff, J. Thomas, H. Lehman, C. Angell, and G. Asato, *J. Am. Chem. Soc.*, **82**, 1254 (1960). ^b P. S. Braterman, R. W. Harrill, and H. D. Kaesz, submitted for publication.

From this point it is possible to make still further simplifying assumptions. The common view of the neutral metal carbonyls is that the central metal atom carries essentially zero charge. Although it is difficult to gather definitive evidence on this point, the isomer shift in the Mössbauer spectrum⁹ of $\text{Fe}(\text{CO})_5$ and related compounds is consistent with near-zero charge on the metal. The appearance potentials of neutral as well as positively charged metal carbonyl fragments parallel the ionization potentials of the metal atoms or ions of corresponding charge remarkably well,¹⁰ a further indication that the over-all charge of the metal carbonyl moiety is a measure of the metal atom charge. It is possible then to consider that the nuclear-nuclear and nuclear-electronic components of ΔW which involve the C and O nuclei and electron density localized in the CO regions cancel for the proton. There remains just the interaction with the central nucleus and transition density centered thereon

$$\Delta W = \frac{Z}{r_{MH}} - \frac{N}{S} \int \rho_{XY}^M(1) \frac{1}{r} d\tau(1) \quad (2)$$

(9) R. H. Herber, R. B. King, and G. K. Wertheim, *Inorg. Chem.*, **3**, 101 (1964).

(10) R. E. Winters and R. W. Kiser, *J. Phys. Chem.*, **70**, 1680 (1966).

If that part of Ψ centered on M is assumed to be invariant to the $X \rightarrow Y$ process, then ρ_{XY} becomes simply the one-electron charge density on M, $\rho_M(1)$

$$\Delta W = \frac{Z}{r_{MH}} - \int \rho_M(1) \frac{1}{r} d\tau(1) \quad (3)$$

We desire $\partial \Delta W / \partial r_{MH} = 0$ at the equilibrium CO distance, which gives

$$\frac{Z}{r_e^2} = \int_0^{\infty} \frac{\rho_M^{(1)}}{r^2} d\tau(1) \quad (4)$$

If ρ_M is spherically symmetric, this is just Platt's model for a diatomic hydride. The force constant follows in the usual way. Although the net charge in the metal carbonyl may be zero as assumed, it is of interest to explore the consequences of the assumption that it is not. We assume again that the CO-CO and CO-M interactions are the same in the X and Y states. Further, the proton-electron and proton-nuclear interactions with the CO groups are assumed to yield a net potential energy, $\sum_i S_i / r_{iH}$, where S_i is the net charge on the i th CO group, and r_{iH} is the distance from the proton to the center of the i th CO bond. Thus, if the metal is assumed to have a net charge of -1 in $\text{Mn}(\text{CO})_5\text{H}$, $+0.20$ unit of charge may be assigned to each CO group. Alternatively, it might be assumed that the axial CO group has a different net charge than the radial, etc. The components of ΔW relating to the central atom and electron density centered there remain unchanged. Then

$$\Delta W = \frac{Z}{r_{MH}} - \int \rho_M \frac{1}{r} d\tau + \sum_i \frac{S_i}{r_{iH}} \quad (5)$$

$$\frac{\partial \Delta W}{\partial r_{MH}} = 0 = \frac{-Z}{r_e^2} + \int \frac{\rho_M}{r^2} d\tau - \sum_i \frac{S_i \cos \theta_{iH}}{r_{iH}^2} \quad (6)$$

The charge density ρ_M in eq 6 is that appropriate to the metal atom in a zero or nonzero charge state, depending on $\sum S_i$ and the total net charge on the parent carbonyl. Aside from assignment of charge state, there is the problem of choosing the appropriate configuration, which may be different from that in the free metal of the same charge. An attempt has been made to evaluate the sensitivity of the results to this variable. It should be pointed out that the scaling procedure applied to diatomic M-H systems^{6,11} has been employed in the same manner as before.

A few qualitative conclusions can be drawn immediately from the proposed model. If the charge on the metal in the parent carbonyl is near zero, then it follows that the metal-hydrogen bond should possess about the same stretching force constant and equilibrium nuclear distance as in the corresponding diatomic hydride. The evidence regarding distances is somewhat tenuous at present (*vide infra*), but the force constant results are qualitatively as expected, as evidenced by the comparisons of observed metal-hydrogen stretching frequencies given in Table II.

Results

Calculations were performed as described in the previous paper, using Clementi's wave functions.¹¹⁻¹³

(11) G. G. Hall and D. Rees, *Mol. Phys.*, **5**, 279 (1962).

(12) E. Clementi, *J. Chem. Phys.*, **41**, 303 (1964), and previous papers referenced therein.

(13) E. Clementi, *IBM J. Res. Develop. Suppl.*, **9**, 2 (1965).

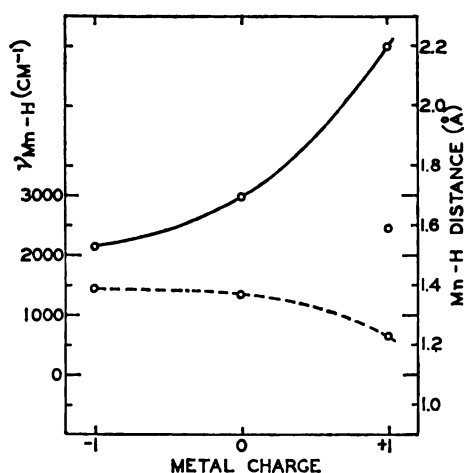


Figure 1. Calculated equilibrium distance and stretching frequency for the Mn-H bond in HMn(CO)_5 , as a function of metal charge.

$\text{Mn(CO)}_5\text{H}$. Calculations were carried out for $\text{Mn(CO)}_5\text{H}$ assuming a +1, 0, and -1 charge on the Fe in the united molecule. Wave functions for the configurations $4s^23d^n$ are available for these three charges. When the charge on the metal is different

Table II

	$\nu_{\text{M-H}}$ cm^{-1}		$\nu_{\text{M-H}}$ cm^{-1}
$\text{Mn(CO)}_5\text{H}^a$	1775	Mn-H	1548
$\text{Co(CO)}_4\text{H}^b$	1934	CoH	1890
$\text{Fe(CO)}_4\text{H}^-$	1900	FeH ⁻	...

^a Reference 10. ^b W. F. Edgell and R. Summitt, *J. Am. Chem. Soc.*, **83**, 1772 (1961).

from zero, it has been assumed that the charge of opposite sign is distributed equally among the five CO groups. The results were not affected by assuming that the axial CO group carries a slightly different charge than the radial. The bond angles and distances observed in solid HMn(CO)_5 ⁷ were employed in the calculation. The resulting equilibrium Mn-H distance as a function of metal charge is shown as the solid line in Figure 1. There is only one other configuration available for testing, namely $4s^03d^7$ for Fe^+ , for which the calculated equilibrium Mn-H distance is shown as the single point on the figure. This configuration represents an unlikely extreme in terms of s character. It is generally assumed from theoretical considerations that the first-row transition metals do employ considerable 4s orbital character in metal carbonyl compounds. The solid curve in Figure 1 is therefore probably satisfactory from the standpoint of s orbital character. The effect of 4p character on the equilibrium Mn-H distance is an important question, which we cannot test for a lack of the appropriate atomic wave functions. Although 4p orbital functions of high accuracy are not available for the first-row transition elements, it is quite clear that the 4p charge densities lie outside the 3d. Richardson and co-workers¹⁴ report that in the neutral atoms the 3d distribution completely screens nuclear charge from the 4p, to

(14) J. W. Richardson, R. R. Powell, and W. C. Nieuwpoort, *J. Chem. Phys.*, **38**, 796 (1963).

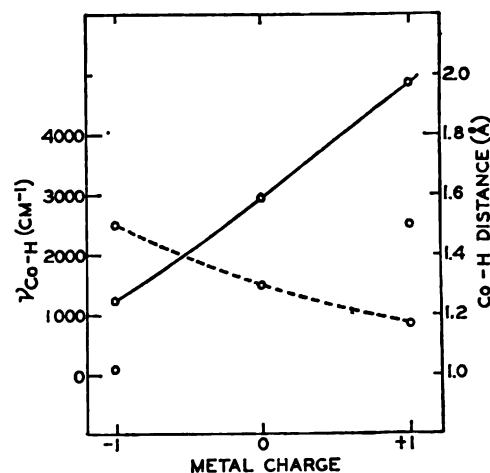


Figure 2. Calculated equilibrium distance and stretching frequency for the Co-H bond in HCo(CO)_4 , as a function of metal charge.

within 1%. We may state with confidence, therefore, that the assumed $4s^23d^n$ configuration will lead to a lower bound estimate of the Mn-H distance for the model chosen. Part of the error resulting from failure to include 4p occupation is cancelled by the assumption of a full two-electron occupation of the 4s.¹⁵ The 4s and 4p have similar radial charge-density dependences.

The dotted line shows the calculated Mn-H stretching frequency, in the harmonic oscillator approximation, as a function of metal charge, for the assumed $4s^23d^n$ configurations. As the metal charge becomes more negative, there is an asymptotic approach to a frequency of about 1500 cm^{-1} , somewhat below the observed frequency of 1775 cm^{-1} . Frequency decreases quite rapidly with increase in charge above zero. The model is in best accord, therefore, with a metal charge of about -0.5; the predicted Mn-H stretching frequency is in the range 1350 to 1450 cm^{-1} ; and the predicted Mn-H bond distance is $1.60 \pm 0.07\text{ Å}$.

$\text{Co(CO)}_4\text{H}$. The procedure described above was followed also for $\text{Co(CO)}_4\text{H}$. Unfortunately, the only configuration of Ni^- for which the wave function is available is $4s^13d^{10}$; this was used along with the wave function of the $4s^23d^8$ and $4s^23d^7$ configurations for Ni and Ni^+ , respectively. The results are graphed in Figure 2. For Ni^+ the configuration $4s^03d^9$ is also available. The result of using the wave function for this configuration is shown as the single point. We take half the difference between this point and the point corresponding to the $4s^23d^7$ configuration as a correction to the $4s^13d^{10}$ point at -1 charge, to make it correspond approximately to a $4s^23d^9$ configuration. This point is used in constructing the solid line in Figure 2.

The calculated equilibrium Co-H distance was found to be quite insensitive to the assumed C-Co-C angles. The data are shown for tetrahedral disposition of the CO groups. Variation of up to 10° in the H-Co-C angles produced a change of less than 0.02 Å in the calculated Co-H distance, even when the charge on the metal is assumed to be +1 or -1.

(15) An extensive approximate Roothaan SCF MO calculation on Ni(CO)_4 , using approximate SCF metal atomic orbitals¹⁴ in the basis set, has been carried out by W. C. Nieuwpoort, *Philips Res. Rept. Suppl.*, **6**, 1 (1965). He obtains a net metal charge, based on a conventional population analysis, of -1. The total Ni orbital populations are $4s^0.44p^{1.7}3d^{8.1}$.

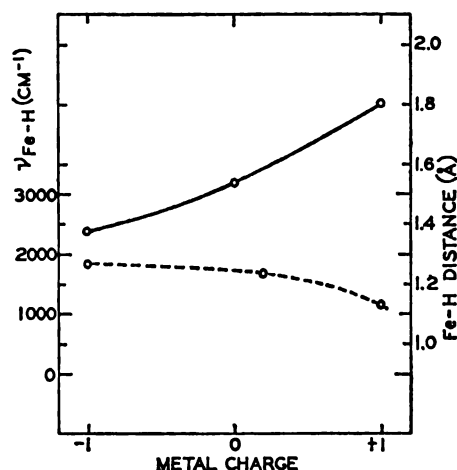


Figure 3. Calculated equilibrium distance and stretching frequency for the Fe-H bond in $\text{HFe}(\text{CO})_4^-$, as a function of metal charge.

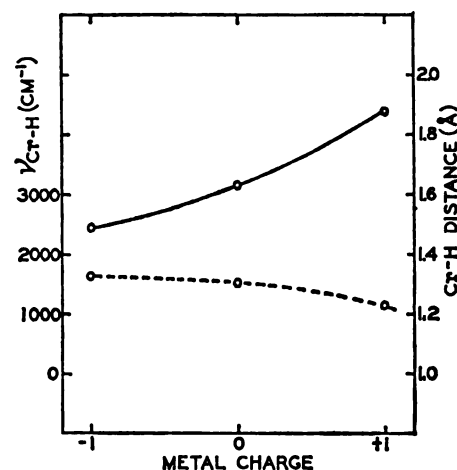


Figure 4. Calculated equilibrium distance and stretching frequency for the Cr-H bond in $\text{HCr}(\text{CO})_5^-$, as a function of metal charge.

the variation in Co-H stretching frequency as a function of assumed metal charge, for the $4s^23d^9$ configuration is shown as the dashed line in Figure 2. The value -1 charge is only approximate, since the $4s^23d^9$ wave function is not available. The observed frequency intersects the line at a metal charge of about -0.5. For this charge the equilibrium Co-H bond distance is calculated to be about 1.40 ± 0.1 Å.

Wave functions for $4s^23d^n$ configurations of Co^- , Co^0 , and Co^+ are available. The results of calculations are as shown in Figure 3. The observed Fe-H stretching frequency is approached in the calculations for a rather negative charge on the metal, the range from -0.5 to -1. The calculated Fe-H distance based on this range of charge is 1.40 ± 0.05 Å. $\text{Cr}(\text{CO})_6$ and $\text{HCr}_2(\text{CO})_{10}^-$. The calculations for $(\text{CO})_5^-$ were carried out as described above for the other cases, using Mn wave functions for $4s^23d^n$ configurations (Figure 4). For a metal charge of about -0.5, the Cr-H frequency is calculated as 1600 cm^{-1} , Cr-H distance as 1.50 ± 0.05 Å.

Certain aspects of the structure of $\text{HCr}_2(\text{CO})_{10}^-$ have recently been described.¹⁶ The hydrogen is presumably located along the Cr-Cr axis and separates $\text{Cr}(\text{CO})_5$ units. If we assume that each unit carries a -0.5 charge, the charge on the Cr in $\text{HCr}_2(\text{CO})_{10}^-$ would be slightly less negative, by perhaps 0.25 e, than $\text{Cr}(\text{CO})_5^-$. Assuming that the charge on the Cr in $(\text{CO})_5^-$ is -0.5, a Cr-H distance of 1.54 Å is estimated from Figure 4. This leads to a predicted Cr-Cr distance of about 3.1 Å, as compared with the experimental value of 3.41 Å.¹⁶ The comparison is rather close, but the agreement is encouraging.

Discussion

There is an unfortunate paucity of data regarding metal-hydrogen distances in metal carbonyl hydrides.

(1) L. B. Handy, P. M. Treichel, L. F. Dahl, and R. G. Hayter, *J. Chem. Soc.*, 88, 366 (1966).

The results obtained here are in good agreement with expectations based on somewhat empirical covalent radii.¹⁶ Thus a value of about 1.65 is expected for the Mn-H distance, as compared with our calculated value of 1.60 ± 0.07 Å.

The only experimental data which relate directly to the M-H distances are the broad-line proton nmr studies of Farrar, Davison, *et al.*¹⁷ These authors conclude that the Mn-H distance in $\text{HMn}(\text{CO})_5$ is 1.28 Å. The Co-H distance in $\text{HCo}(\text{CO})_4$ is estimated on the basis of line-shape data as 1.2 ± 0.1 Å.¹⁸

Both these results are shorter than the estimates from the present calculations. No reasonable modification which retains the simplicity of the model could appreciably shorten the calculated M-H distances. Indeed, the calculated values are probably lower bounds, in view of our neglect of the 4p orbital occupations.

Even if the estimates of metal-hydrogen distances from the nmr studies are subsequently corroborated by neutron diffraction or other data, the results obtained are quite good for such a simple model. The approach is of value in suggesting how the transition metal hydride structures relate to known organometallic structures.^{2,19} It provides a nice rationale for the observation that the M-H stretching frequencies are close to those for the corresponding diatomic metal hydrides. Extension to calculation of other expectation values, notably chemical shift²⁰ and electric field gradient,²¹ would not be difficult.

Acknowledgment. Calculations were performed at the University of Illinois Digital Computer Laboratory.

(17) T. C. Farrar, Sr., W. Ryan, A. Davison, and J. W. Faller, *ibid.*, 88, 184 (1966).

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The ^{19}F Nuclear Magnetic Resonance Spectra of Oxygen Fluorides¹

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Abstract: The ^{19}F nuclear magnetic resonance (nmr) spectra of liquid F_2 , OF_2 , O_2F_2 , and O_3F_2 are presented. The shifts of O_2F_2 and O_3F_2 are the furthest downfield of any simple fluorine compound yet reported. The structural implications of these shifts are discussed. A model for O_3F_2 is postulated in which this species is made up of O_2F_2 and "interstitial" O_2 .

The nuclear magnetic resonance (nmr) spectra of the series F_2 , OF_2 , O_2F_2 , and O_3F_2 have been observed. The shifts observed for O_2F_2 and O_3F_2 represent the least shielded of any fluorine compounds yet reported. The vast difference in chemical shift of O_2F_2 and O_3F_2 indicates that the fluorine nuclei (hence fluorine-oxygen bonding) are considerably different in O_2F_2 and O_3F_2 as compared to OF_2 . A summary of chemical shifts is presented in Table I. The O_3F_2 is given in quotations, since there is some uncertainty about the reality of the compound. This uncertainty will be discussed in some detail later.

Table I. ^{19}F Nmr Shifts for Liquid F_2 , OF_2 , O_2F_2 , and O_3F_2 (CFCl_3 reference)

Compound	Shift, ppm
F_2 (77°K)	-422 ± 1
OF_2 (77°K)	-249 ± 1
O_2F_2 (145°K)	-865 ± 1
" O_3F_2 " (<145°K)	-877 ± 5

The nmr spectra of liquid F_2 and OF_2 have been reported by Nebgen, Rose, and Metz.^{2a} Recently Lawrence, Ogden, and Turner^{2b} have reported the ^{19}F nmr spectrum of O_2F_2 in CF_3Cl to be at -825 ± 10 ppm with respect to a Freon 11 (CFCl_3) reference. This signal is about 40 ppm higher than our observation in the neat liquid. No open literature reports of the ^{19}F nmr signal in O_3F_2 are available; however, Solomon and co-workers have observed the ^{17}O and ^{19}F nmr signals from O_3F_2 .³ Their observations on the ^{19}F nmr spectrum of O_3F_2 at temperatures near 145°K are identical with ours. Solomon, *et al.*, had better means of temperature control than we, and hence could study the chemical shift of O_3F_2 as a function of temperature. They found that the shift was very far downfield (-1900 ppm at 85°K) and moved upfield to -868 ppm at 145°K. The -868 -ppm peak is that of O_2F_2 . This upfield shift with temperature is the same as we observed in O_3F_2 .

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(2) (a) J. W. Nebgen, W. B. Rose, and F. I. Metz, *J. Mol. Spectry.*, **20**, 72 (1966); (b) N. J. Lawrence, J. S. Ogden, and J. J. Turner, *Chem. Commun.*, 102, (1966).

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Experimental Section

Commercially available F_2 (The Matheson Co., Inc.) and OF_2 (General Chemical Division, Allied Chemical Corp.) were used in the studies. Prior to sampling, each of the compounds was passed through a hydrogen fluoride trap. The OF_2 contained additional impurities (primarily oxygen) not removed by the HF trap and was further purified by gas chromatography.

The O_2F_2 and O_3F_2 were prepared using the usual discharge techniques. The reaction vessel is similar to that used by Streng,⁴ with the exception that the whole vessel is made of Pyrex. A standard taper male connection is placed at the bottom of the reactor to attach sample tubes. The sample tubes were 2-mm capillaries for use in a constant-temperature nmr dewar.⁵

The nmr spectra of the liquid F_2 and OF_2 samples were recorded at 77°K on a Varian Associates HA-100 nmr spectrometer operating at a frequency of 94.075 Mc. That of O_2F_2 was recorded at 145°K using liquid CF_4 as a cryogenic. The nmr signals were externally referenced to the ^{19}F signal from CFCl_3 . Referencing was accomplished by carefully removing the sample from the magnet probe and replacing it with the reference material. This transfer occurred while the magnetic field was being swept at a constant rate. No significant variations in the field sweep rate were observed in the transfer operation. Each sample was scanned several times, and the transfer done at different intervals during the field sweep.

The spectrum of O_3F_2 required a different technique. After scanning several samples of O_2F_2 , it became apparent that the recorded signal was due to O_2F_2 which is the major decomposition product. In other words, O_3F_2 is not sufficiently stable to permit scanning over the period of time required for a recorder trace. To circumvent this stability problem, the oscilloscope display of the nmr signals was used.

The signal from pure O_2F_2 was centered on the scope of the HA-100. The O_2F_2 "reference" was removed and replaced with a sample of O_3F_2 at 77°K. The liquid nitrogen in the nmr dewar was then replaced with liquid CF_4 and the scope signal monitored with time. After 1 min, the sample began to melt and a weak signal appeared on the scope downfield from the O_2F_2 "reference." Within 2 min, this signal was fairly well defined. During the third minute the signal shifted, and at 3 min reappeared at the same spot where the O_2F_2 "reference" signal was located. The experiment was reproduced several times, and we feel confident that the signals observed in the first 2 min represent the nmr peak for O_3F_2 which then rapidly decomposes to O_2F_2 and O_2 . The time sequence of spectra, taken from Polaroid photographs of the events, is shown in Figure 1.

Discussion

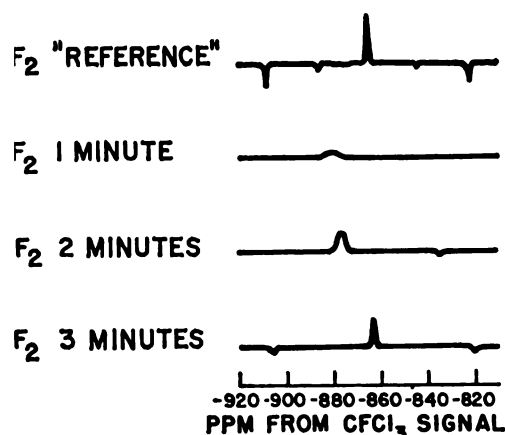
The nmr spectra of F_2 , OF_2 , O_2F_2 , and O_3F_2 clearly indicate that the ^{19}F nuclei in the latter two are very different from those in the former two. Thus some fundamental structural considerations are in order.

Linnett⁶ has discussed a novel approach to electronic structure of molecules using the concept of two

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^{19}F nuclear magnetic resonance spectra of " O_3F_2 " as a function of time.

four electrons around a nucleus rather than the Lewis structures of four sets of two electrons. postulated structures for F_2 , OF_2 , and O_3F_2 structures are presented in Figure 2. In these structures, a heavy line indicates two electrons occupying the same spatial region (between the same pair of atoms) having opposite spins but not occupying the same orbital; and a light line indicates two electrons on the same pair of atoms having opposite spins but not occupying the same orbital; and crosses and circles represent electrons of differing phases in a particular region. Recently Spratley and Ramsey⁹ have proposed a molecular orbital treatment of fluorine bonding which results in essentially the same structure for O_3F_2 .

The structures of F_2 , OF_2 , and O_3F_2 can be well visualized, and hence their ^{19}F nmr signals can be interpreted in accordance with their structures. The "one-electron" bond model in O_3F_2 would result in a species which has a very low shielding constant and is consistent with the ^{19}F nmr spectrum. The theory of ^{19}F nmr shifts as proposed by Saika and Slichter⁸ is inadequate to explain the shift in O_3F_2 . The inadequacy lies in the fact that the theory is consistent with "normal" fluorine bonds and does not account for the "one-electron" fluorine bonds as postulated by Linnett.

Recently, Baker, Anderson, and Ramsey⁹ have discussed nuclear magnetic antishielding of ^{19}F nuclei. Their calculation of antishielding is based on the combination of molecular beam data on spin-rotational transitions in molecules with chemical shift data. The combination is used to calculate the paramagnetic contribution to the nuclear shielding constant in the Ramsey equation.¹⁰

Observations of the ^{19}F nmr signal from O_3F_2 indicate that considerable antishielding exists in this molecule. Furthermore, we suggest that the antishielding is associated with the long O-F bond in O_3F_2 (1.58 Å for O_3F_2 compared to 1.41 Å for OF_2). This suggestion then leads to the possibility that antishielding is associated with the long O-F bond in O_3F_2 .

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Saika and C. P. Slichter, *J. Chem. Phys.*, **22**, 26 (1954).
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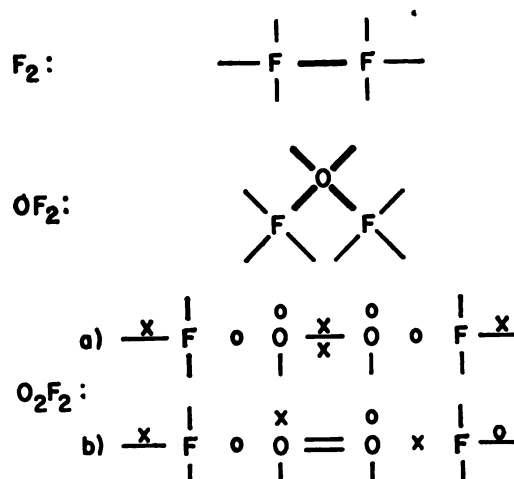


Figure 2. Linnett structures for F_2 , OF_2 , and O_3F_2 .

shielding may be related in some way to the overlap of the fluorine atom p orbital with the antibonding orbitals in the oxygen molecule as postulated by Spratley and Pimentel.⁷

Structural considerations for O_3F_2 are not as straightforward, since supporting data from infrared and microwave are not available as they are for O_2F_2 .¹² In order to interpret the nmr shifts observed, three assumptions about the O_3F_2 molecule must be made. The first assumption is that O_3F_2 is structurally similar to O_2F_2 ; that is to say that the fluorine-oxygen bond is essentially a "one-electron" bond. Secondly, the fluorine nuclei in O_3F_2 are equivalent. This assumption is based on the observation that the intensity which is observed in the O_3F_2 signal is about the same as that observed in the O_2F_2 decomposition product indicating that the same number of fluorine nuclei are giving rise to both signals. The third assumption is that O_3F_2 should have a ready route back to an O_2F_2 decomposition product. This assumption explains the ready decomposition of O_3F_2 to O_2F_2 and the lack of OF_2 and F_2 as decomposition products.

Using these assumptions and following Linnett's rules, several structures for O_3F_2 can be postulated. The classical model of three catenated oxygens terminated by two fluorines (Figure 3a) is not satisfactory since a formal charge of +1 exists on the middle oxygen. If other structures are drawn using this same nuclear distribution, they can be rejected because of excessive charge on the oxygen nuclei and because the fluorine nuclei are nonequivalent. However, the principal reason for rejecting this model (and others involving catenated oxygen atoms) is that there is no simple way to get only O_2F_2 and O_2 as decomposition products.

Another possible structure involves a cyclic configuration of three oxygen atoms with fluorine attached to two of them (Figure 3b). This model can readily release oxygen forming O_2F_2 as a decomposition product; however, the two " O_3F_2 " oxygens each have a formal charge of +1, and the "out-of-line" oxygen has a charge of -1. On the basis of charge distribution, this model is rejected.

A third structure in which O_3F_2 is described as a dimer (Figure 3c) can be postulated. This structure suffers the same shortcomings as the monomer (Figure

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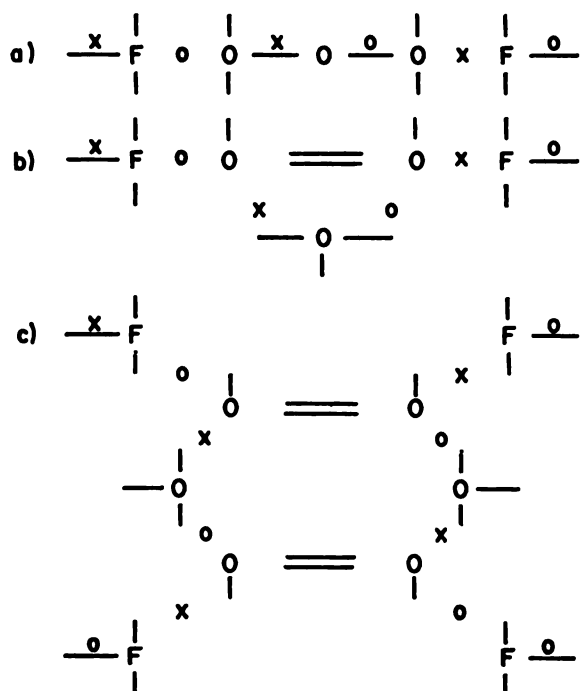


Figure 3. Linnett structures for "O₃F₂" assuming its existence as a molecular entity.

3b) in that excessive formal charge is placed upon the oxygen nuclei.

Thus one is drawn to the conclusion based upon structural considerations and upon electronic distribution considerations that O₃F₂ does not exist as discreet molecular units. This conclusion supports that drawn by Solomon and co-workers³ on their nmr studies and is consistent with the observation of Malone and McGee¹³ that the mass spectral cracking pattern of O₃F₂ does not arise from a single molecular species.

What then is the nature of material with composition O₃F₂? Two possibilities exist. The first possibility is that O₃F₂ is a 1:1 mixture of O₂F₂ and O₄F₂. The structure of O₄F₂ has recently been postulated as (OOF)_n,¹⁴ indicating that this compound is a polymer of the radical OOF. Linnett structures for the OOF radical can readily be drawn and are presented in Figure 4. In this case, "one-electron" bonds are favored over the normal fluorine-oxygen covalent bonds. The appearance of only one signal for "O₃F₂" suggests that the model of discreet O₂F₂ and OOF species from O₄F₂ is not correct. If it were, then two ¹⁹F signals should be observed, one for each fluorine in the two species.

The second possibility, and the one which is preferred by the authors, is a model of O₃F₂ containing "interstitial" oxygen molecules. This "interstitial" oxygen is held in the O₂F₂ by forces too strong for it to be considered dissolved, but too weak for it to be considered bonded, even with "one-electron" bonds. However, the oxygen is bound strongly enough to alter significantly the ¹⁹F nmr shift for O₂F₂.

This model is consistent with several observations on the system. First, although repeated analyses yielded an average stoichiometry of O_{3.0}F₂, individual analyses

(13) T. J. Malone and H. A. McGee, Jr., *J. Phys. Chem.*, **69**, 4338 (1965).

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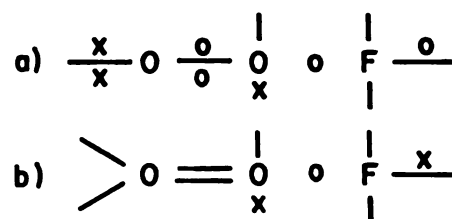


Figure 4. Linnett structures for OOF radical.

ranged from O_{2.5}F₂ to O_{3.1}F₂. Although small amounts of O₃F₂ and O₄F₂ can be formed during the preparation of O₃F₂, procedures were developed to remove both impurities prior to sampling. In addition, a much wider stoichiometric range (O_{2.5}F₂ to O_{3.5}F₂) is found in the analyses if O₄F₂ and O₂F₂ are intentionally prepared with O₃F₂. Secondly, the recorded behavior of O₃F₂ with temperature is indicative of unusual bonding. At 77°K, O₃F₂ is a dark brownish red solid; at 83–84°K, the material melts to a dark red liquid; in the temperature interval 85 to 105°K (where O₂F₂ is said to decompose⁴), the color becomes orange-red and nucleation of O₂F₂ (yellow crystals) can be seen on the sides of sample tubes. The decomposition of the red liquid proceeds rapidly at 109°K and above. The color changes are accompanied by changes in the chemical shift of O₃F₂. However, temperature was found to have little effect on the chemical shift of pure O₂F₂. The shift of pure O₂F₂ varied only about 2 ppm in the range of 110–145°K. Third, the only decomposition products of O₃F₂ are O₂F₂ and O₂. There is no evidence of other decomposition products such as F₂ or OF₂. Finally, epr spectra of samples of O₃F₂ at 77°K showed the same anisotropic pattern present in spectra of O₂F₂ samples at temperatures below 116°K. O₂F₂ is said to melt at 84°K and to decompose quantitatively at 115°K.¹⁵ Epr spectra of O₃F₂ at temperatures between 88 and 115°K do not show the isotropic doublet expected from ·O₂F in liquid O₃F₂, but rather the same anisotropic pattern observed in the spectrum of ·O₂F in solid O₂F₂; a doublet is observed at temperatures above 110°K, the melting point of O₂F₂. From the behavior of the color changes described above and from the epr observations, it is concluded that samples of O₃F₂ contain significant amounts of O₂F₂, and it is the epr spectrum of ·O₂F in the latter compound which is observed from 88 to 115°K.¹⁶

The conclusions which we have reached are somewhat different from those reported by Solomon, *et al.*³ These authors reported two incompletely resolved signals, whereas we observed only one broad signal which became more narrow with increasing temperature. Because of their observation of two ¹⁹F nmr signals, Solomon, *et al.*, concluded that the two signals were due to O₂F₂ and (OOF)_n. However, we observed no significant shift of the ¹⁹F nmr signal from pure O₂F₂ in the range of 110 to 145°K. Solomon, *et al.*, report a considerable shift (–1900 ppm at 85°K) in both signals which they report. It is the opinion of the authors of this paper that if the Solomon model of O₃F₂ as a mixture of O₂F₂ and (OOF)_n is correct, the

(15) A. D. Kirshenbaum and A. V. Grosse, *J. Am. Chem. Soc.*, **81**, 1277 (1959).

(16) F. E. Welsh, private communication.

O_2F_2 signal should remain in its usual region while the $(OOF)_n$ signal would migrate with temperature until it coalesces with that of O_2F_2 . Our results would indicate, and we believe that the temperature studies of Solomon, *et al.*, indicate also, that " O_2F_2 " cannot be as simply described as a mixture of O_2F_2 and $(OOF)_n$.

The ease with which O_2F_2 reverts to O_3F_2 , together with the fact that no really adequate structure can be drawn for O_2F_2 , suggests a model of " O_2F_2 " in which "interstitial" oxygen is being held by O_2F_2 molecules. Such a model fits the observations most fully. This model is further substantiated by mass spectral studies¹⁸ which show that " O_2F_2 " can be described as O_2F_2 plus O_2 .

If one extends the model one step further and considers a 1:1 ratio of O_2F_2 and O_3 , it becomes apparent that the most reasonable structure in this instance is

$(OOF)_n$, or the model for O_4F_2 as suggested by infrared studies.¹⁴

An unequivocal interpretation of the ^{19}F nmr signal from O_2F_2 cannot be made at this time. It would appear that the key lies in the determination of ^{19}F nmr shifts in the O_4F_2 or in the OOF species. Our attempts to determine chemical shifts for O_4F_2 were not successful, since the instability of this species is very much greater than that associated with O_2F_2 or even " O_2F_2 ." With the development of more refined low-temperature nmr techniques, however, such information should be made available.

Acknowledgment. The support of the Advanced Research Projects Agency and of the Air Force Rocket Propulsion Laboratories, Research and Technology Division, Edwards Air Force Base, California, is gratefully acknowledged.

On the Crystal Structure of Trimethylaluminum

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Contribution from the Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208. Received October 3, 1966

Abstract: The crystal structure of trimethylaluminum has been redetermined by three-dimensional, single-crystal X-ray diffraction techniques from photographic data obtained at -50° . Hydrogen as well as aluminum and carbon atoms were located. The structure consists of $Al_2(CH_3)_6$ molecules with symmetrical Al-C-Al bridges. An Al-C-Al bridge angle of $74.7 \pm 0.4^\circ$ and an Al-C bridge distance of 2.14 ± 0.01 Å were found. The nonbridged Al-C distance is 1.97 ± 0.01 Å. An Al-Al distance of 2.600 ± 0.004 Å was found, ~ 0.1 Å longer than previous results indicated. A significant molecular distortion involving the terminal carbon atoms makes the nuclear framework (excluding hydrogen) belong to point group C_{2h} instead of the idealized D_{2h} . There exists no experimental evidence to indicate that the bridge is not correctly described with a carbon sp_2 orbital participating in a four-center, four-electron, electron-deficient bridge bond.

The original example of electron-deficient methyl bridge bonding was tetramethylplatinum,³ which is now generally recognized as nonexistent.⁴ Trimethylgallium has been shown to be monomeric down to very low temperatures⁵ in benzene solution and in the pure liquid at room temperature.⁶ Trimethylindium^{7,8} is, at best, only very weakly bonded into a higher polymer. Hence, there exist at this time only three examples of "five-coordinate carbon" or electron-deficient methyl bridge bonds: dimethylberyllium,⁹ dimethylmagnesium¹⁰ (powder data only), and trimethylaluminum.¹¹ Previously, Amma¹² had attempted a refinement of the three-dimensional data of trimethylaluminum collected

in the original two-dimensional structure determination,¹¹ but the refinement failed to converge properly. Similar results have been obtained for the refinement of the photographic data of dimethylberyllium.¹³ The failure of these refinements is probably due to the quality of the original diffraction data. With the availability of better vacuum-line¹⁴ and low-temperature¹⁵ techniques, we decided to reinvestigate this crystal structure because this compound is the prototype of methyl bridge electron-deficient bridging bonding and is important not only to the understanding of metal-alkyl bonds but also to the nature of intermediates in many organic reactions.

Experimental Section

Trimethylaluminum was purchased from the Ethyl Corp. in a small cylinder, and a sample from this was removed into a storage tube in a vacuum line. The sample was sublimed several times and then sublimed directly into very thin-walled Pyrex capillaries.¹³ The capillaries were then cut off under liquid nitrogen, and the melting point of the sample in each capillary was checked. Crystals were grown in a cold room at 0° and annealed with a small electric

(1) In partial fulfillment of the Ph.D. requirements of the University of Pittsburgh.

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(4) H. C. Brown and L. Dahl, private communications.

(5) N. Muller and A. L. Otermat, *Inorg. Chem.*, **4**, 296 (1965).

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Table I. Positional and Temperature Parameters and Errors ($\sigma' = \sigma \times 10^4$)

Atom ^a	x/a	$\sigma'(x/a)$	y/b	$\sigma'(y/b)$	z/c	$\sigma'(z/c)$
Al	0.4708	3	0.5747	3	0.4073	2
C ₁	0.6221	11	0.3814	13	0.5084	8
C ₂	0.3518	12	0.4325	16	0.2701	8
C ₃	0.5520	11	0.8152	13	0.4098	8
H _{1C1}	0.133	...	0.183	...	0.083	...
H _{2C1}	0.133	...	0.183	...	-0.050	...
H _{3C1}	0.217	...	0.067	...	0.058	...
H _{1C2}	0.260	...	0.466	...	0.234	...
H _{2C2}	0.366	...	0.300	...	0.300	...
H _{3C2}	0.384	...	0.517	...	0.234	...
H _{1C3}	0.133	...	0.300	...	0.416	...
H _{2C3}	0.017	...	0.400	...	0.434	...
H _{3C3}	0.00	...	0.383	...	0.350	...

Thermal Parameters and Standard Deviations

Anisotropic Temperature Factors of the Form $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$; $\sigma' = \sigma \times 10^4$

Atom	β_{11}	σ'	β_{22}	σ'	β_{33}	σ'	β_{12}	σ'	β_{13}	σ'	β_{23}	σ'
Al	0.0025	4	0.0142	4	0.0039	1	-0.0015	3	0.0026	2	-0.0007	2
C ₁	0.0067	15	0.0211	21	0.0086	8	0.0035	13	0.0055	9	0.0010	10
C ₂	0.0084	17	0.0301	27	0.0072	8	-0.0051	16	0.0051	9	-0.0032	11
C ₃	0.0072	15	0.0189	21	0.0089	8	-0.0018	12	0.0044	9	0.0015	10

— Hydrogen atom isotropic temperature factors —

Atom	$B, \text{\AA}^2$	Layer	Scale factor ^c	σ
H _{1C1}	3.5	0kl	1.002	0.034
H _{2C1}	3.5	1kl	1.005	0.015
H _{3C1}	3.5	2kl	0.985	0.024
H _{1C2}	3.5	3kl	1.009	0.026
H _{2C2}	3.5	4kl	1.009	0.022
H _{3C2}	3.5	5kl	1.011	0.031
H _{1C3}	3.5	6kl	0.999	0.022
H _{2C3}	3.5	7kl	0.999	0.036
H _{3C3}	3.5	8kl	1.007	0.036

^a The notation H_{1C1} refers to H₁ on carbon atom C₁. ^b Hydrogen coordinates and temperature factors not varied in least squares and no estimate of coordinate or temperature factor errors given. ^c The ratio of these scale factors was fixed by the isotropic refinement. The absolute value was fixed by the anisotropic refinement using one scale factor. However, the change in going from the isotropic to the anisotropic refinement was small.

light bulb. Crystals were checked for perfection in the cold room under a polarizing microscope and then transferred *via* a dewar to a Weissenberg camera completely enclosed in a double-walled Plexiglass housing,¹⁴ cooled to -50° by sublimation of Dry Ice.

X-Ray Data. The crystals were found to be monoclinic with unit cell constants determined by back-reflection techniques with Cu K α ($\lambda = 1.5405$), K α_1 ($\lambda = 1.5443$): $a = 12.74 \pm 0.02$ Å, $b = 6.96 \pm 0.01$ Å, $c = 14.63 \pm 0.02$ Å, and $\beta = 123^\circ 40' \pm 15'$. The observed systematic extinctions (hkl , $h + k = 2n + 1$; $h0l$, $h = 2n + 1$, $l = 2n + 1$) limited the possible space groups to Cc or C2/c. The X-ray analysis indicated the correct space to be C2/c (*vide infra*). With eight molecules per unit cell the density was calculated as 0.887 g cm^{-3} , in favorable agreement with the density of liquid trimethylaluminum of 0.752 g cm^{-3} . Crystals used for the collection of intensity data were $0.2 \times 0.2 \times 0.3$ mm or less in size. The linear absorption coefficient (μ) with Cu K α radiation is 17 cm^{-1} and with crystals of the size indicated above, μr is sufficiently small that absorption corrections could be neglected.

It was found that crystals could be grown with any of the three crystallographic directions parallel to the capillary axis. Standard equi-inclination multiple-film intensity data were obtained using nickel-filtered Cu K α radiation with the [100] and [010] directions as rotation axis. These data were visually estimated, correlated, and merged to yield 575 independent hkl intensities. The usual Lorentz polarization corrections were made.

Structure Refinement

A three-dimensional Patterson and electron density function were computed to check the previous structure determination.¹⁶ A least-squares refinement was carried out by minimizing the function $\sum w(F_o - F_c)^2$ using

(16) Patterson and electron-density calculations made with the Sly-Shoemaker-van den Hende program, ERF-2.

the Busing and Levy program¹⁷ on the IBM 7090. The Hughes¹⁸ weighting scheme was used with $4F_{\min} = 10.0$. Scattering factors were from standard sources.¹⁹ The variables for the isotropic refinement were the atomic coordinates, individual atom isotropic temperature factors for aluminum carbon, and the scale factors. The scale factors were allowed to vary at this stage, solely to check the accuracy of our data merging. As can be seen from Table I, the interlayer scaling is quite satisfactory. The anisotropic refinement had the atomic coordinates, six β_{ij} for each atom and one scale factor as variables.

Hydrogen atom positions were located from three-dimensional difference maps after the completion of the anisotropic refinement of the nonhydrogen atoms. These difference maps were computed with arbitrary $\sin \theta$ cutoffs and inclusion of $F(\text{calcd})$ terms for unobserved reflections. The best hydrogen atom resolution was obtained with a $\sin \theta$ cutoff of 0.6. Attempts to refine the hydrogen positions by least squares were unsuccessful.

The shifts in atomic coordinates for the last least-squares cycle were less than 5×10^{-5} of a cell edge. The final disagreement index (R),²⁰ the weighted R ,

(17) W. R. Busing and H. A. Levy, OR FLS Program ORNL-TM-305.

(18) E. W. Hughes, *J. Am. Chem. Soc.*, **63**, 1737 (1941).

(19) Scattering factors for neutral Al, C, and H from the compilation of J. A. Ibers, "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1962, p 202.

Table II. Interatomic Distances (Å) and Angles (deg)*

Bonded			
Bridge			
Al-C ₁	2.134 ± 0.010	C ₁ -Al-C ₂	123.1 ± 0.4
Al-C ₁ '	2.153 ± 0.012	C ₁ -Al-C ₁ '	107.2 ± 0.5
Terminal			
		C ₁ '-Al-C ₂	108.7 ± 0.5
Al-C ₂	1.983 ± 0.010	C ₁ -Al-C ₁ '	105.3 ± 0.4
Al-C ₃	1.958 ± 0.011	C ₂ -Al-C ₁	105.1 ± 0.5
Al-Al'	2.600 ± 0.004	C ₂ -Al-C ₁ '	106.1 ± 0.5
Bridge, C-H		H ₁ -C ₁ -H ₂	90
C ₁ -H ₁	1.05	H ₁ -C ₁ -H ₃	96
C ₁ -H ₂	1.12	H ₂ -C ₁ -H ₃	120
C ₁ -H ₃	1.04	H ₁ -C ₂ -H ₄	109
Terminal C-H		H ₁ -C ₂ -H ₅	86
C ₂ -H ₁	1.02	H ₂ -C ₂ -H ₄	100
C ₂ -H ₂	1.03	H ₁ -C ₂ -H ₅	101
C ₂ -H ₃	1.00	H ₂ -C ₂ -H ₅	85
C ₂ -H ₄	0.99	H ₁ -C ₂ -H ₅	88
C ₂ -H ₅	0.92	Al-C ₁ -Al'	74.7 ± 0.4
C ₃ -H ₆	0.93	Al'-Al-C ₂	118.2 ± 0.3
		Al'-Al-C ₃	118.7 ± 0.3

Nonbonded, Intramolecular

C ₁ -C ₁ '	(bridge-bridge)	3.409 ± 0.022
C ₁ -C ₂	(bridge-terminal)	3.251 ± 0.013
C ₁ -C ₃	(bridge-terminal)	3.290 ± 0.016
C ₂ -C ₃	(terminal-terminal)	3.464 ± 0.014
C ₁ -C ₃ '	(bridge-terminal)	3.342 ± 0.017
C ₁ -C ₂ '	(bridge-terminal)	3.331 ± 0.015

Nonbonded, Intermolecular

All intermolecular distance greater than 3.9 Å
 dihedral angle between normals to planes defined by C₂-Al-C₃ and
 C₁'-Al-C₁, 89.2 ± 0.5
 equation of plane defined by Al, C₂, C₃ of the form
 $AX + BY + CZ - D = 0$
 $A = 0.8501, B = 0.5169, C = -0.1010, D = +0.7240$
 Displacement of Al', C₂', and C₃' from this plane = -0.120 Å
 angle between Al-Al' vector and Al-(C₂-C₃ bisector) 2.6 ± 0.3°

* Prime refers to atom related by the center of symmetry at the molecular center; e.g., C₁' refers to C₁ transformed by $\bar{1}$ at center of molecule.

and the standard error were found to be 0.117, 0.145, and 2.00, respectively. Without the hydrogen contribution, the disagreement index was 0.128. Attempts at refinement of the structure in the lower symmetry space group, Cc, led to large correlations ~0.9 for atoms that were symmetry related in C2/c. Refining one set while holding the other set fixed led to the centrosymmetric structure to within less than a standard deviation. Hence, the correct space group is the centric C2/c.

It is of considerable importance (*vide infra*) to ascertain if the bridging carbon (C₁) can be equally well described as disordered along a line parallel to the Al-Al vector. We split C₁ into two carbon half-atoms and displaced them symmetrically about the C₁ position indicated in Table I. It was found that the atomic coordinates of these half-atoms were strongly correlated (>0.9) and could not be refined even with isotropic temperature factors. Attempts at refinement by fixing the coordinates of the carbon half-atoms and varying the coordinates of the other carbon half-atoms were equally unsuccessful. We conclude that within the limits of our experimental data the structure is best described by an ordered model with the thermal parameters indicated in Table III.

(20) $R = \sum ||F_o| - |F_c|| / \sum |F_o|$; weighted $R = \sum w(|F_o| - |F_c|)^2 / \sum wF_o^2$; standard error = $[\sum (F_o - F_c)^2 / (NO - NV)]^{1/2}$ (NO = number of observations = 575; NV = number of variables = 37).

Table III. Rms Component of Thermal Displacement along the Principal Axes of the Thermal Ellipsoid (1, 2, 3) and Angles between These Principle Axes and the Cartesian Coordinate System Defined by (1) (Al-Al'), α ; (2) [(Al-Al') \times (C-C')], β ; and (3) [(1) \times (2)], γ [(1) \times (2)] essentially C-C' direction)

Atom	Rms component, Å	α , deg	β , deg	γ , deg
Al	(1) 0.074 ± 0.017	111.7	120.3	38.7
	(2) 0.166 ± 0.003	129.3	41.3	79.2
	(3) 0.193 ± 0.003	132.7	115.1	126.7
C ₁	(1) 0.142 ± 0.032	95.4	94.2	6.87
	(2) 0.236 ± 0.013	143.3	125.7	96.8
	(3) 0.257 ± 0.012	53.9	143.8	90.2
C ₂	(1) 0.186 ± 0.027	110.3	133.4	50.3
	(2) 0.218 ± 0.012	134.8	50.1	72.1
	(3) 0.293 ± 0.013	128.3	110.0	134.9
C ₃	(1) 0.177 ± 0.020	112.7	147.5	68.1
	(2) 0.223 ± 0.014	127.9	93.7	141.8
	(3) 0.274 ± 0.013	46.5	122.2	119.6

The observed and calculated structure factors are listed elsewhere.²¹ Table I contains the final parameters and errors for the same refinement. Table II gives the interatomic distances, angles, and errors.²²

Description of Structure

The crystal structure of trimethylaluminum consists of two monomers related by a center of symmetry to form a dimer with bridging methyl groups. These dimers are then separated by ordinary van der Waals' distances (Table II) to form a molecular crystal. Although these results are in general agreement with the features of the previous structure determination,¹¹ significant differences were found. In particular (1) the Al-Al distance is 2.600 ± 0.005 Å, ~0.1 Å longer; (2) the Al-C-Al angle is now 74.7 ± 0.4° compared to 70°; (3) the Al-C bridging distance is 2.14 ± 0.01 Å instead of 2.22 Å. However, our Al-C terminal distance is well within error of the earlier results. This terminal distance is in good agreement with the 2.00 Å observed in KF·2Al(C₂H₅)₃²³ and in (C₆H₅)₂Al²⁴ as well as the 2.02 Å in LiAl(C₂H₅)₄.²⁵ In the latter, some elongation is to be expected on chemical grounds. Our C₂-Al-C₃ angle of 123.1° is to be compared with 112.1 and 108° in LiAl(C₂H₅)₄. Although previously unreported, the short bridge methyl-carbon to terminal methyl-carbon distance of 3.3 Å is to be noted. The methyl-methyl nonbonded distances calculated from the sum of the van der Waals radii is 4.0 Å. All the intermolecular distances remain more or less normal, i.e., >3.9 Å (*cf.* Figures 1 and 2).

The most pronounced difference between our structure determination and earlier results is that we find a nonnegligible molecular distortion (Table II). The aluminum and terminal atoms of one dimer are not

(21) This tabulation and a more detailed form of this paper (or extended version, or material supplementary to this article) has been deposited as Document No. 9373 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the document number and by remitting \$1.25 for photoprints, or \$1.25 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

(22) All distances, angles, and errors were computed with a Busing-Levy OR FFE, ORNL-TM-306.

(23) G. Allegra and G. Perego, *Acta Cryst.*, **16**, 185 (1963).

(24) H. McBride, private communication.

(25) R. L. Gerteis, R. E. Dickerson, and T. L. Brown, *Inorg. Chem.*, **3**, 872 (1964).

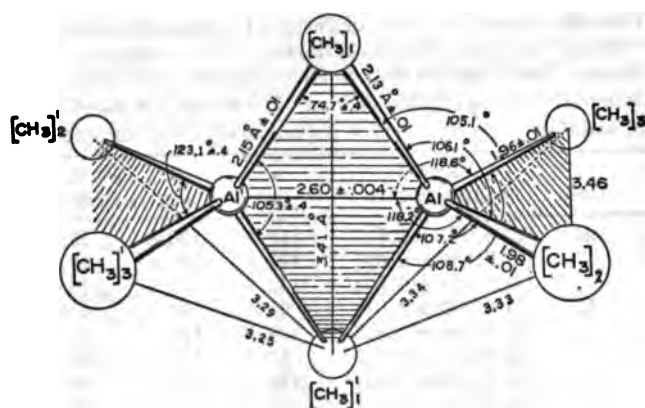


Figure 1. Geometry, bond distances, and bond angles in the dimeric trimethylaluminum molecule. Methyl distances refer to carbon distances. Hydrogen atoms are not shown for reasons of simplicity.

coplanar. A separation of 0.12 Å is found between the parallel planes defined by AlC_2C_3 and $\text{Al}'\text{C}_2'\text{C}_3'$. This distortion can also be seen from the angle of $2.6 \pm 0.3^\circ$ between the $\text{Al}-\text{Al}'$ line and the line defined as $\text{Al}-(\text{bisector of } \text{C}_2-\text{C}_3)$. Since the dihedral angle between the planes defined by $\text{C}_2, \text{Al}, \text{C}_3$ and $\text{C}_1', \text{Al}, \text{C}_1$ is $89.2 \pm 0.5^\circ$, the molecular symmetry (exclusive of hydrogen) is C_{2h} with the twofold rotation axis bisecting the $\text{Al}-\text{Al}'$ line and perpendicular to the $\text{Al}-\text{C}_1-\text{Al}'\text{C}_1'$ plane. The origin of this distortion is not clear at this time.

Although we report hydrogen atom positions, the errors in these atomic coordinates are probably sufficiently large so that no physical significance should be attached to the differences in $\text{C}-\text{H}$ bond distances and $\text{H}-\text{C}-\text{H}$ bond angles.

Discussion

Since it is now clear that only the aluminum alkyls of the group III metal alkyls are dimerized with relatively strong $\text{Al}-\text{C}-\text{Al}$ bridge bonds, the nature of this bridge is of particular importance. The aluminum alkyls have been extensively studied by infrared, Raman,²⁶ and nmr²⁷ spectroscopy, and it seems worthwhile at this point to relate our structure results to these other measurements.

The nmr spectrum of trimethylaluminum at room temperature consists of a sharp singlet in contrast to the two expected for the bridging and terminal groups. This indicates that the two species are either magnetically equivalent or are involved in a rapid exchange process.²⁸ At -75° the spectrum^{27a} consists of two resonances with an area ratio of 2:1, indicating a rapid exchange process at room temperature. At this time it is not possible to distinguish between two mechanisms for this exchange: (1) the breaking of one $\text{Al}-\text{C}$ bridge bond which may re-form with a different methyl group

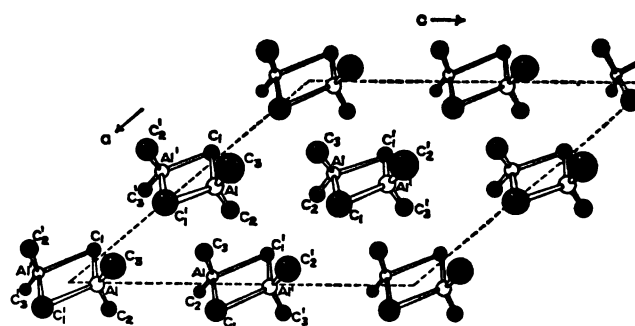
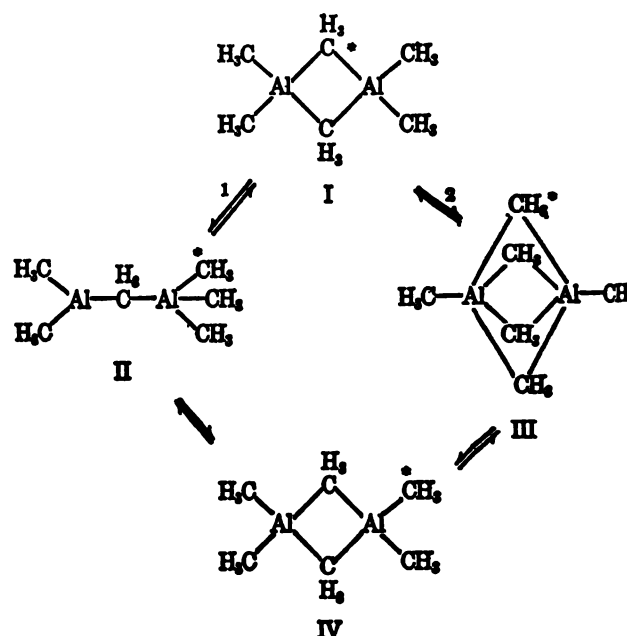


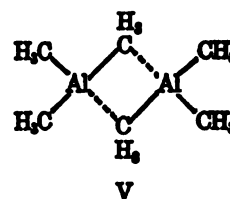
Figure 2. Perspective down the b axis indicating the arrangement of the dimeric molecules in the unit cell.

in the bridge and (2) a deformation of the molecule in which no bonds are broken, leading to an intermediate with four bridging methyl groups. These processes are shown in Scheme I.^{27b}

Scheme I



Neither the nmr spectra, the infrared solution, nor vapor phase spectra down to 300 cm^{-1} can distinguish between the symmetrically bridged structures I and IV (D_{2h} symmetry) or the asymmetric bridge (C_{2h} symmetry) structure V. This has led to speculation that



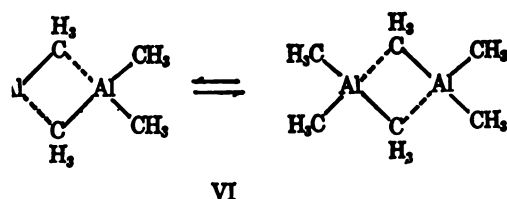
trimethylaluminum actually exists in dynamic equilibrium between the two asymmetrically bridged structures (VI). An equilibrium of this type would facilitate a bridge opening such as II and help to explain the rapid exchange process. Because of the limitations in the earlier diffraction data as well as the lack of computing facilities in that era of crystallography, neither structure V nor the dynamic equilibrium could be fully ruled out. The $\text{Al}-\text{C}$ distances had an estimated stand-

(26) (a) K. Pitzer and H. Gutowsky, *J. Am. Chem. Soc.*, **68**, 2204 (1946); (b) C. P. Van der Kelen and M. A. Herman, *Bull. Soc. Chim. Belges*, **65**, 362 (1956); (c) E. G. Hoffman, *Z. Electrochem.*, **64**, 616 (1960); (d) E. G. Hoffman and G. Schomburg, *ibid.*, **61**, 1101 (1957); (e) A. P. Gray, *Can. J. Chem.*, **41**, 1511 (1963).

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(28) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 218.

tion of ± 0.02 Å, but a more realistic appraisal have been ± 0.04 – 0.05 Å.¹¹



el that our structure determination rules out metric bridge features of structure V, but the r symmetry of the dimer is, nevertheless, C_{2h} ie fact that the aluminum and terminal carbon e not coplanar.

bridge distortion as in structure V was sig- it should manifest itself in one or more of the ; ways. One is a significant asymmetry in d Al'-C bridge distances. This is not ob- The Al-C-Al' bridge is symmetric well within l error (Table III). Another is a statistical ng of the molecules corresponding to two ori- related by a twofold rotation about an axis cular to the Al-Al' line lying in the Al-C₁- lane. Hence, the bridging atoms could be l by two half carbon atoms symmetrically dis- ong the Al-Al' direction. This model would ire the C₂ and C₃ atoms to be disordered above w a plane passing through Al and Al' per- ar to the Al-C₁-Al'-C₁' bridge plane. There dence for any disorder of the terminal carbon No satisfactory refinement could be achieved data on a disordered bridging carbon half- del (see above). Further, this model would at least a pronounced C₁ thermal motion to the Al-Al' line. This is not observed II). Although we make no claims for ac- f hydrogen positions, any disordering of car- is would make the location of hydrogen atoms impossible.

dynamic equilibrium VI existed in the solid en the disorder or thermal motion behavior d above should again be observed. These ady been ruled out. Therefore, we conclude ethylaluminum does not exist as the dynamic um VI. The correct description of the geom- rimethylaluminum is a dimer with symmetric ridge bonds and of point symmetry C_{2h} ex- of hydrogen. The true over-all symmetry of eule would be $\bar{1}$ (Ci).

forth earlier by Rundle,¹¹ the bridge bonding hylaluminum can be described either as a com- of tetrahedral orbitals from aluminum and r as a "methylated double bond," the dif- eeing mostly a matter of taste. In the former on two bonding four-center MO's can be con- from the carbon and aluminum tetrahedral of symmetry a_{1g} and b_{2u} , respectively (assuming metry). The four electrons (one from each n and carbon) then completely fill these two molecular orbitals to give the closed-shell : structure. The b_{2u} MO has a nodal plane through the aluminum and terminal carbon nd consequently this is a distorted π orbital.

With some overlap of the aluminum tetrahedral orbitals a metal-metal bent σ bond may be considered present as well. This formulation²⁹ bears a one-to-one cor- respondence to the description of diborane.³⁰

Rundle¹¹ proposed that four principal factors govern the stability of dimers held together by alkyl bridges. Association is favored by (1) a large difference in elec- tronegativity between the metal and carbon; (2) a low value for the energy required to promote an electron from an s to a p orbital in the valence shell of the metal; (3) a large bond energy for a normal single bond be- tween the metal and carbon; (4) a minimal amount of inner shell repulsion between the two metal atoms separated by internuclear distances demanded by the geometry of the dimer. The first two make dimeriza- tion difficult for trimethylboron, and the last two probably act against formation of dimers by Ga, In, and Tl. If one examines the angles about Al, it is found that the C₁-Al-C₂ angle is 123.1° , the C₁-Al-Al' angle is 118.7° , and the C₁-Al-Al' angle is 118.2° . These are strikingly close to the ideal 120° for sp^3 hybridiza- tion. We would like to suggest, in addition to the above four factors (these are really not four independent variables), that overlap of metal-metal orbitals or metal-metal bonding is also important in the dimeriza- tion of the aluminum alkyls. Since the metal-metal bonding, in general, decreases in going down the peri- odic table (particularly after the 3rd row metals, e.g., Si, Ge, Sn, Pb), this also tends to destabilize the dimer for the group IIIb metal alkyls after aluminum.

If factor 1 above is important, then it is not clear why dimethylberyllium⁹ and dimethylmagnesium¹⁰ are polymeric with methyl bridges but dimethylzinc³¹ is monomeric—particularly since Be and Zn have es- sentially the same electronegativity (1.5, 1.6)^{32a} and the tetrahedral covalent radius of Zn (1.31) is less than that of Mg (1.40).^{32b} However, when viewed in terms of metal-metal bonding, the fact that dimethylzinc is monomeric is not surprising. Alternatively, this trend is also understandable in terms of factor 3.

An examination of the tabulated s \rightarrow p excitation energies³³ shows that factor 2 cannot be the important factor for the lack of dimerization of trimethylboron. (B 2s \rightarrow 2p $\sim 29,000$ cm⁻¹ \sim Al 3s \rightarrow 3p). The most likely reason for the lack of dimerization of trimethyl- boron is probably a simple steric effect. An examina- tion of the methyl-methyl nonbonding intramolecular distances in trimethylaluminum (Table II, Figure 1) shows that the methyl groups are already tightly packed and a substantial reduction in the size of the metal atom would create a good deal of van der Waals repul- sion (covalent radii (Å): Al = 1.26, B = 0.88, but Be = 1.06). Therefore, with the additional data now available, factors 3 and 4 seem to be the most important. However, metal-metal bonding as well as steric repul- sions are not to be neglected.

(29) E. L. Amma, Abstracts, 149th National Meeting of the Ameri- can Chemical Society, Detroit, Mich., April 1965, p 31M.

(30) W. N. Lipscomb, "Boron Hydrides," W. A. Benjamin, Inc., New York, N. Y., 1963, pp 2, 197.

(31) R. E. Rundle, H. Olsen, G. D. Stucky, and G. R. Engebretson, Abstracts, Sixth International Congress and Symposia, Rome, Italy, Sept 9-18, 1963, paper 6-20; *Acta Cryst.*, 16, (1963).

(32) L. Pauling, "Nature of the Chemical Bond," 3rd ed, The Cornell University Press, Ithaca, N. Y., 1960: (a) p 93; (b) p 246.

(33) C. E. Moore, "Atomic Energy Levels," National Bureau of Standards Circular 467, Vol. I-III, U. S. Government Printing Office, Washington 25, D. C., 1949.

In order to eliminate confusion,³⁴ it should be pointed out that a recent complete matrix least-squares anisotropic temperature factor refinement of trimethylindium³⁵ gave In-C distances of In-C₁, -C₂, -C₃ of 2.24 ± 0.06 , 2.25 ± 0.06 , and 2.16 ± 0.04 Å and C-In-C angles of C₂-In-C₁ $120.5 \pm 1.8^\circ$, C₃-In-C₁ $117.3 \pm 1.3^\circ$, and C₂-In-C₃ $122.2 \pm 1.8^\circ$. These distances and angles are not statistically different from

(34) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed, Interscience Publishers, John Wiley and Sons, Inc., New York, N. Y., 1966, p 318.

(35) G. G. Messmer and E. L. Amma, unpublished research.

the earlier results,⁷ but the estimates of error are probably more realistic. It is to be noted that In(CH₃)₃ is still planar well within statistical error, and the "pseudo-tetramer" should be viewed as very weakly bonded together, if at all. Where weak chemical bonds begin and end is by no means a clear-cut, unambiguous decision.

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Steric Effects in Fast Metal Complex Substitution Reactions. II¹

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Abstract: The rate constants for the formation and dissociation of nickel(II) and cobalt(II) complexes with α - and β -aminobutyric acids have been determined by the temperature-jump method. Although rate constants for formation of higher order as well as monosubstituted complexes were measured, the most significant results with respect to a comparison between the two different metal ions concern the rate constants (k_1) for the first substitution. It was determined that substitution for both nickel(II) and cobalt(II) is faster with α -aminobutyric acid than with the β acid. That is, at 20° an ionic strength = 0.1 M for nickel(II) with α -aminobutyrate, $k_1 = 1.0 \times 10^4 M^{-1} \text{ sec}^{-1}$; with β -aminobutyrate, $k_1 = 4.0 \times 10^3 M^{-1} \text{ sec}^{-1}$. Under the same conditions, for cobalt(II) with α -aminobutyrate, $k_1 = 2.5 \times 10^4 M^{-1} \text{ sec}^{-1}$; with β -aminobutyrate, $k_1 = 2.0 \times 10^4 M^{-1} \text{ sec}^{-1}$. The relative error for these rate constants is $\pm 20\%$. The rate constants determined for α -aminobutyric acid are consistent with a mechanism in which release of a water molecule from the metal ion's inner coordination sphere is rate determining. In reaching this conclusion, it is shown that an empirical factor of $1/3$, to account for the partial absence of spherical symmetry in these chelating agents, must be used when comparing these (and the β) values with rate constants previously determined for other ligands. The slower reactions with β -aminobutyric acid are explained by the kinetic chelate effect, in which chelate ring closure is the rate-determining step. The steric effect is appreciably greater for cobalt(II) than for nickel(II) because of the inherently greater lability of the former ion.

Studies of fast metal complex substitution reactions can be explained by a previously proposed mechanism for the formation of complexes between divalent ions and simple anionic ligands.²⁻⁶ The initial process is the diffusion-controlled, ion-pair formation between the aquated metal ion and ligand. For most monodentate and certain polydentate ligands, the rate-determining step is the loss of a water molecule with concomitant substitution of the reactant ligand into the inner coordination shell. Since the rate-determining step is controlled by the rate of release of a water molecule from the inner coordination sphere, it is therefore a characteristic of the metal ion.

For metal complexes with multidentate ligands, the stability of the metal chelate is, in part, governed by the chelate structure.⁷ The thermodynamic data for divalent metal ions with amino acids show that a five-membered ring is more stable, unless a linear complex is formed. For example, the stability constants for α - and β -aminobutyric acids differ by over a factor of 10 (see Table I).

Recently, evidence has been reported that there is also a kinetic chelate effect.⁶ Studies of divalent metal chelates with α - and β -alanine show that there is a decrease in rate when changing the ligand from α -alanine to β -alanine. This decrease in rate is explained by the difficulty in forming a six-membered, as opposed to a five-membered, ring with an aminocarboxylic acid ligand. The mechanism is the same as that originally proposed, but the rate-determining step is believed to be closing of the chelate ring rather than the release of a water molecule from the inner coordination sphere of the metal ion.

The kinetics for the formation of nickel(II) and cobalt(II) chelates with α - and β -aminobutyric acid (α -

(1) The authors gratefully acknowledge partial support from PHS Research Grant GM-08893-05 from the National Institute of General Medical Sciences, Public Health Service, and wish to thank the National Science Foundation for College Faculty Summer Participation Grant GY-687 to A. K. and R. F. P.

(2) Departments of Chemistry: (a) Lowell Institute of Technology, Lowell, Mass.; (b) Ithaca College, Ithaca, N. Y.; (c) Polytechnic Institute of Brooklyn, Brooklyn, N. Y.

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(6) K. Kustin, R. F. Pasternack, and E. M. Weinstock, *J. Am. Chem. Soc.*, **88**, 4610 (1966).

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Table I. Stoichiometric Equilibrium Constants^a at 20° and Ionic Strength 0.1 M

Ligand	Metal ion	K_{HL}, M	K_{H_2L}, M	K_1, M^{-1}	K_2, M^{-1}	K_3, M^{-1}
α -Aminobutyric acid	Ni ²⁺	6.57×10^{-11}	2.25×10^{-8}	3.16×10^4	3.02×10^4	1.55×10^3
	Co ²⁺	6.57×10^{-11}	2.25×10^{-8}	2.27×10^4	2.79×10^3	2.63×10^3
β -Aminobutyric acid	Ni ²⁺	2.39×10^{-11}	3.01×10^{-4}	5.72×10^4	4.86×10^3	5.36×10^3
	Co ²⁺	2.39×10^{-11}	3.01×10^{-4}	7.63×10^3	6.8×10^3	2.6×10^3
Indicator		K_{In}, M				
Phenolphthalein		$2.51 \times 10^{-10}^b$				
Phenol red		$1.26 \times 10^{-8}^c$				

$\zeta_{HL} = [H][HL]/[H_2L]$; $K_{HL} = [H][L]/[HL]$; $K_n = [ML_n]/([ML_{n-1}][L])$, $n = 1, 2, 3$; $K_{In} = [H]/[In]/[HIn]$. ^b A. Thiel and G. Coch., *Z. g. Allgem. Chem.*, **217**, 353 (1934). ^c I. M. Kolthoff, *J. Phys. Chem.*, **34**, 1466 (1930).

Table II. Results for Nickel(II) with α - and β -Aminobutyric Acids

[Ni] ₀	[Abu] ₀	[HIn] ₀	pH	$\tau_{\text{exptl}} \times 10^3$	$\tau_{\text{calcd}} \times 10^3$
A. Nickel (II) with α -Aminobutyric Acid					
1.00×10^{-3}	4.04×10^{-3}	1.00×10^{-3b}	8.5	$\tau_1 = 11$ $\tau_2 = 2.5$	$\tau_1 = 15$ $\tau_2 = 2.3$
1.01×10^{-3}	8.08×10^{-4}	1.00×10^{-3b}	8.5	18	12
1.01×10^{-3}	2.02×10^{-3}	1.00×10^{-3b}	8.5	10	10
2.00×10^{-3}	4.04×10^{-3}	1.00×10^{-3b}	8.5	8.6	6.1
2.00×10^{-3}	6.07×10^{-3}	1.00×10^{-3b}	8.5	$\tau_1 = 8.9$ $\tau_2 = 1.7$	$\tau_1 = 8.6$ $\tau_2 = 1.7$
2.00×10^{-3}	8.08×10^{-3}	1.00×10^{-3b}	8.6	$\tau_1 = 12$ $\tau_2 = 1.3$	$\tau_1 = 12$ $\tau_2 = 1.6$
1.00×10^{-3}	2.50×10^{-3}	8.00×10^{-4c}	9.0	19	16
B. Nickel(II) with β -Aminobutyric Acid					
2.00×10^{-4}	4.00×10^{-3}	4.00×10^{-3a}	9.2	14	16
2.00×10^{-4}	1.30×10^{-3}	1.00×10^{-3b}	8.4	31	26
2.00×10^{-3}	4.00×10^{-3}	4.00×10^{-3c}	9.0	8	12
2.00×10^{-3}	2.00×10^{-3}	9.80×10^{-3b}	8.5	10	16
1.00×10^{-3}	2.00×10^{-3}	9.80×10^{-3b}	8.5	17	16

The subscript zero refers to total stoichiometric concentration. All concentrations are molar and at all times are in seconds. ^b HIn = ol red. ^c HIn = phenolphthalein.

α and β -Abu, respectively) have been examined to investigate further the possibility of a kinetic chelate effect. The stability constants for all the aminobutyric ligand-metal complex systems have not been previously reported. The stability constants that have been used were measured in this laboratory by a potentiometric method. The details for the determination of these constants will be published separately.⁸ The results of thermodynamic investigation, as well as other pertinent equilibrium constants, are given in Table I.

Experimental Section

Reagent grade KNO_3 , $Ni(NO_3)_2 \cdot 6H_2O$, and $Co(NO_3)_2 \cdot 6H_2O$ were used without further purification, as were all other reagents. The α -aminobutyric acid and β -aminobutyric acid were from Biochemical Co. products. Phenolphthalein (Baker reagent grade) and phenol red (Aldrich reagent grade) were used as indicators.

Stock solutions of the metal nitrate, acid ligand, and indicator were prepared. The solutions to be studied were made up by mixing the desired amounts of stock solutions into 100-ml volumetric flasks and diluting to the mark. The pH was adjusted by dropwise addition of solutions of NaOH and/or HNO_3 . The final pH value was measured by a pH meter (Radiometer, Copenhagen), within 0.01 pH unit.

The ionic strength of all solutions was 0.1 M. The temperature of the study was $20 \pm 1^\circ$ for all experiments. The details of the temperature-jump instrumentation have been described elsewhere.⁹

⁸ K. Kustin and R. Davidow, submitted for publication. Cf. L. G. Sillen and A. E. Martell, "Stability Constants of Metal-Ion Complexes," Chemical Society, London, 1964, Table 249, in which the first- and second-step stability constants for cobalt(II) and α -aminobutyric acid are given as $K_1 = 1.9 \times 10^4$, $K_2 = 2.1 \times 10^3 M^{-1}$ at ionic strength 0.1 M and 30° .

Blank experiments with solutions containing only the metal and indicator, or the acid ligand and the indicator (both solutions at ionic strength 0.1 M), did not show any relaxation effect in the time range of the instrument.

Results

The relaxation times for the various solutions were computed and averaged from at least three (generally, five) photographs of the oscilloscopic traces. The averages of the relaxation times are reported in Tables II and III together with the pH and total concentrations of metal and ligand. The relaxation times thus evaluated have errors of $\pm 20\%$ with respect to the reported averages. It should also be noted that the pH range of this study is from pH 8.0 to 9.2. The calculated relaxation times in Tables II and III were obtained (*vide infra*) by use of the best set of rate constants without the introduction of any pH-dependent terms.

A pH dependence of the rate constant would result from side reactions involving the neutral ligand, HL, or any hypothetical species MOH^+ , where $M = Ni^{2+}$ or Co^{2+} . The lack of a dependence of the rate constants on pH makes these steps insignificant under the conditions of this investigation. A more extensive variation of pH was precluded at the upper end by the precipitation of the metal (as metal hydroxide, presumably) and, at the lower end, by diminution of the amplitude of the relaxation effect. Indeed, by lowering the pH, the free L^- concentration decreases with respect

(9) P. Hurwitz and K. Kustin, *Inorg. Chem.*, **3**, 823 (1964).

Table III. Results for Cobalt(II) with α - and β -Aminobutyric Acids

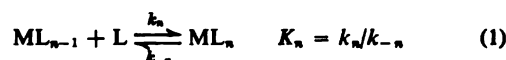
[Co] ₀	[Abu] ₀	[HIn] ₀	pH	$\tau_{\text{exptl}} \times 10^3$	$\tau_{\text{calcd}} \times 10^3$
A. Cobalt(II) with α -Aminobutyric Acid					
1.00×10^{-3}	2.00×10^{-3}	1.00×10^{-5b}	8.5	0.74	0.66
1.00×10^{-3}	2.50×10^{-3}	1.00×10^{-5b}	8.5	0.64	0.61
1.00×10^{-3}	2.50×10^{-3}	4.00×10^{-5c}	9.0	0.71	0.79
1.00×10^{-3}	6.00×10^{-3}	4.00×10^{-5c}	9.0	0.60	0.69
1.00×10^{-3}	8.00×10^{-3}	4.00×10^{-5c}	9.1	0.56	0.64
B. Cobalt(II) with β -Aminobutyric Acid					
2.00×10^{-3}	4.00×10^{-3}	1.00×10^{-5b}	8.5	4.5	6.7
1.00×10^{-3}	5.00×10^{-3}	9.8×10^{-5b}	8.6	10	7.9
1.00×10^{-3}	10.0×10^{-3}	9.8×10^{-5b}	8.6	7.7	7.3
1.00×10^{-3}	20.0×10^{-3}	1.00×10^{-5b}	8.6	8.0	6.6
1.00×10^{-3}	15.0×10^{-3}	1.00×10^{-5b}	8.6	7.2	6.7
1.00×10^{-3}	10.0×10^{-3}	4.00×10^{-5c}	8.9	6.4	6.6
1.00×10^{-3}	10.0×10^{-3}	1.00×10^{-5b}	8.0	7.3	8.7
2.00×10^{-3}	1.00×10^{-3}	2.00×10^{-5b}	8.5	7.0	9.1

* The subscript zero refers to total stoichiometric concentration. All concentrations are molar and all times are in seconds. ^b HIn = phenol red. ^c HIn = phenolphthalein.

to the relatively inert HL, thus depriving the solution of reacting ligand.

The equilibrium concentrations for the species M, ML, ML₂, ML₃, L, HL, and H₂L for the various solutions were calculated using the constants in Table I, with the help of a computer program run on an IBM 1620.

The relaxation processes observed were interpreted in terms of reactions of the type



where $n = 1, 2$, or 3 . The symbol L refers to the anionic form of the ligand, which is responsible for complexation of the metal ion. (Charges have been neglected in this and all other equations.) The general treatment given by Hammes and Steinfeld⁴ for a system of two coupled reactions has been used in calculating the relaxation times. The relation

$$\tau^{-2} - \tau^{-1}(a_{11} + a_{22}) + (a_{11}a_{22} - a_{12}a_{21}) = 0 \quad (2)$$

derived from the solution of the secular determinant

$$\begin{vmatrix} a_{11} - 1/\tau & a_{12} \\ a_{21} & a_{22} - 1/\tau \end{vmatrix} = 0 \quad (3)$$

where $1/\tau$ is the eigenvalue, was used to find the rate constants when two reactions of type 1 were present. In (3), the a_{ij} 's are related to (1) the concentrations of the appropriate reactants, (2) the rate constants, and (3) the equilibrium constants for the coupled fast (relative to the metal complexation) reactions



where the symbol In represents the indicator anion form.⁴

Calculation of τ by trial-and-error methods employing appropriately varying values of the k_n for the two processes where $n = 1$ and 2 were performed. In some cases the concentration of ML₃ was sufficiently high to enable the determination of all three rate constants, via solutions of (2) in which $n = 2$ and 3 . The rate

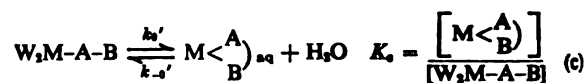
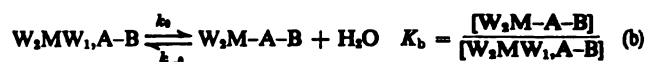
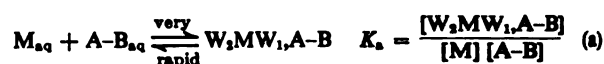
Table IV. Rate Constants of Metal Complexation at 20° and $\mu = 0.1 M$

Metal	n	α -Abu	β -Abu
$k_n, M^{-1} \text{ sec}^{-1}$			
Co ²⁺	1	2.5×10^4	2.0×10^4
	2	1.9×10^4	7.0×10^4
	3
Ni ²⁺	1	1.0×10^4	4.0×10^3
	2	1.5×10^4	8.0×10^3
	3	3.0×10^4	3.0×10^3
k_{-n}, sec^{-1}			
Co ²⁺	1	11.0	2.6
	2	6.8×10^3	1.0×10^3
	3
Ni ²⁺	1	3.2×10^{-3}	7.0×10^{-3}
	2	0.5×10^{-1}	1.6
	3	19	5.6

constants used to calculate the relaxation times reported in Tables II and III are given in Table IV.

Discussion

General Mechanism. The mechanism for metal chelate substitution reactions may be written as shown in eq a-c, where W₁ and W₂ represent the two water



molecules in the inner coordination sphere which are eventually replaced by the bidentate ligand. The two binding sites of the ligand are represented as A and B. Reaction a is the formation of the ion pair, W₁MW₁A-B with K_a the ion-pair formation constant.

If we restrict our attention to the first substitution only, and use the assumptions made in part I,⁶ we can relate the observed rate constants to the above mechanism by eq 4a and b. This mechanism shows two limit-

$$k_1 = k_0K_a \left(\frac{k_0'}{k_{-0} + k_0'} \right) \quad (4a)$$

$$k_{-1} = k_{-0} \left(\frac{k_{-0}'}{k_{-0} + k_0'} \right) \quad (4b)$$

ing types of behavior, depending upon the relative magnitudes of the two rate constants k_{-0} and k_1' . These cases are summarized below as normal substitution, $k_0' \gg k_{-0}$, $k_1 = k_0K_a$ ($M^{-1} \text{ sec}^{-1}$), $k_{-1} = k_{-0}/K_c$ (sec^{-1}); and sterically controlled substitution, $k_{-0} \gg k_0'$, $k_1 = k_0'K_aK_b$ ($M^{-1} \text{ sec}^{-1}$), $k_{-1} = k_{-0}'$ (sec^{-1}).

If the complex formation is a "normal" substitution, then by using a calculated value for the ion-pair constant, K_a, one obtains a value for k_0 , the rate constant for the elimination of water from the first coordination sphere. Swift and Connick¹⁰ have determined k_1 by the use of nmr line-broadening measurements. Their values are 3×10^4 and $1 \times 10^6 \text{ sec}^{-1}$ for nickel-

(10) T. J. Swift and R. E. Connick, *J. Chem. Phys.*, **37**, 307 (1962); **41**, 2553 (1964).

nd cobalt(II), respectively. The results for glycine and α -alanine⁶ are in good agreement with the k_1 values. The results for k_1 ($=k_0K_a$) reported for Ni^{2+} and Co^{2+} with α -aminobutyric acid are 10^4 and $2.5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, respectively, which agree qualitatively with the nmr data, and with data obtained with other ligands.

For more evidence on the nature of metal complex formation reactions accumulates, resort is being made to investigations with increasingly larger and more complex ligands. It would be worthwhile to reexamine the applicability of ion-pair formation constant relations in this regard. The constant for ion-pair formation between two ions leading to a solvated species L can be calculated with the function derived independently by Fuoss¹¹ on statistical and by Eigen¹² on theoretical grounds, namely

$$K_a = \frac{4\pi N a^3}{3000} \exp(b) \exp[-b\kappa a/(1 + \kappa a)] \text{ M}^{-1} \quad (5)$$

In the above expression, N is Avogadro's number; $-\ln \gamma_{\pm}/(1 + \kappa a) = \gamma_{\pm}^2$, which is the square of the Debye-Hückel mean activity coefficient; a is the minimum approach distance between the charged particles; the Bjerrum ratio between potential and kinetic energy ($b = |Z_M Z_L| e_0^2 / a D k T$) where Z_M and Z_L are the charges, e_0 is the elementary charge, k is the Boltzmann constant, D is the dielectric constant, and T is the absolute temperature; the parameter κ is the reciprocal of the Debye length (the distance between the central ion and the ionic atmosphere at the maximum of its charge density according to the Debye-Hückel theory).

Equation 5 has been based on models in which the solvent is assumed to be a continuum and the ions are considered to be rigid spheres of radii $a/2$. It is evident that for the anions discussed in this study this model does not fit, even to a first approximation, the molecular structures of these amino acids. The extension is, moreover, strongly dependent on the distance a . Choosing $a = 5 \text{ \AA}$, as has been done,⁴ leads to a value of $K_a = 2 \text{ M}^{-1}$. While this procedure yields reasonable results, in some cases, we feel that to expect agreement with the theory for ligands of different complexity is impractical. On the other hand, attempts to adapt the model—and, hence, the theory—to the present situation, would involve efforts out of keeping with a kinetic study. We are mainly interested in a direct comparison of the observed k_1 between α - and β -aminobutyric acid complexes with cobalt(II) and nickel(II). Therefore, even if the absolute value of K_a is unknown, some of its characteristics with respect to two ligands may be inferred, and we may draw valid conclusions about the mechanism.

The k_1 value for nickel with α -aminobutyric acid is what lower than the corresponding value for other ligands (e.g., glycine, α -alanine, diglycine). And, the same is true for the cobalt values, and, as will later be shown, the rate constants for β -aminobutyric acid, as well. To find the reason for this decrease, we start by examining eq 5. This expression consists of two parts. The preexponential factor is of ionic nature. It increases with increasing ionic size, reflecting the enhanced probability of pairing

as the reaction cross section increases. The exponential factor is the energy part and is controlled mainly by the electrostatic interaction. This factor decreases with increasing ionic size. Calculations indicate that, at this temperature and ionic strength, the function is at this minimum point, being almost insensitive to size for $3 < a < 8 \text{ (\AA)}$. Moreover, the electrostatic (exponential) term begins to show inappreciable change with ionic size as a increases beyond 5 or 6 \AA . It would thus appear that, in this range, larger ligand size makes the electrostatic interactions less significant, while increasing K_a , which would also increase the observed rate constants, rather than decrease them.

However, an increase in ligand size has been achieved in this case at the expense of spherical symmetry. This effect would be directly manifested in the rate constant for formation of the ion pair (as shown by Eigen, *et al.*,¹³), thereby reducing K_a in magnitude. Essentially then, we assume that the important effect on K_a is given by the diminished accessibility of ion-pairing sites on the ligand. To adjust for this reduction in the solid angle corresponding to reactive encounters, we shall introduce an empirical factor of approximately $1/2$ into eq 5.¹⁴ The basis for introducing this factor will be explained more fully as we discuss each ion in detail.

Nickel(II). The observed value of k_1 for Ni^{2+} and α -aminobutyrate is $1.0 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$. The value for α -alanine, also determined in this laboratory, is $2.0 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, from which the previously discussed empirical factor of $1/2$ has been obtained by taking the ratio of these rate constants. The increased rates of formation of the higher order complexes is explained by a loosening in the binding between the metal ion and the remaining coordinated waters.⁴ The results for the α -aminobutyric acid, in comparison to α -alanine, lead to the conclusion that the mechanism of substitution is "normal"; that is, the rate-determining step is given by reaction b.

The value of k_1 for Ni^{2+} and β -aminobutyrate is less than that reported for the α complex, *viz.*, $4 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ as compared to $1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$. This difference is most interesting when one considers that a similar result was observed for α - and β -alanine, the value of the latter being one-half as large as the α -Ala k_1 (where Ala = alanine). If the reduction in the β -aminobutyric acid rate constant is assumed to indicate partial steric control, then one-half the k_1 for α -aminobutyric acid (where $1/2 = k_1(\beta\text{-Ala})/k_1(\alpha\text{-Ala})$), or $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$, should be the approximate value for k_1 when β -aminobutyric acid is the ligand. The measured value of $4 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ is in good agreement with this hypothesis.

Cobalt(II). The rate constants for formation of the first and second α complexes, as given in Table IV, are $k_1 = 2.5 \times 10^5$ and $k_2 = 1.9 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$, while k_3 could not be determined. The fact that k_2 is larger than k_1 corresponds to the loosening of the waters in the first coordination sphere, as in the nickel case. This effect is larger than for nickel(II), however, and may reflect the greater crystal-field stabilization of a d^8 ion. As noted before, the value of k_1 is somewhat less

R. M. Fuoss, *J. Am. Chem. Soc.*, **80**, 5059 (1958).

M. Eigen, *Z. Physik. Chem. (Frankfurt)*, **1**, 176 (1954).

(13) M. Eigen, W. Kruse, G. Maass, and L. DeMaeyer, *Progr. Reaction Kinetics*, **2**, 287 (1964).

(14) R. A. Alberty and G. G. Hammes, *J. Phys. Chem.*, **62**, 154 (1958).

than anticipated for normal substitution. The empirical factor can be calculated from the ratio of rate constants as $k_1(\alpha\text{-Abu})/k_1(\alpha\text{-Ala}) = 2.5/6 = 0.42$ and $k_1(\alpha\text{-Abu})/k_1(\text{Gly}) = 0.54$ (Gly = glycine). The average value is, again, approximately $1/2$. This result compares favorably with the procedure adopted for the Ni^{2+} complexes. Thus, this relatively small difference in the value of k_1 can be explained, and the substitution classified as normal.

For β -aminobutyric acid, values of $k_1 = 2 \times 10^4$ and $k_2 = 7 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ were found. Although k_2 is larger than k_1 , the effect is not nearly as pronounced as for α -aminobutyric acid. Moreover, the value of k_1 is significantly lower than the corresponding value for α -aminobutyric acid or glycine, being reduced, primarily, by the factor $(1 + k_{-0}/k_0')^{-1}$. Here, a steric effect due to the difficulty of closing the six-membered ring in the chelate complex can be postulated, as in the case of β -alanine,⁸ where it was also indicated that the

limiting case ($k_{-0} \gg k_0'$) was not reached. It is thus possible to predict the value of k_1 for the β complex by a semiempirical calculation as follows.

Let us assume that the steric effect appearing in Co^{2+} - β -alanine reactions is roughly equal to the steric effect with β -aminobutyric acid. Then the rate constant for $\text{Co}^{2+} + \beta$ -aminobutyrate is $k_1(\beta\text{-Abu}) = k_1(\alpha\text{-Abu}) \cdot [k_1(\beta\text{-Ala})/k_1(\alpha\text{-Ala})] = 2.5 \times 10^4 (7.5/60) = 3.1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$. The same calculation can be performed in an alternate way. Suppose that the ratio (7.5/60) expresses the steric control contribution to the closing of the six-membered ring with respect to the five-membered ring. Then, the β rate constant can be calculated from $k_1(\text{Gly})$ by the introduction of the statistical collision factor $P = 1/2$, to adjust for the decreased active "surface of reaction." Therefore, $k_1(\beta\text{-Abu}) = Pk_1(\text{Gly})[k_1(\beta\text{-Ala})/k_1(\alpha\text{-Ala})] = 1/2(4.6 \times 10^4)(7.5/60) = 2.9 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, while the experimental value is $k_1 = 2.0 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$.

Nucleophilic Reactivity in Substitution Reactions of Square-Planar Metal Complexes. II. A Comparison of the Kinetic Behavior of Platinum(II) and Gold(III) Complexes

L. Cattalini, A. Orio, and M. L. Tobe

Contribution from Istituto di Chimica Generale, Centro Composti di Coordinazione del C. N. R., Padua, Italy, and the William Ramsay and Ralph Forster Laboratories, University College, London W.C.1., England. Received January 16, 1967

Abstract: The kinetics of the displacement of chloride from the $[\text{AuCl}_4]^-$ anion by pyridine, NO_2^- , N_3^- , Br^- , I^- , and SCN^- in methanol have been studied over a range of temperature and reagent concentration. The usual two-term rate law is observed, and the rate constants and Arrhenius parameters are reported and compared with the data for the analogous $[\text{PtCl}_4]^{2-}$ anion. The discriminating power of the Au(III) reaction center is found to be very much greater than that of Pt(II) in a similar ligand environment, and an explanation is offered in terms of the extent to which the mechanism moves from an associative toward a synchronous bimolecular process.

Although kinetic studies of nucleophilic displacement of ligands from square complexes of d^8 transition metal ions have, in the past, been limited mainly to those of platinum(II),¹ sufficient information about the behavior of corresponding gold(III) complexes has now become available for it to be possible to attempt to make a preliminary general comparison of the kinetic behavior of Pt(II) and Au(III) substrates.

In part I,² the factors which determine the reactivity of nucleophiles toward Pt(II) complexes were discussed. It was shown that, apart from biphilic reagents, such as NO_2^- , SeCN^- and thiourea, the sequence of relative reactivity followed a linear free-energy relationship with the index, n_{Pt} ,³ defined by $n_{\text{Pt}} = \log(k_2/k_3)$, where k_2 and k_3 are the second-order rate constant for the entry of the nucleophile in question and the

first-order rate constant for the solvolysis by methanol, respectively, of the reference substrate *trans*- $[\text{Pt}(\text{py})_2\text{Cl}_2]$. This was taken to be a measure of the "softness" or micropolarizability of the entering nucleophile since its basicity appeared to have only a minor effect upon its reactivity.

In order to make the comparison between Pt(II) and Au(III) complexes, it was necessary to augment the available data relative to nucleophilic displacement reactions of the gold(III) derivatives. Apart from the isotopic exchange⁴ of chloride ion with $[\text{AuCl}_4]^-$ and from the reactions⁵ of some nucleophiles on the cationic complex $[\text{Au}(\text{dien-H})\text{Cl}]^+$, the processes studied until now were mainly limited to the use of pyridine derivatives, either as entering^{6,7} or leaving^{8,9} groups. We have therefore studied the reactions of $[\text{AuCl}_4]^-$ with

(1) For a review on this subject, see C. H. Langford and H. B. Gray, "Ligand Substitution Processes," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 2 and references therein.

(2) L. Cattalini, A. Orio, and M. Nicolini, *J. Am. Chem. Soc.*, **88**, 5734 (1966).

(3) U. Belluco, L. Cattalini, F. Basolo, R. G. Pearson, and A. Turco, *ibid.*, **87**, 241 (1965).

(4) R. L. Rich and H. Taube, *J. Phys. Chem.*, **58**, 1 (1954).

(5) W. H. Baddley and F. Basolo, *Inorg. Chem.*, **3**, 1087 (1964).

(6) L. Cattalini, M. Nicolini, and A. Orio, *ibid.*, **5**, 1674 (1966).

(7) L. Cattalini, A. Doni, and A. Orio, *ibid.*, **6**, 280 (1967).

(8) L. Cattalini and M. L. Tobe, *ibid.*, **5**, 1145 (1966).

(9) L. Cattalini, A. Orio, and M. L. Tobe, *ibid.*, **6**, 75 (1967).

ine and with the anionic nucleophiles NO_2^- , Br^- , I^- , and SCN^- in methanol. This has not provided a new set of data and a sequence of nucleophilicity toward an anionic Au(III) substrate, but it also made it possible to make a direct comparison of the behavior of the isoelectronic and isosubstituted $[\text{AuCl}_4]^-$ and $[\text{PtCl}_4]^{2-}$. This second point is important, since the kinetic behavior of both anionic Au(III) and Pt(II) substrates appears to depend as much upon the nature of the ligands coordinated to the metal as it does upon the total charge of the complex.

For example, it has been shown² that, in Pt(II) complexes, the nucleophilic discrimination factor,³ s , by eq 1, changes from 0.8 to 1.6 in a series of

$$\log k_2 = s(n_{\text{Pt}}) + \log k_a \quad (1)$$

anionic complexes, whereas it is 0.312 for $[\text{PtCl}_4]^{2-}$. Similarly, the Brønsted coefficient, α , in eq 2, which

$$\log k_2 = \alpha(\text{p}K_a) + \text{constant} \quad (2)$$

relates the basicity of the substituted pyridine with the free energy of activation of their reaction with gold(III) substrates, changes from 0.21 to 0.89 in a series of monocationic complex cations,⁷ whereas 0.15 for $[\text{AuCl}_4]^-$ as substrate.

Experimental Section

Materials. Chloroauric acid was recrystallized and its purity checked by analysis and comparison of its ultraviolet spectrum with published values.^{10,11} The other chemicals used were all analytical reagent grade materials. The methanol was dried by refluxing over $\text{Mg}(\text{CH}_2\text{O})_2$, and the distilled product was stored under anhydrous conditions. There was no indication that rigorous purification of the materials was necessary in order to obtain reproducibility.¹²

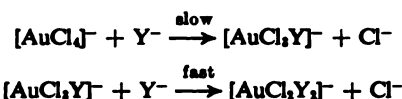
Techniques. The reactions were studied spectrophotometrically by the procedure described in part I² in which the changes of optical density at a selected wavelength in the ultraviolet region were followed over a period of time by means of an Optical-CF4 double-recording spectrophotometer, with the appropriate attachment to maintain the cells at constant temperature ($\pm 0.1^\circ$). Reactions were started by mixing known volumes of standard solutions of the reagents in the spectrophotometer cell which also served as the reaction vessel. Constant ionic strength was maintained by the addition of lithium perchlorate solution. Freshly prepared solutions of HAuCl_4 were used for each experiment in order to avoid the formation of significant quantities of the solvent adducts. The entering reagent was always present in sufficient concentration to provide pseudo-first-order conditions and to avoid complications from the reverse reactions. The pseudo-first-order rate constants, k_{obsd} , were calculated from the slope of the plot of $\log(D_\infty - D_t)$ against time, where D_t and D_∞ are the optical densities of the reaction mixture at time t and at the end of the reaction, respectively.

its

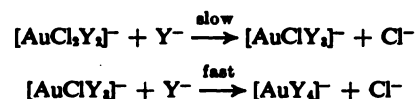
the problems of following the kinetics of nucleophilic ligand displacements from $[\text{AuCl}_4]^-$ are, in principle, similar to those encountered in the study of the reactions of $[\text{PtCl}_4]^{2-}$ since, in both the substrates, there are four replaceable groups. However, the lower reactivity of the gold(III) substrate and the possibility of complication by redox processes can add extra difficulty. Owing to the relatively high nucleophilicity of $[\text{AuCl}_4]^-$, we have had to limit our study to nucleophiles pyridine, NO_2^- , N_3^- , Br^- , I^- ,

SCN^- , and CH_3OH . Fortunately, as was previously reported for the nucleophilic substitutions of neutral complexes of the type $[\text{AuCl}_3\text{am}]$,⁸ the reduction of Au(III) to Au(I), or even to metallic gold, either did not occur or else was relatively slow in comparison to the ligand displacement reaction. No evidence was found for any irreproducible redox-catalyzed substitution of the type observed by Rich and Taube¹² in their studies of the chloride exchange.

All the reaction rates reported in this paper are concerned with the replacement of the first of the four chloride ligands bonded to the gold. As far as the reagents NO_2^- , N_3^- , and Br^- are concerned, the identification of the reaction steps and the products is based upon the same arguments that were previously used for the reactions of $[\text{AuCl}_3\text{am}]$.⁸ In each case, two reaction steps can be observed, and the isosbestic points for the second step occur at least at one wavelength where there is a large enough change in optical density corresponding to the first step. These isosbestic points are identical with those observed in the appropriate stages of the analogous reactions with the $[\text{AuCl}_3\text{am}]$ substrate,^{8,9} and the kinetics of the first stage were studied at these wavelengths. In these cases it is also found that the general kinetic behavior, after the first stage of the reaction, also corresponds to that observed for the substrates of the type $[\text{AuCl}_3\text{am}]$, and the final spectra are also in agreement with those previously observed. Consequently, the reactions can be described as



followed by the second identifiable step



The rates of the second reaction step are not reported here.

The reactions with NO_2^- were carried out in the presence of a small quantity of CH_3O^- in order to avoid the formation of HNO_2 . Some preliminary experiments showed that this species can exert a catalytic effect similar to that observed for the reactions of some platinum(II) complexes.¹³ It should be pointed out that a similar effect was not observed in the reactions of $[\text{AuCl}_3\text{am}]$, and further studies of this phenomenon are now in progress.

With pyridine and methanol as entering groups, the reaction appears to stop when only one chloride is replaced. The reaction with pyridine at 25° has been reported previously.⁶ The rate constant for the reaction with the solvent methanol is the k_1 value from the two-term rate law.

The reactions with I^- and SCN^- appear to occur in a single stage. The initial spectrum corresponds to that of the $[\text{AuCl}_4]^-$ starting material, and so the rate-determining step is the replacement of the first chloride. The final spectrum for the reaction with I^- corresponds exactly to that of $[\text{AuI}_4]^-$.¹⁰ An attempt was made to follow the reaction with thiourea at 6° . The reaction

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Table I. Pseudo-First-Order Rate Constants, k_{obsd} , for the Displacement of the First Chloride in $[\text{AuCl}_4]^-$ in Methanol^a

Entering group, Y	[Y], M	Temp, °C	k_{obsd} , sec ⁻¹	Entering group, Y	[Y], M	Temp, °C	k_{obsd} , sec ⁻¹
Pyridine ^b	0.195	6.0	0.086	Br ⁻	0.0500	15.0	0.0032
	0.0975		0.043		0.0250		0.0014
	0.0487		0.021		0.100	25.0	0.0164
	0.0650	15.0	0.055		0.0750		0.0132
	0.0487		0.040		0.0500		0.0084
NO ₂ ⁻	0.0284		0.024	I ⁻	0.0250		0.0054
	0.00975		0.0078		0.0100		0.0035
	0.100	15.0	0.00175		0.0015	6.0	0.031
	0.0800		0.00150		0.0010		0.023
	0.0400		0.00088		0.0010		0.021
	0.0200		0.00048		0.00050		0.0111
	0.100	25.0	0.0031		0.00050		0.0102
	0.0750		0.0025		0.00025		0.0053
	0.0400		0.0017		0.0010	15.0	0.045
	0.0200		0.0010		0.00075		0.033
	0.100	35.0	0.0058		0.00050		0.021
	0.0800		0.0050		0.00030		0.013
	0.0400		0.0031		0.00075	25.0	0.061
	0.0200		0.0019		0.00060		0.046
	0.0100		0.0015		0.00050		0.042
N ₃ ⁻	0.100	6.0	0.0152	SCN ⁻	0.00040		0.032
	0.0750		0.0112		0.00025		0.021
	0.0500		0.0074		0.00010		0.0088
	0.0250		0.0030		0.0100	6.0	0.0186
	0.100	15.0	0.0215		0.0075		0.0145
	0.0750		0.0164		0.0050		0.0080
	0.0500		0.0118		0.0025		0.0044
	0.0250		0.0055		0.0075	15.0	0.026
	0.100	25.0	0.039		0.0050		0.0176
	0.0750		0.031		0.0025		0.0088
	0.0500		0.022		0.0010		0.0038
	0.0250		0.0126		0.0100	25.0	0.070
	0.100	6.0	0.0036		0.0075		0.056
	0.0750		0.0026		0.0050		0.042
	0.0500		0.00156		0.0025		0.0182
Br ⁻	0.0250		0.00077	Thiourea	0.0010		0.0072
	0.100	15.0	0.0068		0.0001	6.0	0.038
					0.0001		0.038

^a With the anionic entering groups the ionic strength was held constant at 0.10 by adding the appropriate amount of lithium perchlorate. ^b The data for pyridine at 25.0° are reported in ref. 6. ^c In reactions involving the nitrite ion, the solutions also contain 0.0002 M NaOCH₃.

Table II. Specific Rate Constants for the Displacement of One Chloride from $[\text{AuCl}_4]^-$ in Methanol Solution (Ionic Strength = 0.1)

Entering group	Temp, °C	Rate constant	ΔH^\ddagger , kcal/mole	ΔS^\ddagger , cal/deg ⁻¹ /mole ⁻¹	Rate constant ^a for $[\text{PtCl}_4]^{2-}$
CH ₃ OH	15	10 ⁴ k ^c			10 ⁴ k ^c
	25	2			0.4
	35	5			
NO ₂ ⁻		10			k ₂ ^d
	15	0.0155			
	25	0.028	8.3	-33	0.0009
N ₃ ⁻	35	0.042			
	6	0.16			
	15	0.21	6.5	-39	
Br ⁻	25	0.35			
	6	0.034			
	15	0.065	12.3	-22	0.0018
I ⁻	25	0.140			
	6	21.5			
	15	44	12.0	-9	0.0065
SCN ⁻	25	84			
	6	1.85			
	15	3.6	12.0	-14	0.0021
Pyridine	25	7.4			
	6	0.45			
	15	0.84	10.6	-22	
	25	1.6 ^b			

^a Data for aqueous solution from ref. 2. ^b Data from ref. 6. ^c In sec⁻¹. ^d M⁻¹ sec⁻¹.

was very fast, even at low concentrations of this reagent, and it is possible only to say that the second-order rate constant k_2 is approximately 400 l. mole⁻¹ sec⁻¹.

The pseudo-first-order rate constants (k_{obsd}) obtained in these studies are listed in Table I. All the reactions follow the usual two-term rate law, viz., rate = $(k_1 + k_2[\text{Y}^-])[\text{complex}]$, where Y is the entering nucleophile. The values of k_1 and k_2 were obtained as the intercepts and slopes, respectively, of linear plots of k_{obsd} against [Y]. The values of k_1 and k_2 are collected in Table II together with the derived activation parameters.

Discussion

On comparing the rate constants for the entry of the various nucleophiles into the $[\text{AuCl}_4]^-$ anion with those for the analogous reactions of $[\text{PtCl}_4]^{2-}$, which are also given in Table II, it is apparent that, in all cases, the Au(III) complex reacts considerably faster than does that of Pt(II).¹⁴ This cannot be explained simply by

(14) The data for $[\text{PtCl}_4]^{2-}$ in Table II have been corrected for ionic strength effects and therefore refer to a standard state of pure water. No attempt has been made to treat the data for $[\text{AuCl}_4]^-$ in a similar fashion because of the unreliability of an extrapolation from an ionic strength of 0.1 when methanol (with its smaller dielectric constant) is

; that the Pt(II) data refer to aqueous solution or the lower charge of the $[\text{AuCl}_4]^-$ anion causes less electrostatic repulsion between the approaching reagent because this observation is more general. For example, the exchange of isotopically labeled chloride $[\text{AuCl}_4]^-$ has a k_2 value of $0.147 \text{ M}^{-1} \text{ sec}^{-1}$ in water^{10,4} whereas with $[\text{PtCl}_4]^{2-}$ the bimolecular exchange of chloride is not experimentally detectable and reaction occurs entirely by way of the solvolytic pathway.¹⁵ The rate of hydrolysis increases by a factor of 5 on going from $[\text{PtCl}_4]^{2-}$ to $[\text{AuCl}_4]^-$.^{11,15} The ratio of k_2 for the replacement of the coordinated chloride by bromide in $[\text{Au}(\text{dien})\text{Cl}]^{2+}$ and $[\text{Pt}(\text{dien})\text{Cl}_2]^+$ are 380 and $5.3 \times 10^{-3} \text{ M}^{-1} \text{ sec}^{-1}$, respectively, at 25°C ,^{15,16} and $190 \text{ M}^{-1} \text{ sec}^{-1}$ in the monocationic $[\text{Au}(\text{dien-H})\text{Cl}]^+$ ⁵ (dien-H = di(2-aminoethyl)amine that has lost one proton). Furthermore, the reactions of $[\text{Au}(\text{bipy})\text{Cl}_2]^+$ with amines are faster than those of $[\text{Pt}(\text{bipy})\text{Cl}_2]^+$,^{7,17} even though a strict comparison cannot be made because the reactions have not been studied in the same solvent.

One must consider the factors that determine the nucleophilicity of the reagents toward the planar substrates: micropolarizability, π interactions, and basicity. One can observe, from the data in Table II, that all of these factors become more important on going from the Pt(II) to the Au(III) substrate. As far as Br^- and I^- are concerned, the micropolarizability has probably a overwhelming influence upon the nucleophilicity. I^- is some 600 times more reactive than Br^- toward $[\text{AuCl}_4]^-$, whereas the ratio of $k_2(\text{I}^-) : k_2(\text{Br}^-)$ is only 3.6 in the reactions with $[\text{PtCl}_4]^{2-}$. Thus, only does Au(III) act as a "soft" reaction center (it is a better reagent than Br^-), but it has a greater discriminating ability than Pt(II). The same is true if we compare thiocyanate and bromide since $k_2(\text{SCN}^-)/k_2(\text{Br}^-)$ is 53 and 1.18, respectively, for reactions with $[\text{AuCl}_4]^-$ and $[\text{PtCl}_4]^{2-}$, although in this case it is not possible to know whether the thiocyanate reacts by the same end in both the transition states.

As far as π interactions are concerned, it should be pointed out that the azide ion has no nucleophilic properties when it reacts with a Pt(II) substrate,² whereas its nucleophilic properties are quite important in its reactions with Au(III) substrates.^{8,9} It also appears that the nucleophilic reagents, N_3^- and NO_2^- , are characterized, in the reactions listed in Table II, by a low value of ΔS^\ddagger and a large negative ΔS^\ddagger . This may be due to the stringent stereochemical requirements of the transition states.

The effect of the basicity of the reagent upon its nucleophilicity can be shown to be greater for the Au(III) complexes by applying eq 2 to corresponding Pt(II) and Au(III) derivatives.^{6,7} The Brønsted coefficient, α , which is very small when the coordinated chloride in $[\text{Pt}(\text{bipy})\text{Cl}_2]^+$ is displaced (0.06),¹⁷ becomes 0.15 for $[\text{AuCl}_4]^-$ (0.15)⁶ and even greater for cationic Au(III) complexes of the type $[\text{Au}(\text{phen})\text{Cl}_2]^+$ (0.21),

vent. The errors introduced by not comparing the data under identical conditions of ionic strength are small compared to those introduced by not comparing them in the same solvent, and even these are small when compared to the magnitudes of the differences we are investigating.

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$[\text{Au}(\text{bipy})\text{Cl}_2]^+$ (0.46), and $[\text{Au}(5\text{-NO}_2\text{-phen})\text{Cl}_2]^+$ (0.89).⁷ It should also be noted that, on going from $[\text{AuCl}_4]^-$ to *trans*- $[\text{Au}(\text{CN})_2\text{Cl}(\text{am})]$, the *cis* effect of the cyanide ligands is ascribed to a positive inductive effect that increases the amount of negative charge at the reaction center.⁹ The anomalously high reactivity of pyridine and even CH_3OH toward $[\text{AuCl}_4]^-$ might also be ascribed to this effect and to the greater importance of electrostatic effects in general.

All of these results agree well with the original proposal of Baddley and Basolo⁵ that the extent to which bond formation develops in the rate-determining transition state is more important in the case of Au(III) than it is in Pt(II). However, it is also clear, mainly from the studies of heterocyclic amines as leaving groups,^{8,9} that the extent of bond breaking is also more important for Au(III) than it is for Pt(II). It has now been observed in a number of studies that, although the nature of the leaving group affects the rate of reaction of a Pt(II) complex, it has no effect upon the nucleophilic discrimination factor. For example, it has been shown that, in a series of complexes of the types $[\text{Pt}(\text{dien})\text{X}]^{2+}$ ^{18a} ($\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{or } \text{N}_3$) *trans*- $[\text{Pt}(\text{C}_6\text{H}_{11}\text{N})_2\text{NO}_2\text{X}]^{18b}$ and $[\text{Pt}(\text{bipy})\text{NO}_2\text{X}]^{19}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{NO}_2$, or N_3), when ligand X is replaced by a series of nucleophiles, a change of X does not lead to any change in the nucleophilic discrimination factor as measured by s in eq 1 but only affects the intrinsic reactivity ($\log k_2$ in eq 1). In other words, plots of $\log k_2$ against n_{Pt} produce a series of parallel straight lines for the different leaving groups in any one series of complexes. This behavior has been interpreted as evidence for a relative independence of the bond-making and the bond-breaking aspects of the substitution. In so far as data are available, it is clear that no such simple relationship exists in the case of the Au(III) complexes, and it has already been pointed out, in the reactions of $[\text{AuCl}_4]^-$, where the heterocyclic amine (am) is the leaving group, that not only is the nucleophilic discrimination power of the Au(III) dependent upon the nature of the leaving group but the order of relative nucleophilicity can also be changed.⁸ This indicates a much closer interdependence of the bond-making and bond-breaking aspects of substitution. The observation that the reaction rates of the Au(III) complexes appear to be more sensitive than those of Pt(II) to both the nature of the entering group and that of the leaving group is in no way a paradox. The fact that bond making is more important does not, in any way, require that bond breaking is less important, or *vice versa*. It might be possible to approach such a situation, but certainly not reach it, in an associative mechanism when the stability of the five-coordinate intermediate increases sufficiently. In Figure 1 there is a collection of diagrammatic free-energy profiles for a bimolecular reaction showing how the truly synchronous process, with no intermediate, which represents one extreme (A), can develop into one where an intermediate of higher coordination number can form (B) and live long enough to come to thermal equilibrium with its environment. The increasing stability of this intermediate is represented by a deepening of the trough (C), and a situation can be envisaged

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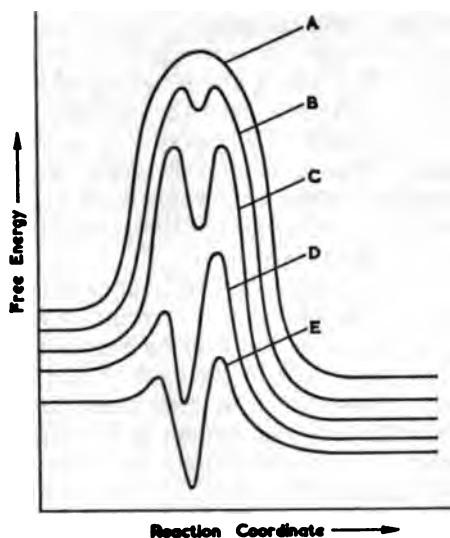


Figure 1. Diagrammatic representation of the free-energy profiles for a series of bimolecular substitutions where the stability of the trigonal bipyramidal intermediate increases with respect to the rate-determining transition state from A (no intermediate) to E (stable intermediate).

where the intermediate is more stable than the mixture of the reagents but less stable than the products (D). Finally a situation can be reached where the five-coordinate intermediate is more stable than either form of the four-coordinate system (E) and is not realistically referred to as a substitution reaction. Case A is typical of an S_N2 process involving substitution at a tetrahedral carbon atom. Case D represents a situation recently reported²⁰ where the addition of amines to $[C_6H_{10}RhClSb(p\text{-tolyl})_3]$ results in the rapid formation of a five-coordinate intermediate which then slowly loses the stibine ligand in the rate-determining step to give planar $[C_6H_{10}RhCl(am)]$. The behavior of Pt(II) and Au(III) complexes is represented by a situation between A and D.

We would like to suggest that the progressive stabilization of the five-coordinate intermediate on going from A to E in Figure 1 (provided that this is trigonal

bipyramidal in form) represents the increasing covalency of all five metal-ligand bonds which, in valence-bond terms, could be expressed as the increasing utilization of the fifth orbital in the $d + s + p^3$ set of the metal. As this intermediate becomes more stable, the process of bond making becomes more and more divorced from that of bond breaking. In the limit, the addition of the incoming group to the complex is affected by the leaving group only in so far as this is one of the four ligands already present in the complex. The process of bond breaking would be affected in the same way by the now entered fifth ligand. In this way both must have some effect upon the reaction rates. However, if the rate-determining transition state is developed before the intermediate,²¹ it would be reasonable to expect that the factors leading to the formation of the bond with the incoming group would have a much greater effect upon the rate of reaction than those leading to the subsequent breaking of the bond with the leaving group. If this transition state developed after the intermediate was formed, the reverse situation would obtain. As the intermediate becomes less stable and the mechanism approaches a synchronous process, it no longer becomes possible to divorce bond making from bond breaking and, in the rate-determining transition state, the bond with the incoming group is not fully developed and that with the leaving group is partly broken. It is therefore possible to explain the gross differences between Pt(II) and Au(III) reaction centers by saying that the five-coordinate intermediate developed in the reaction of a gold(III) substrate is less stable, with respect to the rate-determining transition state, than that appearing in the reactions of platinum(II). Both of these are less stable than the intermediate formed in the substitution reactions of planar Rh(I) where, in one case at least, the species can be observed without difficulty. This is in accord with the concept that the utilization of all five orbitals for covalent bonding becomes progressively more difficult as the effective nuclear charge of the central atom increases, *i.e.*, $Rh(I) > Pt(II) > Au(III)$.²²

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Spin-Spin Coupling in Binuclear Complexes. IV.¹ Substituted Heterocyclic N-Oxide Complexes of Copper(II) Halides. III.² Magnetic and Spectral Properties of Complexes with Substituted Quinoline N-Oxides

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Abstract: The magnetic and spectral properties of 1:1 and 1:2 copper(II) halide complexes with substituted quinoline N-oxides have been investigated. The condensed complexes may be divided into three types based on these properties and dependent upon the donor characteristics of the ligands, as measured by their pK_a values. Members of the first class, containing ligands of relatively high pK_a 's, display the subnormal magnetic moments typical of the pyridine N-oxide-copper(II) halide systems. Complexes derived from ligands of low pK_a values constitute the second class, and the third is formed by species of empirical formula $(CuCl_2)_mL_n$, where $1 < m/n < 2$, containing ligands of intermediate pK_a 's. Both of these types exhibit normal magnetic moments. The differences in magnetic behavior are correlated with a change in structure from oxygen-bridged to halogen-bridged entities, a conclusion which is supported by far-infrared spectral evidence for the chlorides. The 1:2 complexes all display normal magnetic moments which are temperature independent.

Recently there has been considerable interest in the copper(II) halide complexes of substituted pyridine N-oxides.^{2,3} From the observed antiferromagnetic behavior of the 1:1 complex of pyridine N-oxide with copper(II) chloride, the presence of a di- or polymeric species was inferred. This was later substantiated by an X-ray crystallographic examination,⁴ where it was shown that the dimeric molecule consists of two distorted tetrahedra sharing an edge with the oxygen atoms of the pyridine N-oxide ligands acting as bridging units. The temperature dependence of the magnetic susceptibility of this and other 1:1 complexes with substituted pyridine N-oxides has been interpreted in terms of a spin-spin coupling occurring *via* a superexchange mechanism through the orbitals of the bridging oxygen atoms. The observed copper-copper internuclear distance of 3.23 Å for the pyridine N-oxide complex is consistent with the superexchange mechanism. These studies have now been extended to include the magnetic and spectral properties of copper(II) halide complexes with substituted quinoline N-oxides, some of which show extremely interesting and unusual magnetic behavior, not observed with the pyridine N-oxide complexes. A previous communication indicated the preliminary results of our investigations,⁵ and these are now reported in full.

Experimental Section

Preparation of the Substituted Quinoline N-Oxides. Quinoline N-oxide, the 4-substituted-quinoline N-oxides, and 6-methylquinoline N-oxide were prepared by the method of Ochiai.⁶ Other literature methods were employed for the preparation of 4-chloro-

6-methylquinoline N-oxide,⁷ 4-nitro-6-methylquinoline N-oxide,⁷ and 3-nitro-6-methylquinoline N-oxide.⁸ The melting points of all the ligands were consistent with reported values.

Preparation of the Complexes. Method A. In general, the complexes were prepared by mixing a solution of $CuCl_2 \cdot 2H_2O$ or $CuBr_2$ in warm ethanol, 2-propanol, or 1-butanol with a stoichiometric amount of the ligand in the same solvent. The products either crystallized immediately or after standing for a short time and were filtered, washed well with the solvent, and dried in the air.

Method B. In some cases the use of stoichiometric quantities for the preparation of 1:1 complexes resulted in the isolation of 1:2 species. The condensed complex was then prepared using a tenfold excess of the copper(II) halide in hot 1-butanol as solvent.

Analytical Data. Microanalyses for carbon, hydrogen, and nitrogen were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Copper analyses were determined by EDTA titration using Snazox as indicator.⁹ The analytical data are presented in Table I together with the method of preparation of the complexes.

pK_a Determinations. The pK_a values of the ligands were determined spectrophotometrically¹⁰ using the ultraviolet absorption spectra of the free and protonated bases in solutions of known pH. Since the pH values involved were too low to be accurately measured with a pH meter, values of the acidity functions H_0 were employed.¹¹ The spectra of the two species were compared and significant differences in peak maxima noted. In general, for the neutral, and presumably unprotonated solution of the ligand, one peak was found to increase markedly in intensity from that present in the strongly acidic, protonated solution. The wavelength of this peak was noted. A series of solutions, of pH approximately equal to the estimated pK_a of the ligand, and differing from each other by 0.2 pH unit, was prepared. The optical densities of these solutions were measured at the wavelength of the above peak, and by comparison with the spectra of protonated and unprotonated species the extent of protonation could be determined. Thus, for each solution a value of the pK_a of the ligand was obtained and the mean of these results gave the accurate pK_a value.

Magnetic Susceptibility Determinations. Magnetic susceptibilities were determined as a function of temperature by the Faraday method, using equipment and procedures which have been described

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Table I. Analytical Data

Ligand	Halide	Method of prepn	Ligand: salt ratio	C, %		H, %		N, %		Cu, %	
				Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd
4-Methylquinoline N-oxide	CuCl ₂	A	1:1	41.03	40.85	2.89	3.07	4.77	4.77	21.40	21.65
	CuBr ₂	A	1:1	31.60	31.37	2.48	2.35	3.49	3.66	16.42	16.62
6-Methylquinoline N-oxide	CuCl ₂	B	1:1	40.86	40.85	3.12	3.07	4.58	4.77	21.79	21.65
	CuBr ₂	B	1:1	31.20	31.37	2.40	2.35	3.89	3.66	16.50	16.62
Quinoline N-oxide	CuCl ₂	B	1:1	38.94	38.67	2.57	2.52	5.20	5.01	22.73	22.72
	CuBr ₂	A	1:1	29.10	29.33	1.87	1.92	3.90	3.80	16.82	17.24
4-Chloro-6-methylquinoline N-oxide	CuCl ₂	B	2:3	30.32	30.38	2.38	2.04	3.53	3.54	23.84	24.11
	CuCl ₂	A	2:1	45.42	46.04	2.44	3.10	5.25	5.36	12.16	12.18
	CuBr ₂	B	1:1	28.80	28.80	1.87	1.93	3.30	3.36	15.00	15.24
	CuBr ₂	A	2:1	40.15	39.34	2.72	2.64	4.59	4.59	10.16	10.41
4-Chloroquinoline N-oxide	CuCl ₂	B	2:3	28.24	28.32	1.53	1.57	3.20	3.67	25.45	25.00
	CuCl ₂	A	2:1	43.52	43.78	2.46	2.43	5.68	5.44	12.88	12.87
	CuBr ₂	A	1:1	26.89	26.80	1.52	1.49	3.53	3.47	15.73	15.77
	CuBr ₂	A	2:1	37.32	37.09	2.29	2.06	4.60	4.81	10.56	10.91
3-Nitro-6-methylquinoline N-oxide	CuCl ₂	B	3:4	31.11	31.32	2.17	2.10	...	7.31	22.30	22.10
	CuCl ₂	A	2:1	44.47	44.26	3.19	2.97	10.31	10.32	11.56	11.71
	CuBr ₂	B	1:1	28.25	28.09	2.03	1.89	6.31	6.55	14.52	14.86
	CuBr ₂	A	2:1	37.73	38.03	2.81	2.55	8.55	8.87	10.20	10.06
4-Nitro-6-methylquinoline N-oxide	CuCl ₂	B	1:1	35.87	35.47	2.35	2.38	7.68	8.27	18.81	18.76
	CuCl ₂	A	2:1	44.04	44.26	2.97	2.97	10.18	10.32	11.78	11.71
	CuBr ₂	A	2:1	38.61	38.03	2.94	2.55	8.41	8.87	9.95	10.06
4-Nitroquinoline N-oxide	CuCl ₂	B	1:1	33.40	33.30	1.78	1.86	8.43	8.63	19.50	19.57
	CuCl ₂	A	2:1	42.07	41.99	2.50	2.35	10.74	10.88	12.20	12.34
	CuBr ₂	A	2:1	36.52	35.81	2.16	2.00	9.17	9.28	10.46	10.53
4-Nitropyridine N-oxide	CuCl ₂	B	1:1	21.99	21.85	1.66	1.46	10.05	10.20	23.09	23.14

previously.¹ Mercury tetrathiocyanatocobaltate(II) was used as magnetic susceptibility standard,¹² and diamagnetic corrections were estimated from Pascal's constants.¹³

Spectral Measurements. For the pK_a measurements ultraviolet absorption spectra were recorded with a Beckman DU spectrophotometer. Diffuse reflectance spectra of solid samples were measured using the standard reflectance attachment and employing a block of magnesium carbonate as standard. Infrared spectra in the range 1300–250 cm^{-1} were recorded with a Perkin-Elmer 521 double-beam spectrometer.

Results

The Complexes. As the data in Table I show, not all possible complexes were obtained. Thus 2:1 complexes of the ligands 6-methyl-, 4-methyl-, and quinoline N-oxide with both CuCl_2 and CuBr_2 did not form, and 4-nitro-6-methyl- and 4-nitroquinoline N-oxide yielded 1:1 adducts only with CuCl_2 . The use of both methods A and B for the preparation of 1:1 copper(II) chloride complexes with several ligands did not yield the expected products but species of a polymeric nature, as indicated by elemental analyses. Thus both 4-chloro-6-methyl- and 4-chloroquinoline N-oxide afforded compounds of empirical formula $(\text{CuCl}_2)_2\text{L}_2$ and 3-nitro-6-methylquinoline N-oxide yielded a species which analyzed as $(\text{CuCl}_2)_4\text{L}_4$.

Magnetic Data. Magnetic susceptibilities were determined at 300, 196, and 77°K only, since these measurements sufficed to distinguish between different types of magnetic behavior. A considerable body of data already exists for the full temperature variation (350–77°K) of the magnetic susceptibility of substituted pyridine N-oxide-copper(II) halide complexes,^{2,3} and it was considered unnecessary to repeat these detailed measurements for the quinoline N-oxide derivatives. The magnetic data, together with the observed pK_a

values of the ligands, are presented in Table II. The molar magnetic susceptibilities were calculated on the basis of a molecular weight per copper(II) ion in all cases, and magnetic moments were obtained from the expression $\mu_{\text{eff}} = 2.84(\chi_m^{\text{cor}}T)^{1/2}$. It is immediately apparent that the complexes fall into two principal classes. The first class includes the condensed complexes, the majority of which display the low magnetic moments indicative of the binuclear oxygen-bridged unit which has been established for the pyridine N-oxide-copper(II) chloride complex.⁴ The second class contains the complexes with a ligand:salt ratio of 2, which all exhibit normal magnetic moments, *i.e.*, a moment greater than or equal to 1.73 BM per copper(II) ion, and which are virtually independent of temperature. The condensed complexes may be further subdivided into those displaying low magnetic moments, the 1:1 species with normal magnetic moments, and thirdly, the compounds of polymeric nature which also show magnetically normal behavior. With the exception of the 3-nitro-6-methylquinoline N-oxide derivative, all the condensed copper(II) bromide complexes exhibit low magnetic moments. It may be significant that no polymeric species are formed when the salt is copper bromide.

pK_a Data. The pK_a values of the ligands lie in the anticipated order, both by comparison with their pyridine N-oxide analogs and on the basis of simple electronic effects. The previously reported value of -0.8 for the pK_a of 4-nitroquinoline N-oxide^{2c} does not agree with our experimental results. However, the value of -1.39 observed here is more consistent with the pK_a of -1.7 ± 0.15 reported for 4-nitropyridine N-oxide.¹⁴

Far-Infrared Spectra. Table III records the maxima observed in the spectra of the ligands and their copper(II) chloride complexes in the region 400–250 cm^{-1} .

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(13) J. Lewis and R. G. Wilkins, "Modern Coordination Chemistry," Interscience Publishers, Inc., New York, N. Y., 1960, p 403.

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ble II. Magnetic and pK_a Data

Ligand	pK_a	μ_{eff} , BM per Cu(II) ion					
		Condensed complex			2:1 complex		
		300°	196°	77°	300°	196°	77°
Copper(II) Chloride Complexes							
4-Methylquinoline N-oxide	1.44	0.56	0.43	0.38			
6-Methylquinoline N-oxide	1.01	0.41	0.30	0.24			
Quinoline N-oxide	0.86	0.37	0.30	0.23			
4-Chloro-6-methylquinoline N-oxide	0.61	1.69	1.66	1.55 ^{a,b}	1.97	1.93	1.85
4-Chloroquinoline N-oxide	0.47	2.07	2.04	1.89 ^{a,b}	1.88	1.85	1.83
3-Nitro-6-methylquinoline N-oxide	-0.69	1.91	1.91	1.90 ^{a,c}	1.81	1.87	1.82
4-Nitro-6-methylquinoline N-oxide	-1.20	1.92	2.01	1.96	1.87	1.89	1.92
4-Nitroquinoline N-oxide	-1.39	2.13	2.12	2.14	1.86	1.89	1.85
Copper(II) Bromide Complexes							
4-Methylquinoline N-oxide	1.44	0.40	0.43	0.34			
6-Methylquinoline N-oxide	1.01	0.60	0.31	0.24			
Quinoline N-oxide	0.86	0.36	0.32	0.21			
4-Chloro-6-methylquinoline N-oxide	0.61	0.38	0.28	0.28	1.82	1.87	1.87
4-Chloroquinoline N-oxide	0.47	0.39	0.34	0.30	1.83	1.90	1.82
3-Nitro-6-methylquinoline N-oxide	-0.69	1.72	1.75	1.75	1.98	1.90	1.95
4-Nitro-6-methylquinoline N-oxide	-1.20				1.85	1.88	1.84
4-Nitroquinoline N-oxide	-1.39				1.83	1.88	1.81

^a 1:1 complexes not formed here. ^b Empirical formula $(CuCl_2)_2L_2$. ^c Empirical formula $(CuCl_2)_4L_2$.

ble III. Far-Infrared Spectra in the Region 400–250 cm^{-1} ^a

Pyridine N-oxide						
CuCl ₂ -L	397 m			330 w, sh	311 vs	
CuCl ₂ -L ₂	385 m				310 s	286 s
4-Methylquinoline N-oxide		363 s				
CuCl ₂ -L		357 m	334 vs	325 s, sh		
6-Methylquinoline N-oxide		359 m				
CuCl ₂ -L		362 m	340 m, sh	328 s		
Quinoline N-oxide	390 vw	372 w		327 w, sh	313 m	296 w, sh
CuCl ₂ -L	393 w, sh		344 s	332 s		
4-Chloro-6-methylquino-	392 m	355 w	336 m		302 w, sh	298 m
line N-oxide						
(CuCl ₂) ₂ -L ₂			345 w		307 m, sh	280 s
CuCl ₂ -L ₂	396 w		336 w, sh	320 m		290 s
4-Chloroquinoline N-oxide		350 w	335 m	326 w, sh		
(CuCl ₂) ₂ -L ₂	388 m	347 m		317 w, sh	308 s	290 s
CuCl ₂ -L ₂	392 w		335 m		310 s	300 s, sh
3-Nitro-6-methylquino-		355 m		329 w		285 w
line N-oxide						
(CuCl ₂) ₂ -L ₂			335 w		306 m, sh	290 s, sh
CuCl ₂ -L ₂	390 m	352 w, sh	342 s			
4-Nitro-6-methylquinoline	380 m			315 w	300 w	280 m
N-oxide						
CuCl ₂ -L			342 w		308 s, sh	280 vs
CuCl ₂ -L ₂	395 m	380 w, sh	334 w, sh	316 vs		
4-Nitroquinoline N-oxide			350 w	326 m	305 m, sh	
CuCl ₂ -L			342 w		307 vs	290 s
CuCl ₂ -L ₂	397 m	385 w	335 w, sh	318 s		

^a Maxima which are italicized are assigned as copper-chlorine stretching frequencies. w = weak, m = medium, and s = strong intensity; v = very and sh = shoulder.

re spectra of the 1:1 and 2:1 adducts of pyridine N-oxide with copper(II) chloride are also included. Previous far-infrared spectral studies on complexes containing metal-halogen bonds indicate that metal-chlorine stretching frequencies occur in the range 250–400 cm^{-1} and metal-bromine frequencies from below 400 to 250 cm^{-1} .¹⁶ Thus for the complexes discussed here the observation of infrared-active metal-chlorine stretching frequencies may be anticipated, whereas it is likely that the corresponding metal-bromine vibrations will lie outside the range of the instrument, the lower limit of which occurs at ca. 245 cm^{-1} . Several of the ligands show no absorptions in the range 250–400 cm^{-1} , and consequently the metal-chlorine vibrations may be assigned without difficulty. Although

(15) R. J. H. Clark, *Spectrochim. Acta*, 21, 955 (1965).

maxima were observed with some ligands in this region of the spectrum, the bands present in the complexes were considerably more intense and may be assigned as infrared-active metal-chlorine stretching frequencies with a reasonable degree of certainty. Those peaks which are italicized in Table III are assigned as metal-chlorine stretching vibrations. For the copper(II) bromide complexes, as anticipated, the situation is considerably less clear. The region 290–350 cm^{-1} is frequently free of absorptions, further substantiating the assignment of the metal-chlorine stretching frequencies. Below 290 cm^{-1} spectra of all the bromides display an area of increasing absorption and several show maxima at ca. 250 cm^{-1} . However, the bands were very broad and indistinct at this wavelength and are not recorded here.

Table IV. Diffuse Reflectance Spectra*

Ligand	Maxima, mμ					
Condensed CuCl ₂ Complexes						
4-Methylquinoline N-oxide	390	420 sh	500 sh	610	730	875 sh
6-Methylquinoline N-oxide	375	420	510 sh	620 sh	755	860 sh
Quinoline N-oxide	380	430	510 sh	610 sh	720	850 sh
4-Chloro-6-methylquinoline N-oxide	385		530 sh		835	900 sh
4-Chloroquinoline N-oxide	385	450 sh	520 sh	570 sh	840	900 sh
3-Nitro-6-methylquinoline N-oxide	345	390 sh	520 sh		830	900 sh
4-Nitro-6-methylquinoline N-oxide		410 sh	550 sh		840	
4-Nitroquinoline N-oxide	350		530 sh		840	930 sh
Condensed CuBr ₂ Complexes						
4-Methylquinoline N-oxide	400	440 sh	475 sh	560 sh	730	900 sh
6-Methylquinoline N-oxide		420	480 sh	510 sh	735	
Quinoline N-oxide	400	430 sh	500 sh		730	880 sh
4-Chloro-6-methylquinoline N-oxide	400		490 sh	540 sh	735	900 sh
4-Chloroquinoline N-oxide	400		510		740	900 sh
3-Nitro-6-methylquinoline N-oxide	365, 410 sh				790	900 sh
2:1 CuCl ₂ Complexes						
4-Chloro-6-methylquinoline N-oxide		420 sh		520 sh	680 sh	810
4-Chloroquinoline N-oxide	370	420 sh		510 sh	680 sh	815
3-Nitro-6-methylquinoline N-oxide	380			520 sh	760	820 sh
4-Nitro-6-methylquinoline N-oxide	350	420 sh	450 sh		620	785
4-Nitroquinoline N-oxide	390 sh	460 sh		550		890 960 sh

* sh = shoulder.

Visible Spectra. The diffuse reflectance spectra of the complexes are summarized in Table IV and representative spectra of the condensed complexes exhibited in Figures 1 and 2. Since the complexes were found to

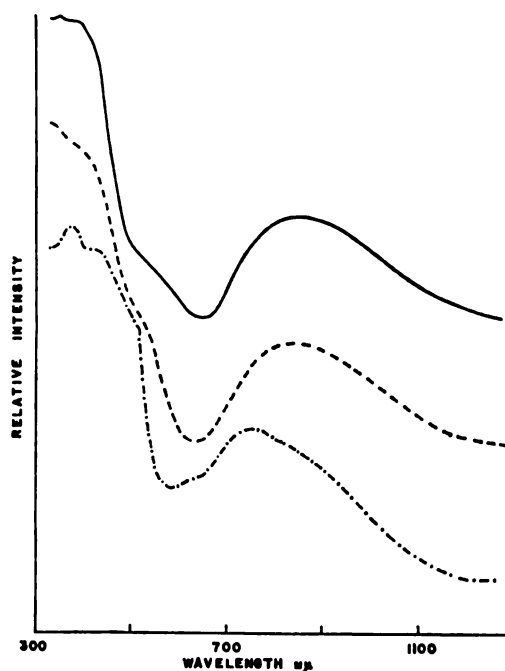


Figure 1. Diffuse reflectance spectra of three representative condensed copper(II) chloride complexes: —, $CuCl_2$ -4-methylquinoline N-oxide; ----, $(CuCl_2)_2$ -(4-chloro-6-methylquinoline N-oxide)₃; — · —, $CuCl_2$ -4-nitroquinoline N-oxide.

decompose in solution, no solution spectra are recorded. The copper(II) bromide complexes were all rather dark in color and several of the 2:1 compounds black. It was necessary to dilute the black compounds with magnesium carbonate in order to obtain a measurable spectrum, and even then only indistinct broad bands were observed. Consequently, the reflectance spectra of the 2:1 adducts of the ligands with copper(II)

bromide are not reported here. Figure 1 includes representative spectra of the three classes of condensed copper(II) chloride complexes. The main feature of interest is the shift in position of the band occurring at 700–900 $m\mu$ dependent upon the class of complex formed. For the compounds displaying low magnetic

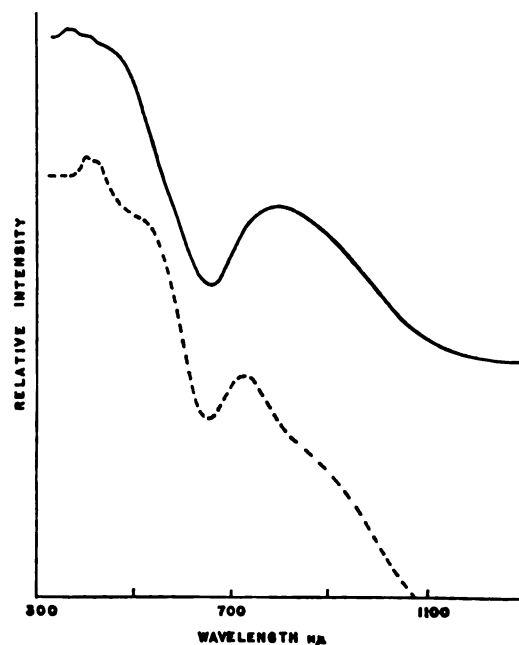


Figure 2. Diffuse reflectance spectra of two representative 1:1 copper(II) bromide complexes: ----, $CuBr_2$ -quinoline N-oxide; —, $CuBr_2$ -3-nitro-6-methylquinoline N-oxide.

moments, the maximum occurs at ca. 750 $m\mu$, with a shoulder at ca. 875 $m\mu$, and these are shifted to 850 and 900 $m\mu$, respectively, in the magnetically normal complexes. In addition, a shoulder at ca. 570 $m\mu$ occurs in the spectra of the polymeric compounds but is absent for the other two classes. With the exception of 3-nitro-6-methylquinoline N-oxide, spectra of the 1:1 complexes of the ligands with copper(II) bromide are

extremely similar. Figure 2 shows a comparison of the spectrum of the copper(II) bromide complex of quinoline N-oxide with that of 3-nitro-6-methylquinoline N-oxide.

Discussion

Magnetic Data. Based on the similarity of the magnetic behavior of the complexes displaying low magnetic moments with that of the copper(II) halide-pyridine N-oxide series, the presence of a similar structure may be inferred, *i.e.*, a dimeric molecule composed of two copper atoms bridged by the oxygen atoms of the N-oxide system. Because of the extremely small forces measured for these complexes with low magnetic susceptibilities, the values of μ_{eff} are only accurate to within 0.1 BM. Thus it is not possible to make any comments concerning the trend of these values. The previously reported 1:1 complexes of this type all exhibit low magnetic moments, with the exception of the copper(II) chloride 4-nitroquinoline N-oxide derivative, which is reinvestigated here. This complex has a room-temperature magnetic moment of 2.13 BM, which is temperature independent. The hitherto unreported 1:1 complex of copper(II) chloride with 4-nitropyridine N-oxide was prepared by mixing a hot 1-butanol solution of the ligand with a large excess of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ dissolved in hot 1-butanol. The product crystallizes as yellow-orange plates and has been characterized by elemental analysis. It shows a room-temperature magnetic moment of 1.01 BM which decreases to 0.33 BM at 77°K.

The normal magnetic moment of $\text{Cu}(\text{4-nitroquinoline N-oxide})\text{Cl}_2$ has been interpreted in terms of the electronic effects incurred by the introduction of the nitro group to the 4 position of the quinoline ring.^{3c} Muto and Jonassen postulate that an electron-attracting entity such as the nitro group will tend to reduce the electron density in the N-O bond (of the quinoline N-oxide system) and consequently the electron density in the π orbitals of the bridging oxygen atom. The interaction between the unpaired electrons in the π orbitals of the copper ions and oxygen π electrons is thus lessened, and the observed magnetic moment will be greater than that of the unsubstituted quinoline N-oxide complex. By this argument the energy difference between the singlet and triplet states is expected to be much greater for the copper(II) chloride complex of 4-nitroquinoline N-oxide than with the quinoline N-oxide derivative itself. The observed magnetic moments indicate that this is the case. However, if the electronic effects of the substituents are the only factors influencing the variation of singlet-triplet splitting energies, then these values for the condensed 4-nitroquinoline N-oxide and 4-nitropyridine N-oxide-copper(II) chloride complexes should be of comparable magnitude. The observed room-temperature magnetic moments of 2.13 and 1.01 BM, respectively, indicate that this is not so and that the "electronic" effect of 4-nitroquinoline N-oxide is considerably greater. Thus it becomes apparent that additional factors should be taken into consideration.

An alternative approach is to consider the increased steric requirements of the quinoline N-oxide system when compared with pyridine N-oxide. It is possible that the decreased donor strength of 4-nitroquinoline N-

oxide with respect to the unsubstituted quinoline N-oxide, *coupled* with the steric factors, cause a change in the structural properties of the molecule. It has been shown that binuclear species formed by bridging copper ions with chloride ions do not tend to be diamagnetic,¹⁶ and thus a structure containing chloride bridges rather than oxygen bridges would account for the observed magnetic properties.

Thus for the condensed copper(II) chloride complexes, ligands with relatively low donor strengths, *i.e.*, very low pK_a values, would give rise to chloride-bridged species, whereas ligands with high donor strengths afford the usual oxygen-bridged species. For ligands of intermediate donor strengths a third class of compound is formed, members of which display a high magnetic moment and possess polymeric, halogen-bridged structures.

All the 1:1 copper(II) bromide complexes prepared in this study, with the exception of the 3-nitro-6-methylquinoline N-oxide derivative, exhibited low magnetic moments. The one exception possibly contains bromide bridges. No compounds of polymeric nature are formed with copper(II) bromide, and this may be due to the reduced tendency of the bromide ion, as compared with the chloride ion, to act as a bridging group.

The magnetic properties of the 4-nitropyridine N-oxide-copper(II) chloride complex may be explained solely in terms of the electronic effects of the substituent, and no change in structure from the oxygen-bridged parent compound of the series need be invoked.

Both copper(II) chloride and copper(II) bromide complexes with two molecules of the substituted quinoline N-oxide exhibit normal magnetic moments which are virtually independent of temperature.

Far-Infrared Spectra. The far-infrared spectral data provide support for the suggestion that there is a structural difference between the classes of condensed complexes. In this discussion it should be recognized that the terms "terminal" and "bridging" are used only in a relative sense. It is probable that a chloride ion bonded directly to one copper ion will interact to some extent with neighboring copper ions and in such a sense could then be termed as bridging. However, for our purposes a terminal chlorine atom is defined as one which is bonded to a copper ion when the binuclear oxygen-bridged species is known to be present, and a bridging chloride ion as one which is bridging two copper ions to form a dimeric or polymeric molecule. Two distinct types of bridging chlorine atoms may be envisaged: firstly, those which are symmetrically disposed between the two copper atoms giving equal bond lengths and, secondly, those which are unsymmetric giving rise to one short and one long copper-chlorine bond distance.

Although the literature contains numerous references to metal-chlorine vibrations of bridging chlorine atoms in copper(II) chloride complexes, the evidence for terminal copper-chlorine stretching frequencies is rather meager, presumably owing to the lack of suitable compounds. Thus the complex $\text{Cu}(\text{pyridine})_2\text{Cl}_2$ is polymeric in the solid state and its structure composed of distorted octahedra connected by bridging chlorine atoms.¹⁷ In each octahedron there are two long (3.05

(16) P. H. Vossos, L. D. Jennings, and R. E. Rundle, *J. Chem. Phys.*, **32**, 1590 (1960); R. D. Willett, C. Dwiggin, Jr., R. Kruh, and R. E. Rundle, *ibid.*, **38**, 2429 (1963).

(17) J. D. Dunitz, *Acta Cryst.*, **10**, 307 (1957).

A) and two short (2.28 Å) copper-chlorine bonds. In the far-infrared spectrum of this compound, absorptions attributed to copper-chlorine stretching vibrations occur at 228 and 287 cm^{-1} , and these probably represent the vibrations of the long and short bonds, respectively.^{18,19} Conversely, for steric reasons, the complex $\text{Cu}(\text{quinoline})_2\text{Cl}_2$ cannot contain two bridging chlorine atoms of the above type since the presence of the quinoline ring results in a copper-chlorine "long" bond distance too great to give rise to a stretching frequency.¹⁸ Thus the assignment of a copper-chlorine stretching mode at 330 cm^{-1} should represent the vibration of the copper-chlorine "short" bond, which is also bridging in character. The addition of substituents adjacent to the nitrogen atom in pyridine complexes of this type has a pronounced effect on the metal-halogen stretching frequency;^{18,20} on substituting the 2 and 5 positions with various groups, the maxima are found to occur in the range 323–309 cm^{-1} , whereas, for substituents in the 3 and 4 positions, corresponding peaks occur at 294–278 cm^{-1} . Recently a report of the far-infrared spectra of some substituted quinoxaline derivatives of copper(II) halides indicates that for these compounds terminal metal-chlorine bonds show absorptions at 368–337 cm^{-1} , and bridging bonds occur at ca. 320 cm^{-1} .²¹

Considering the available evidence, it becomes apparent that the values of metal-chlorine stretching frequencies are very dependent upon the ligand used, even when the structures of the complexes are thought to be the same. However, as a rough guide, the dividing line between bridging and terminal metal chlorine stretching frequencies may be considered to lie at ca. 330–340 cm^{-1} .

The structure of the 1:1 complex of pyridine N-oxide is known to contain copper-chlorine bonds which do not interact with any neighboring copper atoms,⁴ and thus these are terminal in character. The far-infrared spectrum of this complex shows maxima at 311 (vs) and 330 cm^{-1} (w, sh) which may be attributed to copper-chlorine stretching frequencies. Thus for the quinoline N-oxide complexes, we may infer that the observation of metal-chlorine stretching vibrations at frequencies higher than, say, 320 cm^{-1} indicates the presence of terminal metal-chlorine bonds and hence oxygen-bridged structures.

For clarity, maxima assigned as metal-chlorine stretching vibrations in the condensed copper(II) chloride-quinoline N-oxide complexes are summarized in Table V. In the compounds with low magnetic moments and presumably oxygen-bridged structures, maxima observed at ca. 330 and 340 cm^{-1} are assigned as terminal metal-chlorine stretching frequencies. These bands are absent in the spectra of complexes with normal magnetic moments and here two peaks at ca. 280 and 300 cm^{-1} are observed in all cases. This significant shift to lower wavelength, which correlates with the change in magnetic properties, is considered to reflect the difference between structures containing terminal and bridging metal-chlorine bonds. In support of this conclusion the magnitude of the shift, ca.

(18) M. Goldstein, E. F. Mooney, A. Anderson, and H. A. Gebbie, *Spectrochim. Acta*, **21**, 105 (1965).

(19) R. J. H. Clark and C. S. Williams, *Inorg. Chem.*, **4**, 350 (1965).

(20) C. W. Frank and L. B. Rogers, *Ibid.*, **5**, 615 (1966).

(21) D. E. Billing, A. E. Underhill, D. M. Adams, and D. M. Morris, *J. Chem. Soc., Sect. A*, 902 (1966).

Table V. Summary of Metal-Halogen Stretching Vibrations for the Condensed Copper(II) Chloride Complexes*

Ligand	cm^{-1}			
4-Methylquinoline N-oxide	334 vs	325 s, sh		
6-Methylquinoline N-oxide	340 m, sh	328 s		
Quinoline N-oxide	344 s	332 s		
4-Chloro-6-methylquinoline N-oxide			307 m, sh	280 s
4-Chloroquinoline N-oxide			308 s	290 s
3-Nitro-6-methylquinoline N-oxide			306 m, sh	290 s, sh
4-Nitro-6-methylquinoline N-oxide			308 s, sh	280 vs
4-Nitroquinoline N-oxide			307 vs	290 s
Pyridine N-oxide	330 w, sh	311 vs		

* w = weak, m = medium, s = strong intensity; v = very and sh = shoulder

35–45 cm^{-1} , is of a similar order to that observed with the quinoxaline complexes mentioned above.²¹

X-Ray crystallographic evidence for the 2:1 complex of pyridine N-oxide with copper(II) chloride shows the presence of the same basic structure as in the corresponding 1:1 species.²² In the far-infrared spectrum of the former complex, two metal-chlorine stretching frequencies are observed at 310 and 286 cm^{-1} . Although the oxygen bridged unit is still present, the inclusion of an extra pyridine N-oxide ligand into the coordination sphere of each copper ion presumably has the effect of weakening the metal-chlorine bonds, thus causing a reduction in the metal-halogen stretching frequencies.

Since this compound displays a subnormal magnetic moment, whereas all the 2:1 quinoline N-oxide complexes show normal magnetic properties, it is not possible to effect comparisons. However, in view of the magnetic results and the relatively low metal-halogen stretching frequencies, it seems likely that the latter compounds possess polymeric halogen-bridged structures.

Spectra of the 2:1 derivatives with ligands containing nitro groups show only one band attributable to a metal-chlorine stretching vibration, and these occur at slightly higher frequencies than the mean value of 300 cm^{-1} for complexes not containing nitro substituents. In particular, the 3-nitro-6-methylquinoline N-oxide complex shows a maximum at 342 cm^{-1} . The explanation of this is not clear.

Visible Spectra. The spectra of the condensed copper(II) chloride complexes may be divided into two main band systems, the first occurring at 350–450 $\text{m}\mu$ and the second at 700–850 $\text{m}\mu$, of which the relative intensity of the latter is considerably less. The first band system is probably associated with charge-transfer transitions, and the second may be attributed to transitions within the d shell. Most of the bands are obviously multiple in character, and an indistinct shoulder is observed in all cases at about 900 $\text{m}\mu$ on the side of the lower energy band. The shift in position of the maximum associated with the d-d transition, which correlates with the differences in magnetic proper-

(22) J. C. Morrow, private communication.

ties of the complexes, probably reflects the differing environments of the copper ion in the two cases.

Except for the appearance of an intense band at *ca.* 500 $m\mu$, spectra of the 1:1 copper(II) bromide derivatives are essentially similar to those of the chlorides displaying low magnetic moments. Also, the shoulder at 900 $m\mu$ is more pronounced in the case of the bromides. The origin of the 500- $m\mu$ band is uncertain, although as seen in Figure 1 spectra of the chlorides do show shoulders of much weaker relative intensity in this region. As with the condensed chloride complexes with high magnetic moments, the spectrum of the 1:1 copper(II) bromide-3-nitro-6-methylquinoline N-oxide derivative is significantly different from those of the corresponding complexes displaying low magnetic moments. As indicated in Table IV, the d-d band is shifted from *ca.* 730 $m\mu$ down to 790 $m\mu$ in the bromide-bridged species. This again is probably an indication of the different environments of the copper ion in the oxygen-bridged and bromide-bridged species.

The spectra of the 2:1 complexes with copper(II) chlorides show similar features to those of the con-

densed complexes. The maxima due to transitions within the d shell are shifted to slightly higher energy in the 2:1 derivatives.

Conclusion

The spectral and magnetic properties of the condensed copper(II) halide complexes of substituted quinoline N-oxides indicate that either oxygen-bridged or halogen-bridged derivatives may be formed. The experimental evidence indicates that there must be a critical relationship between such factors as the donor properties and steric requirements of the ligands and the lattice energies of the various compounds in favoring the formation of one species over another.

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The Dissociative Interchange Mechanism for the Formation of Acidopentaamminecobalt(III) Ions¹

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Contribution from the Moore Laboratory of Chemistry, Amherst College, Amherst, Massachusetts 01002. Received January 21, 1967

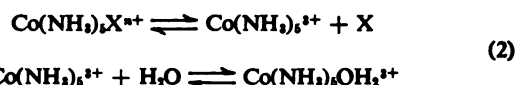
Abstract: The rates of formation of the complex ions, $\text{Co}(\text{NH}_3)_5\text{X}^{n+}$, are discussed with special attention to the rate of reaction in the outer-sphere complex (or ion pair) $\text{Co}(\text{NH}_3)_5\text{OH}_2^{3+} \cdots \text{X}^{(3-n)-}$. (New data are presented for entry of chloride and thiocyanate ions at 45° and unit ionic strength.) It is observed that the rates are similar for all anions studied so far and are a nearly constant fraction (0.2) of the water exchange rate for $\text{Co}(\text{NH}_3)_5\text{OH}_2^{3+}$. These results may be understood in terms of an activation process which is *dissociative*, leading to a *transition state* in which entering and leaving ligands are at most weakly bound *but* in which no intermediate of significant lifetime is formed. The similarity of rates of entry implies weak binding in the transition state. The anion entry rates appear to be related to the water exchange rate through a statistical factor connected with the probability that an anion is to be found in an outer coordination sphere site when a cobalt-water dissociation event occurs.

This paper is concerned with the kinetics and equilibrium of reaction 1, where X is a univalent anionic ligand or sulfate and *n* is 2 or 1, respectively. Two



mechanistic pathways for this process have often been discussed, and neither seems to give an entirely felicitous account of the details. In one case,² the process has been regarded as a simple nucleophilic attack of the entering group on the complex, leading to a concerted substitution which is bimolecular and adequately represented by eq 1. The alternative account³ suggests

the participation of five-coordinate intermediate of the pathway represented by



The kinetics of eq 2 require the prediction that X and H_2O compete for the intermediate. Strong evidence against eq 2 was presented by Pearson and Moore⁴ who were able to show for the case of $\text{X} = \text{Br}^-$ or NO_3^- that addition of SCN^- to the solution did not lead to any detectable direct production of $\text{Co}(\text{NH}_3)_5\text{NCS}^{3+}$. The experiment is conclusive because sufficient kinetic and equilibrium data are available to predict³ the rate of capture of the intermediate by SCN^- if the reaction were going by mechanism 2.

The alternative account which focuses attention on the bimolecularity of the substitution is unsatisfactory in the

(1) This work was supported by Grant 2329-A5 from the Petroleum Research Fund of the American Chemical Society. Some preliminary work was done during the spring of 1964 when C. H. L. was a visiting member of the Chemistry Department of Columbia University. Thanks are extended to that department for its hospitality and especially to Professor Harry B. Gray for many valuable discussions.

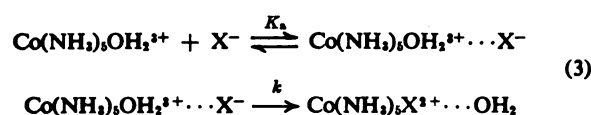
(2) (a) S. C. Chan, *J. Chem. Soc.*, 2375 (1964); (b) S. C. Chan and J. Miller, *Rev. Pure Appl. Chem.*, 15, 11 (1965).

(3) A. Haim and H. Taube, *Inorg. Chem.*, 2, 1199 (1963).

(4) R. G. Pearson and J. W. Moore, *ibid.*, 3, 1334 (1964).

sense that studies of structure variation (e.g., a linear free-energy relationship between rates and equilibria as the leaving group is varied⁵) strongly imply a transition state for the reaction with at most very weak bonds to the participating ligands.

Here, we wish to explore the applicability of a mechanistic scheme which assumes that the transition state is reached *dissociatively* but assumes *no* intermediate along the reaction pathway of *sufficient stability to be selective in its reactions*. We assume that the transition state must incorporate a ligand from its immediate solvation shell (outer coordination sphere) so that although activation is dissociative the reaction is "accidentally bimolecular." The entering group must be present in advance of the transition state. Such a scheme is designated "dissociative interchange"⁶ (I_d), dissociative to denote the activation process and interchange to indicate that the substitution process is a rearrangement between inner and outer coordination spheres (a process first discussed by Alfred Werner). The I_d mechanism is shown in eq 3 for the complex formation reaction.



Note that the degree of ion association characterized by the association constant K_a is quite important and, if the activation process is genuinely dissociative, the rate constant, k , should be independent of the nature of the entering group. There is an additional important prediction from this scheme. In a simple 1:1 outer-sphere complex (ion pair), $s = 1$ of the outer-sphere sites will be occupied by solvent (water) molecules if s is the solvation number of the complex. If the anionic partner occupies outer-sphere sites randomly, dissociation of the coordinated water will not normally occur adjacent to the anion; $(s - 1)/s$ dissociative events will lead to water exchange and only a fraction, $1/s$, will lead to anation. Thus, the I_d mechanism predicts that anations occur at very nearly the *same rate* in 1:1 outer-sphere complexes as the nucleophilicity of the entering group is varied *but* that all anations occur at approximately $1/s$ times the rate of solvent exchange.

Experimental Section

Materials. The complexes $[\text{Co}(\text{NH}_3)_5\text{Cl}](\text{ClO}_4)_2$, $[\text{Co}(\text{NH}_3)_5\text{NCS}](\text{ClO}_4)_2$, and $[\text{Co}(\text{NH}_3)_5\text{OH}_2](\text{ClO}_4)_2$ were prepared by well-known methods⁷ and characterized spectrophotometrically. Extinction coefficients at wavelengths important to this study are collected in Table I. Reagent grade sodium chloride and sodium thiocyanate were used without further purification. Sodium perchlorate solutions for ionic strength control were prepared by titration of standardized concentrated sodium hydroxide solutions with perchloric acid and dilution to the required volume. Stock solutions of sodium chloride, sodium perchlorate, and water used in preparing reaction mixtures were adjusted to pH 3 by addition of perchloric acid to repress acid dissociation of $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$ (in experiments with thiocyanate, the pH was adjusted to 5).

Equilibrium Studies. The equilibrium between $[\text{Co}(\text{NH}_3)_5\text{Cl}]^{2+}$ and $[\text{Co}(\text{NH}_3)_5\text{OH}_2]^{2+}$ was studied at 45.0° as a function of NaCl

Table I. Some Features of Visible Spectra of Complexes Used in This Study (Absorption Maxima and Wavelengths Used in Reaction Studies)

Complex	λ_{max} , m μ	ϵ_{max} , M ⁻¹	λ , m μ	ϵ , M ⁻¹	Ref
$\text{Co}(\text{NH}_3)_5\text{Cl}^{2+}$	532	50.7	555	44.0	This work 6b, 10
	532	51.0	
$\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$	491	48.6	555	18.2	This work 6b, 10
	491	47.5	
$\text{Co}(\text{NH}_3)_5\text{NCS}^{2+}$	500	177	500	177	This work 4
	500	174	

concentration in a medium maintained at an ionic strength of 1.00 with NaClO₄ (pH 3) and in a medium of variable ionic strength (no NaClO₄, pH 3). Solutions maintained in constant-temperature baths for more than seven half-lives of the approach to equilibrium reaction were quenched to 25° and examined spectrophotometrically in 5.00-cm cells on a Beckman DU equipped with a Gilford photometer unit or in 1.00-cm cells on a Cary Model 14 equipped with a 0.0–0.2-absorbance unit slidewire. Total cobalt complex concentrations were chosen in the range from 5×10^{-4} to 1.5×10^{-3} M. Sodium chloride concentrations were varied from 0.03 to 0.7 M. The wavelengths examined were 555 and 530 m μ .

Kinetic Studies. The rate at which reaction 1 approaches equilibrium was examined in the case that $\text{X} = \text{Cl}^-$ in the same media as those employed in the equilibrium studies. The experiments were carried out at 45.0° in the thermostated cell chamber of a Cary 14 spectrophotometer using 1.00-cm cells and a 0.0–0.2-absorbance unit slidewire. Good pseudo-first-order rate plots were obtained over more than two half-lives of the reaction. Rates of the reaction of $[\text{Co}(\text{NH}_3)_5\text{OH}_2]^{2+}$ with thiocyanate (which goes to "completion") were examined under similar conditions except that the pH was 5, the spectrophotometer was a Beckman DU, and the wavelength used was 490 m μ .

Ion-Association Study. The extent of association between $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$ and Cl^- was explored by analysis of the enhancement of ultraviolet absorption by the complex at 230 m μ at 25° (pH 3, $\mu = 1.00$). Data were analyzed by the method of Newton and Arcand as employed by Evans and Nancollas.⁸ The concentration of the cobalt complex was 1×10^{-4} M, and the chloride concentration was varied from 0.003 to 0.5 M.

Results

The first column of Table II presents the equilibrium concentration ratio $[\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}]/[\text{Co}(\text{NH}_3)_5\text{Cl}^{2+}]$ as a function of chloride concentration. Rates of approach to equilibrium are also collected in Table II.

Table II. Equilibrium Concentration Ratios and Rates of Approach to Equilibrium as a Function of Chloride Concentration

[Cl ⁻], M	[RCl]/[ROH ₂] ^a		k , sec ⁻¹	
	μ variable	$\mu = 1.00$	μ variable	$\mu = 1.00$
0.05	0.26	0.14	2.8×10^{-4}	0.7×10^{-4}
0.1	0.44	0.25	3.2×10^{-4}	1.7×10^{-4}
0.2	0.68	0.42	3.7×10^{-4}	2.7×10^{-4}
0.3	0.84	0.52	4.1×10^{-4}	3.2×10^{-4}
0.4	0.92	0.57	4.4×10^{-4}	3.6×10^{-4}
0.5	0.98	0.62	...	3.8×10^{-4}
0.6	...	0.67	...	3.9×10^{-4}

^a Rate of approach to equilibrium.

Since chloride is in excess, these rates are resolved into pseudo-first-order forward (acid hydrolysis) and reverse (anation) rates with the aid of the equilibrium data and the formalism for opposed first-order reactions.⁹ The acid hydrolysis rates are shown in Figure

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(9) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, p 186.

(5) C. H. Langford, *Inorg. Chem.*, **4**, 265 (1965).

(6) (a) C. H. Langford and H. B. Gray, "Ligand Substitution Processes," W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1. (b) The term interchange was introduced by H. Taube and F. A. Posey, *J. Am. Chem. Soc.*, **75**, 1463 (1953).

(7) (a) F. Basolo and R. K. Murmann, *Inorg. Syn.*, **4**, 171 (1953); (b) A. Werner and E. H. Müller, *Z. Anorg. Chem.*, **22**, 101 (1900).

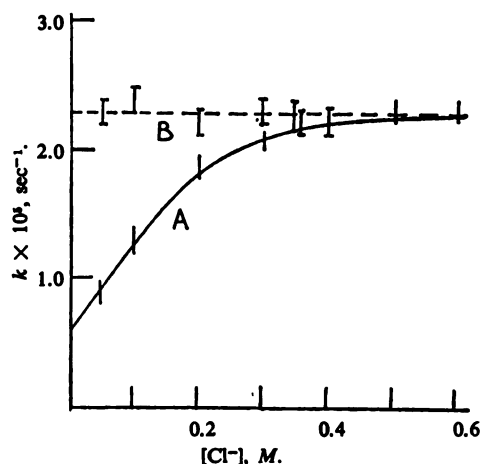


Figure 1. Rates of acid hydrolysis of the chloropentaamminecobalt(III) ion as a function of chloride concentration: (A) constant ionic strength, (B) variable ionic strength (no perchlorate added).

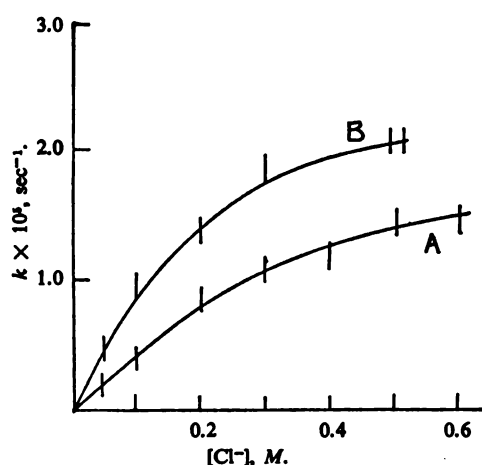


Figure 2. Rates of formation of the chloropentaamminecobalt(III) ion from the corresponding aquo complex as a function of chloride concentration: (A) constant ionic strength, (B) variable ionic strength (no perchlorate added).

and the anation rates in Figure 2. Since anation by thiocyanate ion goes to completion, only anation is given. They appear in Figure 3. According to the dissociative interchange mechanism described in eq 3, the chloride or thiocyanate dependence (X^- dependence) of the observed pseudo-first-order rate constants, k' , is given by eq 4, which employs

$$k' = \frac{kK_a[X^-]}{1 + K_a[X^-]} \quad (4)$$

notation of (3). The distinct curvature in Figures 2 and 3 indicate that the term $K_a[X^-]$ is not small.

A trial-and-error analysis based on a least-squares criterion was employed to find best choices of the parameters K_a and k , the outer-sphere association constant, and rate constant for interchange, respectively. Values of the parameters with the associated standard deviations are given in Table III along with interchange rate constants from the work of Taube and his collaborators.^{6b,10}

The value of K_a for association of chloride with $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$ was not checked independently at 45°

(a) W. Schmidt and H. Taube, *Inorg. Chem.*, **2**, 698 (1963); (b) J. Hunt and H. Taube, *J. Am. Chem. Soc.*, **80**, 2642 (1958).

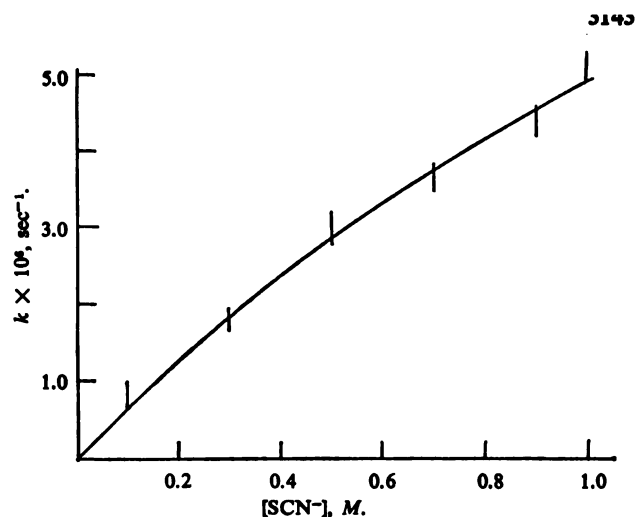


Figure 3. Rates of formation of the thiocyanatopentaamminecobalt(III) ion from the corresponding aquo complex as a function of thiocyanate concentration at constant ionic strength.

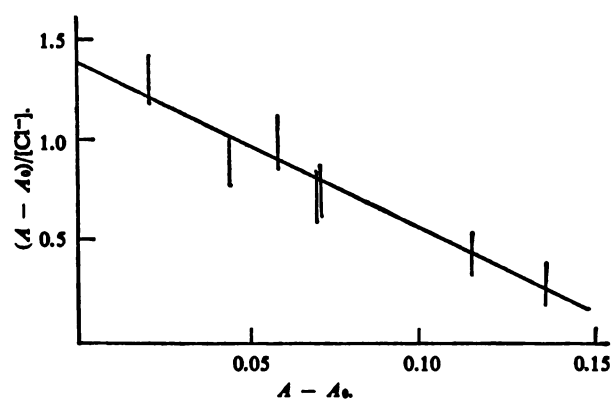


Figure 4. Determination of the outer-sphere association constant of chloride with the aquopentaamminecobalt(III) ion by the method of ref 8. The enhancement of absorbance at 230 m μ ($A - A_0$) is studied as a function of chloride concentration (25.0°, $\mu = 1.00$, and pH 3).

because of the relatively rapid formation reaction. However, it was measured at 25° utilizing the effect of chloride on the absorption spectrum of $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$ at 230 m μ . A plot of the function $(A - A_0)/[Cl^-]$

Table III. Conditional Equilibrium Constants for Formation of Outer-Sphere Complexes (K_a) and Rate Constants for Formation of Inner-Sphere Complexes from Outer-Sphere Complexes*

X	K_a , M^{-1}	k , sec^{-1}	Std dev	k/k (water exchange)	Ref
SO_4^{2-}	...	2.4×10^{-5}		0.24	6b
Cl^-	3.1	2.1×10^{-5}	0.078×10^{-5}	0.21	This work
SCN^-	0.43	1.6×10^{-5}	0.016×10^{-5}	0.16	This work
H_2PO_4^-	...	0.77×10^{-5}		0.13	10a
H_2O	...	1.0×10^{-4}		...	10b
		5.8×10^{-5}			10b

* At 45° except where noted. ^b At 25°.

$[Cl^-]$ against A , where A is the absorbance at a given $[Cl^-]$ and A_0 is the absorbance in the absence of chloride, should be linear with the slope equal to $-K_a$ and the intercept equal to $K_a A_1$, where A_1 is the absorbance of the ion pair.⁷ This plot is shown in Figure 4. The

slope yields a value of $K_a = 3.2 \pm 0.3$ in good agreement with the value from analysis of kinetic data and with values obtained at other wavelengths. Note that the results of Evans and Nancollas⁸ suggest that the result should be insensitive to temperature, a view which receives direct support from equilibrium studies of the $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$ -chloride system reported elsewhere.¹¹

Discussion

1. The Importance of Ion Association. Since the extent of ion association between triply charged cobalt ammine complexes and simple anions has been a subject of some controversy,¹² we note that substantial *specific* ion effects are seen in all of the equilibrium and kinetic curves. This would seem to justify the approach adopted here. Additional support is derived from independent spectrophotometric measurement of outer-sphere association between $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$ and Cl^- which gives a value of $K_a = 3.2$ at 25° and unit ionic strength in reasonable agreement with the value in Table III. However, *it must be emphasized that the "constants" reported are in no sense thermodynamic equilibrium constants.* They simply provide a convenient measure of the extent of ion association in these media and indicate anion concentrations at which the equilibrium is "saturated" and a limiting rate for complex formation is reached.

2. The Values of "Limiting" Complex Formation Rates. Compare the first-order rate constants in Table II. The limiting rates for complex formation for the outer-sphere complexes $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+} \cdots \text{SO}_4^{2-}$ and $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+} \cdots \text{H}_2\text{PO}_4^-$ are reasonably accurately known since the association constants, K_a , proved large enough to permit fairly unambiguous determinations. They are seen to differ by a factor of about 2, being respectively 0.24 and 0.13 times the water exchange rate. In order to assess the role of the entering group in the transition state for complex formation, it was desirable to obtain similar rate constants for significantly different entering groups. The values have proved more difficult to obtain because of smaller K_a values and are presumably less accurately determined. But, the values for $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+} \cdots \text{Cl}^-$ and Co -

$(\text{NH}_3)_5\text{OH}_2^{2+} \cdots \text{NCS}^-$ are estimated to be 0.21 and 0.16 times the water exchange rate. Thus, the variation in these first-order rate constants is *less than a factor of 2* for formation of a series of complexes differing in stability by about two powers of ten. That is, with nucleophiles of charge -2 or -1 and donor atoms varying on Cl, O, and N, only very small rate differences are detected. These results lend substantial support to the view that the absence of a five-coordinate intermediate in these reactions does not imply assistance from an entering nucleophile in the activation process. Activation is apparently dissociative (d).

3. Comparison to Water Exchange Rate. The most striking feature of the results is that *all* complex formation rates are *less than* the water exchange rate by a factor near 5. Since anion entry rates are so similar, this might be considered surprising, but it is easily rationalized under the idea of dissociative interchange (I_d). If the transition state is reached by very substantial weakening of the bond to the leaving group but the system does not have access to any reasonably stable five-coordinate state, it must stabilize by adding the immediately available ligand. Since the majority of outer-sphere sites are still occupied by water molecules in the 1:1 outer-sphere complex (ion pair) between $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$ and an anion, the most probable fate of an activated complex is recombination with an outer-sphere water molecule. Except in the study of water exchange (when all outer-sphere sites are occupied by water), water exchange is an undetectable, fruitless process. Thus, anion entry (complex formation) is expected to proceed at a rate less than water exchange and governed by the probability that the anion in the 1:1 outer-sphere complex occupies the site adjacent to the leaving inner-sphere water molecule. The factor of 5 seems reasonable.

Finally, it is important to note that the relationship between interchange complex formation rates and solvent exchange rates discussed for the $\text{Co}(\text{NH}_3)_5\text{OH}_2^{2+}$ system is not an isolated example. Murray and Barraclough observed a sulfate entry rate 0.25 times the water exchange rate for formation of *cis*- $\text{Co}(\text{en})_2\text{OH}_2^+$ - SO_4 ,¹³ and Earley and Duffy¹⁴ observed entry rates for chloride and thiocyanate of about 5% of the water exchange rate in studies of formation of $\text{Cr}(\text{NH}_3)_4\text{X}^{2+}$ ($\text{X} = \text{Cl}^-, \text{SCN}^-$).

(13) R. Murray and C. Barraclough, *J. Chem. Soc.*, 7047 (1965).

(14) J. E. Earley and N. V. Duffy, *J. Am. Chem. Soc.*, **89**, 272 (1967).

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Bis(pyridine)boronium Salts. Syntheses and Formation Kinetics

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Contribution from the Department of Chemistry, University of Florida, Gainesville, Florida 32601. Received August 11, 1966

Abstract: Salts of bis(pyridine)boronium ion have been synthesized in pyridine by four routes: from trimethylamine borane and iodine, from trimethylamine borane and bis(pyridine)mercury(II) chloride, from sodium borohydride and iodine, and from trimethylamine chloroborane. In addition, the B-deuterated ion has been prepared. The reaction between trimethylamine borane and iodine exhibits a deuterium isotope effect, which was established from competitive rates and from the reaction rates of the hydrogen and deuterium compounds ($k_H/k_D = 2.0$). A reaction mechanism is discussed.

Boronium salts, where two tertiary amines are coordinated to a BH_3^+ group, have been reported by Muetterties.¹ The basic structure was produced from an amine borane by reaction with an ammonium salt or, alternately, with diborane or $B_2H_6^{2-}$ salts. Either method requires relatively high temperatures and the use of high pressure. In our hands, the first method proved to be quite sensitive to reaction conditions, producing yield-reducing side reactions. The second method suffers from relatively low yields (~25%) and from the convenience of handling a reactive gas or preparing the intermediate borane anion.

We wish to report several new synthetic approaches to boronium salts, exemplified by the bis(pyridine)boronium ion, which allow synthesis from readily obtained starting materials, under mild and convenient conditions, and in high yield.

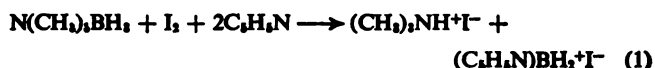
Experimental Section

Materials. Trimethylamine borane was used as obtained from Callery Chemical Co. Some lots were purified by sublimation. Sodium borohydride and sodium borodeuteride were supplied in good purity by Metal Hydrides, Inc. All other compounds were reagent-grade materials and were used without further purification. Trimethylamine monochloroborane was prepared in 50% yield from trimethylamine borane and concentrated aqueous HCl mixed with benzene.^{2,3} It was recrystallized from CCl_4 by slow addition of hexane: mp 82–84°, lit.⁴ 85°. Alternately, the material could be prepared by passing anhydrous HCl into a trimethylamine borane solution in benzene.

Diborane- d_6 was prepared on the vacuum line from 1 g of sodium borodeuteride and boron trifluoride in diglyme solution.⁵ The gas was allowed to react with excess trimethylamine to afford deuterated trimethylamine borane. After vacuum sublimation it melted sharply at 91°. The infrared spectrum agreed well with the published data.⁶ The relative proportions of B–H and B–D bonds were established by comparison of the absorbancies at 2370 and 1790 cm^{-1} after calibration with a known mixture. The compound was 93% deuterated.

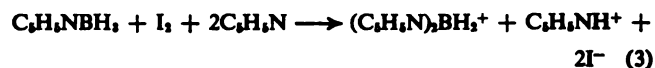
Preparation of Bis(pyridine)boronium Ion. From Trimethylamine Borane and Iodine. Trimethylamine borane, 3.64 g (50.0 mmoles), was dissolved in 30 ml of pyridine, and solid iodine, 12.7 g (50.2 mmoles), was added in small portions over a 15-min period. An exothermic reaction started immediately and was finished after 1 hr while warming the mixture gradually to a final temperature of 70°. After cooling, the precipitate of trimethylammonium iodide was filtered off, and the filtrate was evaporated at room temperature,

affording 14.7 g of bis(pyridine)boronium iodide (99% yield). The ammonium salt after washing with benzene and a small amount of ether weighed 8.75 g (94% yield). The identity of the ammonium salt was established by its infrared spectrum and its iodide analysis. Reaction had thus proceeded according to the equation



2. From Trimethylamine Borane and Bis(pyridine)mercury(II) Chloride. Trimethylamine borane, 3.76 g (56 mmoles), and mercury(II) chloride, 13.06 g (48.1 mmoles), were heated with 50 ml of pyridine to light reflux for 5 hr. During this period the solution turned cloudy and eventually deposited liquid mercury. After filtering off the metallic mercury (9.266 g, 96% recovery), 20 ml of benzene and 20 ml of carbon tetrachloride were added to the filtrate, yielding 14.42 g of light yellow solid as a precipitate. On adding excess potassium hexafluorophosphate to a water solution of this solid there was recovered, after washing with water and ether, 5.40 g (26.2 mmoles) of $(C_5H_5N)_2BH_3PF_6$ for a 55% yield of boronium salt. The compound was identical in spectrum and melting point with preparations from the iodide salt.

3. From Sodium Borohydride and Iodine. (a) Sodium borohydride (94% hydride purity), 1.80 g (44.8 mmoles), was slurried with 25 ml of pyridine. While this solution was stirred in an ice bath, an 0.00984 M iodine solution was very slowly added. The iodine color was discharged immediately while a gas, presumably hydrogen, evolved. After 22.5 ml (22.2 mmoles) of iodine solution had been added, the reaction rate of iodine decreased abruptly and gas evolution ceased. The solution was now heated while more iodine was added; a persistent iodine color was obtained after an additional 44.5 ml (43.7 mmoles) of iodine solution had been added. The amounts of iodine used correspond closely to the quantities calculated from the equations representing two successive and separated reactions steps.



(b) Accordingly, in a similar experiment, the reaction was stopped after the first stage, the excess pyridine was evaporated, and the resulting residue of white solid and yellow liquid was extracted with carbon tetrachloride. After evaporation of the solvent there was obtained a 99% yield of pyridine borane, identical in infrared spectrum with an authentic sample. The solid, insoluble in carbon tetrachloride, was sodium iodide contaminated with water and pyridine.

Bis(pyridine)boronium iodide was isolated from reaction 3 by precipitating it with carbon tetrachloride. Preparations by this procedure always contained varying amounts of carbon tetrachloride which could not be removed by pumping.

4. From Trimethylamine Monochloroborane. Trimethylamine monochloroborane, 0.551 g (5.19 mmoles), was refluxed with 15 ml of pyridine for 45 min. The mixture was evaporated to dryness and the water-soluble residue (0.954 g) was converted to the hexafluorophosphate salt by precipitation with excess NH_4PF_6 in 15 ml of water (crude yield, 0.936 g). A portion of this was recrystallized from water to give pure $(C_5H_5N)_2BH_3PF_6$, mp 114.5–115°, in 41%

(1) (a) N. E. Miller and E. L. Muetterties, *J. Am. Chem. Soc.*, **86**, 1033 (1964); (b) E. L. Muetterties, *Pure Appl. Chem.*, **10**, 53 (1965).

(2) K. Borer and J. Deuring, British Patent 881,376 (Nov 1, 1961).

(3) J. W. Wiggins, Ph.D. Dissertation, University of Florida, 1966.

(4) H. Noeth and H. Beyer, *Chem. Ber.*, **93**, 2251 (1960).

(5) Vapor pressure, 239 mm at -112° ; lit. 238.5 mm [A. B. Burg, *J. Am. Chem. Soc.*, **74**, 1340 (1952)].

(6) B. Rice, R. J. Galiano, and W. J. Lehmann, *J. Phys. Chem.*, **61**, 1222 (1957).

Table I. Analyses (%)

		C	H	N	B	P or As	I or F	Mp, °C
$C_{10}H_{12}N_2BI$	Calcd	40.31	4.06	9.40	3.63		42.60	120–125
	Found	40.08	4.28	9.13	3.49		41.76	
$C_{10}H_{12}N_2BPF_6$	Calcd	38.01	3.82	8.87	3.42	9.80	36.05	116
	Found	37.92	3.84	8.92	3.66	9.52	35.80	
$C_{10}H_{12}N_2BAsF_6$	Calcd	33.37	3.36	7.78	3.01	20.87	31.67	110.5–111
	Found	33.60	3.48	7.61	3.20	20.97	31.47	

recovery. The maximum yield of chloride salt, according to the eq 4 was thus 88%; the minimum over-all yield of pure PF_6^- salt was 25%.



Derivatives. The halide salts are very soluble in water as well as in many organic solvents (alcohols, acetone, acetonitrile, chloroform, methylene chloride) but insoluble in carbon tetrachloride, ether, or pentane. The complex fluorides show similar solubility relations but are much less soluble in cold water.

The halides readily absorb water from the atmosphere. The anhydrous iodide (0.5143 g, 1.72 mmoles) was exposed in a closed container to saturated water vapor at room temperature. After 30 hr the sample had come to constant weight, 0.5438 g. The calculated weight for a monohydrate is 0.5453 g. Simultaneously there appeared in the infrared spectrum a doublet at 3500 and 3430 cm^{-1} and a sharp band at 1580 cm^{-1} , and two bands at 760 and 740 cm^{-1} . The first three bands apparently correspond to the stretching and bending modes of water, respectively, whereas the latter two absorptions may be caused by librational modes of lattice water.⁷ The absorbed water could be removed quantitatively by evacuation over P_2O_5 .

The iodide or chloride was readily converted to the less soluble perchlorate (mp 97–99°), hexafluorophosphate, or hexafluoroarsenate by precipitating these salts from aqueous solution with $NaClO_4$, NH_4PF_6 , or $KAsF_6$, respectively. The latter two salts are easily recrystallized from hot water. The chloride salt was obtained from the iodide by reaction with a slight excess of mercury(II) chloride in aqueous solution, which resulted in precipitation of HgI_2 . Excess Hg^{2+} was removed immediately by shaking with metallic mercury in order to avoid oxidation of the boronium ion. On evaporation of the filtered solution, the chloride was obtained in 30% yield as the hydrated salt, mp 59–62°.

On shaking aqueous solutions of the iodide with CCl_4 , there resulted a white precipitate which proved to be very similar to the product obtained when the boronium salt was precipitated with CCl_4 from pyridine solution. The materials showed all the infrared absorption bands of the pure boronium salt but contained from 0.25 to 0.9 mole of CCl_4 per mole of $(C_5H_5N)_2BH_2I$. Carbon tetrachloride could be removed either by heating under vacuum above the melting point (110–125°) or by distilling a solution; depending on the water content of the system, either the hydrate or the anhydrous salt was thus obtained.

Preparation of Deuterated Bis(pyridine)boronium Hexafluorophosphate. Trimethylamine borane- d_3 (1.00 mmole) in 5 ml of pyridine was allowed to react with iodine (0.98 mmole) for 40 hr at 25°. After evaporating the solvent below room temperature, the resulting iodide salt was converted to the hexafluorophosphate derivative in the usual manner. The amount of deuteration on boron in the recrystallized product (mp 114.5–115°) was the same as in the starting material, as evidenced by the infrared spectrum.

In an abortive attempt to deuterate the boronium salt by exchange, 1.15 mmoles of the iodide salt was dissolved in 1 ml of D_2O ; the relative intensity of the B–H absorption at 2480 cm^{-1} remained unchanged over 24 hr. at room temperature. Neither did there appear an absorption at 1900 cm^{-1} , characteristic of B–D, even when a solution acidified (pH ~1) with thionyl chloride was left at room temperature for 3 days.

Characterization. All the boronium salts had similar infrared spectra, except for the expected differences caused by the known absorptions of the complex anions. The main features are the two bands, 2480 and 2380 cm^{-1} , showing relatively high wavenumbers for B–H bonds, which are shifted to 1900 and 1760 cm^{-1} , respectively, in the deuterated compound. The B–H deformations appear at

1160 (B–D, 915) and 1065 cm^{-1} (B–D, probably masked by anion and solvent absorptions). In addition, a sharp absorption at 1640 cm^{-1} indicates the presence of the pyridine ring.

In the ultraviolet spectrum there are three bands in all the salts with similar molar absorptivities, a : 2538 Å, $a = 6.90 \times 10^3$; 2591 Å, $a = 7.58 \times 10^3$; 2657 Å, $a = 5.01 \times 10^3$. Elemental analyses are given in Table I.

The cation, like the bis(trimethylamine) compound previously reported,¹ is stable toward acid or base; no change in the ultraviolet spectrum was noticed in 0.1 M HCl or 0.1 M NaOH, even after a week at room temperature.

The B^{11} nuclear resonance spectra were kindly obtained by Dr. Brey of this department at 19.3 Mc in CH_2Cl_2 . The undeuterated and deuterated salts showed identical shifts of +16.2 ppm relative to trimethyl borate. Because of the broadness of the resonance, the B–H and B–D coupling constants could not be determined.

The proton spectrum, obtained with a Varian A-60A spectrometer at ambient temperature, showed the expected pattern for the pyridine-ring hydrogens: a doublet, a triplet, and a triplet with relative integrated intensities of 2.0:1.0:2.0. The resonances had considerable fine structure and were, in water solution, centered about –8.78, –8.35, and –7.35 ppm, respectively, relative to external tetramethylsilane. In $CDCl_3$ with internal tetramethylsilane, the resonances appeared at –9.08, –8.38, and –8.00 ppm, respectively. No resonances arising from boron-attached protons could be detected in either solvent.⁸

Deuterium Isotope Effect in Trimethylamine Borane–Iodine Reaction. 1. **Competitive Reactions.** Normal and deuterated (1.00 mmole of each) trimethylamine boranes in 5 ml of pyridine were mixed with 0.99 mmole of iodine; after 8 hr at room temperature (24°) the iodine color had disappeared. Following removal of the solvent below room temperature, the hexafluorophosphate salt was prepared as above but not recrystallized, and the deuterium content was determined by an infrared analysis of CH_2Cl_2 solutions from the ratio of absorbancies at 2460 and 1890 cm^{-1} .⁹ In a second experiment, a similar mixture was heated for 3.5 hr at 90° prior to adding iodine to the cooled solution. The reaction in this instance was completed in less than 3.5 hr. The results are given in Table II and are compared with the results calculated from the rate constants.

Table II.

Initial concn, mmole		I_2 , mmole	Final ratio BH:BD
BH_3	BD_3^a		
1.05	1.04	0.99	1.84
1.01	0.96	0.99	1.72 ^c
1.00	1.00	1.00	1.77 ^c

^a 93%. ^b Calculated from k_B/k_D . ^c Heated prior to reaction.

2. **Specific Rates in Pyridine Solution.** Weighed amounts of normal or deuterated trimethylamine borane were dissolved in 3.00 ml of pyridine in the absorption cell, 100 μ l of approximately 0.2 M I_2 in pyridine was immediately injected, and the change of absorbance at 400 $m\mu$ was recorded using a Beckman DB-G spectrophotometer with scale expansion attachment and a logarithmic recorder. The data gave an excellent fit for a reaction first order in iodine concentration, over a 15-fold change, provided that the mixture was first allowed to react completely, and data were taken

(8) In bis(trimethylamine)boronium iodide the quartet arising from the BH_3 group is also very broad and barely detectable.

(9) The accuracy of the measurement was checked by calibration with mixtures of known deuterium content.

(7) J. van der Elsken and D. W. Robinson, *Spectrochim. Acta*, **17**, 1249 (1961).

Table III

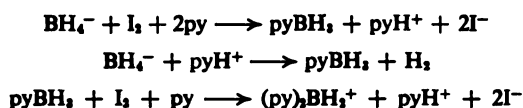
Compound	Concn, <i>M</i>	1st-order rate constant $\times 10^4$, sec^{-1} ^a	2nd-order rate constant $\times 10^3$, $\text{l. mole}^{-1} \text{sec}^{-1}$
(CH ₃) ₃ NBH ₃	0.054	10.0	1.85
		10.3	1.91
(CH ₃) ₃ NBH ₃	0.038	7.21	1.90
		7.55	1.99
(CH ₃) ₃ NBH ₃	0.028	5.17	1.85
		5.46	1.95
		Average	1.90
(CH ₃)NBD ₃	0.054	4.89	0.906
		5.24	0.970
		Average	0.938
		$k_H/k_D = 2.03$	

^a 24 ± 1°.

after a second portion of iodine was injected.¹⁰ The rate dependence on trimethylamine borane concentration agreed well with a first-order dependence on this component. The results are listed in Table III.

Discussion

The formation of bis(pyridine)boronium ion from sodium borohydride occurs *via* a clear-cut reaction sequence involving hydride transfer from borohydride to iodine,¹¹ trapping of the BH₃ group by the solvent base, and a second similar sequence involving the intermediate pyridine borane. Hydride transfer to the iodine species in pyridine results in iodide ion and pyridinium ion, which also produces pyridine borane in a side reaction with borohydride.¹² The processes can be represented by

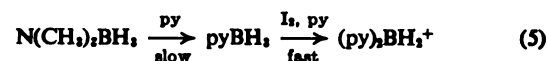


The great difference in reactivity between BH₄[−] and pyBH₃ toward electrophilic attack by either iodine or pyH⁺ makes it possible to observe a clean separation of the reaction steps. The data also imply that the borohydride-pyridinium reaction proceeds more rapidly than the pyridine borane-iodine reaction; otherwise, more than the observed stoichiometric ratio of iodine should have been used at the point where hydrogen evolution had stopped.

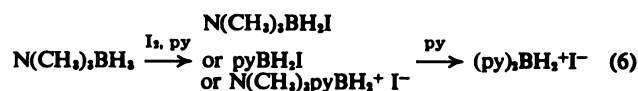
The foregoing suggests a somewhat similar sequence in the reaction of trimethylamine borane with iodine. But since in this reaction the bispyridine ion is obtained in high yield, the question arises as to which stage of the reaction the necessary displacement of trimethylamine occurs: before or after attack on the B-H bond by iodine.

In separate experiments it was verified that pyridine borane reacts with the halogen much more rapidly than trimethylamine borane.¹³ Thus, the displacement

would have to be rate determining if it occurred prior to reaction with iodine (eq 5)



The alternate path would produce N(CH₃)₃BH₃I, N(CH₃)₃pyBH₃⁺, or pyBH₃I as intermediates, and, finally, (py)₂BH₃⁺ (eq 6). In view of the results ob-



tained with trimethylamine chloroborane, the proposed iodoborane intermediates could hardly be expected to survive long without iodide solvolysis in the reaction medium, but one might expect the mixed boronium ion to be capable of isolation.¹⁴ Nevertheless, it was not possible to isolate this material even from mixtures which were not heated. If this compound indeed appears as an intermediate, it is also solvolyzed rather rapidly.¹⁵

The experiments with the deuterated borane, however, do allow a distinction between paths 5 and 6. The rate-determining transamination should not be sensitive to deuterium substitution on boron, whereas a hydride transfer should exhibit a pronounced isotope effect.¹⁶ Moreover, in eq 5 the rate of disappearance of iodine should be independent of iodine concentration, but path 6 would predict a simple rate dependence on iodine. The experimental results clearly show that the rate depends on the iodine concentration (first order) and that there is a large deuterium isotope effect ($k_H/k_D = 2.0$). The directly determined rate constants lead to a calculated isotope distribution in the product from the competitive reactions in most satisfactory agreement with the observed distribution. It is therefore concluded that the initial reaction step is a hydride abstraction from trimethylamine borane and that this step is the rate-determining one.

The maximum value for the ratio k_H/k_D can be estimated from the B-H and B-D stretching vibrations under the assumption that the rate constants differ primarily because of different zero-point energies in the ground state which are lost on stretching the bonds in the transition state. The ratio calculated from the experimental frequencies for trimethylamine borane is 4.4 at 25°. One can interpret the substantially lower experimental value, $k_H/k_D = 2.0$, as being the consequence of incomplete loss of zero-point energy in the transition state, corresponding to the retention of some bonding between boron and hydrogen. Nevertheless, the present value constitutes the largest isotope effect for reactions on B-H bonds which have come to our attention.^{17,18}

It now seems plausible to view the reaction with the mercury(II) complex as analogous to the above examples: hydride transfer from the borane to the mer-

(10) In the initial reaction log *A* vs. *t* plots had a slight curvature; the slope of log (rate) vs. log *A* plots indicated an apparent initial order of 0.8.

(11) G. F. Fueguard and L. H. Long, *Chem. Ind. (London)*, 471 (1965), report a high yield of diborane from NaBH₄ and I₂ in diglyme.

(12) P. A. Chopard and R. F. Hudson, *J. Inorg. Nucl. Chem.*, 25, 801 (1963); D. F. Gaines and R. Schaeffer, *J. Am. Chem. Soc.*, 85, 395 (1963); H. Noeth and H. Beyer, *Chem. Ber.*, 93, 928 (1960); G. W. Schaeffer and E. R. Anderson, *J. Am. Chem. Soc.*, 71, 2143 (1949).

(13) Pyridine borane in fivefold excess over iodine reacted completely in 15 min; trimethylamine borane under the same conditions required more than 2.5 hr.

(14) Muetterties¹ reports displacement at 180° for 10 hr.

(15) We have prepared several salts of NMe₃pyBH₃⁺; it is converted to (py)₂BH₃⁺ in boiling pyridine within 5 min.

(16) K. Wiberg, *Chem. Rev.*, 55, 713 (1955).

(17) $k_H/k_D = 1.45$ for H₂ elimination in (CH₃)₂HNBH₃; ref 3, to be published.

(18) $k_H/k_D = 1.52$ for hydrolysis of pyB(C₆H₅)₃; H. M. F. Hawthorne and E. S. Lewis, *J. Am. Chem. Soc.*, 80, 4296 (1958).

cury atom, followed by decomposition of the complex into atomic mercury, the ligands, and a proton. The question whether the mercury-attached ligand can transfer simultaneously to the boron atom, or whether it leaves the reaction sphere, at present remains un-

resolved, but we hope to contribute in the future to the solution of this problem.

Acknowledgment. Partial support of this research by the National Institutes of Health under Grant GM13650 is gratefully acknowledged.

Spectra and Structure of Some Transition Metal Poly(1-pyrazolyl)borates

J. P. Jesson, S. Trofimenko, and D. R. Eaton

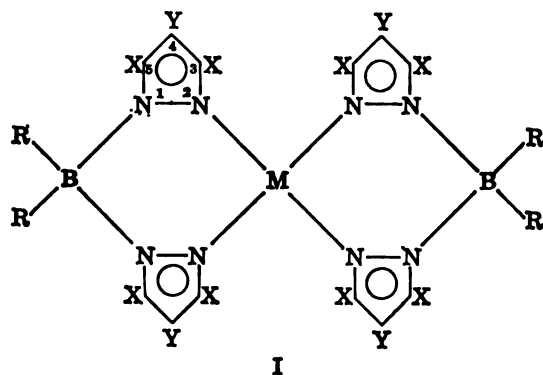
Contribution No. 1265 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898.

Received December 7, 1966

Abstract: Spectral and magnetic data are presented for a new family of transition metal chelates involving poly(1-pyrazolyl)borate ligands. These molecules behave as univalent ligands which can be either bidentate or tridentate depending on the number of pyrazolyl groups. Neutral complexes with the ions Mn^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} have been studied. The bidentate Ni^{2+} and Cu^{2+} complexes are essentially planar. Other complexes with bidentate ligands are tetrahedral. The tridentate ligands give rise to octahedral complexes. Thus the poly(1-pyrazolyl)borate ligands provide an opportunity for physical studies of a range of complexes with different geometries and different metal ions but with essentially constant ligand characteristics. The results of such a study are reported.

In another publication¹ the synthesis and properties of a number of poly(1-pyrazolyl)borate transition metal complexes have been reported briefly. The series of complexes with divalent transition metal ions is of particular interest in that these ligands offer the opportunity of forming chelates of the same metal ion with different geometries. In the present paper, nuclear magnetic resonance, magnetic susceptibility, and electronic spectral data are described for complexes with the ions Mn^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} . Both bidentate and tridentate ligands are involved, and the physical evidence presented suffices to characterize the geometries of the complexes. In the following paper the spin equilibria found with the Fe^{2+} complexes will be discussed in more detail.²

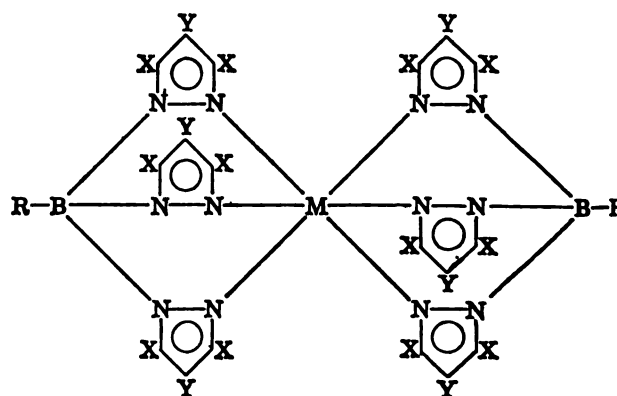
The complexes fall into two general classes. It is shown that in the first of these the bis(1-pyrazolyl)borate unit behaves as a bidentate chelating ligand and that the resulting compounds have structures of type



I

I, where R is H, alkyl, or aryl, and the pyrazolyl residues may contain substituents. We adopt the convenient abbreviation $M[R_2B(pz)_2]_2$ and will indicate specifically when substituted pyrazolyl groups are involved. These complexes may have either an essentially planar configuration about the metal (Ni^{2+} , Cu^{2+}) or an essentially tetrahedral array (Mn^{2+} , Fe^{2+} , Co^{2+} , Zn^{2+}).

In the second class, tridentate ligands are involved as exemplified by structure II, and this structure occurs



II

with all six metals. We adopt the abbreviation $M[R_2B(pz)_3]_2$. R may be an alkyl or aryl group or another 1-pyrazolyl residue. Here we are dealing with a basically octahedral array of nitrogen atoms about the metal. Molecular models indicate that these tridentate complexes can be formed without strain, and the resulting molecule is highly symmetrical and compact. When R, X, and Y are hydrogen, molecules of type II have a structure belonging to the D_{3d} point group, and a predominantly octahedral ligand field is expected with a pronounced trigonal component. The evidence on

(1) S. Trofimenko, *J. Am. Chem. Soc.*, **88**, 1842 (1966).
(2) J. P. Jesson, S. Trofimenko, and D. R. Eaton, *ibid.*, **89**, 3158 (1967).

Table I. Room-Temperature Effective Moments in Solution (BM)

	Mn	Fe	Co	Ni	Cu
M[H ₂ B(pz) ₂] ₂	5.99 ± 0.02 ^a	5.20 ± 0.02 ^a	4.53 ± 0.05 ^b	0 ^b	1.9 ± 0.1 ^b
M[HB(pz) ₂] ₂	6.11 ± 0.05 ^b	... ^c	5.40 ± 0.05 ^b	3.24 ± 0.05 ^b	2.12 ± 0.15 ^b
M[B(pz) ₂] ₂	5.98 ± 0.05	0	5.24 ± 0.10	3.22 ± 0.05	2.05 ± 0.15

^a Moment measured for complex I (X = CH₃, Y = H). ^b Measured in dichloromethane solution. All others measured in chloroform. ^c Moment is strongly temperature dependent.

which the individual complexes are assigned their various structures will be considered in the light of magnetic and spectral data.

The optical data have been analyzed in terms of the crystal-field theory, and consideration is given to the position of the ligands in the spectrochemical and nephelauxetic series.

Epr studies of the Co²⁺ compounds have also been made and have been reported elsewhere.³ The evidence for the structures postulated above will first be summarized and the various physical measurements then discussed in detail.

Summary of Evidence for Geometric Structures

The assignment of octahedral geometry to complexes of the form M[HB(pz)₂]₂ and M[B(pz)₂]₂ is based on the following observations.

1. All the complexes M[HB(pz)₂]₂ have been shown to be isomorphous. They are stable, well-characterized compounds with analyses and molecular weights corresponding closely to the formulas given.

2. The room-temperature effective magnetic moments of the pairs M[HB(pz)₂]₂, M[B(pz)₂]₂ are closely similar and consistent with those found for octahedral coordination in the literature.

3. The electronic spectra of the pairs M[HB(pz)₂]₂, M[B(pz)₂]₂ are closely similar and agree well with other octahedral spectra in the literature.

4. The diamagnetism of Fe[B(pz)₂]₂ gives strong evidence for octahedral coordination. Low-spin ferrous complexes are relatively common, the six d electrons filling the t_{2g} orbitals to give a ¹A_{1g} ground state.

5. Proton nuclear resonance for the Co complexes shows that the six pyrazolyl residues in Co[HB(pz)₂]₂ are equivalent, and the additional two in Co[B(pz)₂]₂ are different. The resonances of the six equivalent pyrazole residues are in approximately the same positions for the two complexes.

6. Single crystal epr data for the Co²⁺ complexes can only be interpreted in terms of an axially distorted octahedral crystal field about the cobalt atom.³ The magnetically dilute powder epr spectra of Co[HB(pz)₂]₂ and Co[B(pz)₂]₂ are very similar.

7. The fact that the tris- and tetrakis(1-pyrazolyl)-borate ions are tridentate, uninegative ligands provides a ready explanation of their inability to form neutral chelates with trivalent metal ions of the type usually found for bidentate ligands. Thus iron(III) reacts with B(pz)₂⁻ forming the complex ion Fe[B(pz)₂]₂⁺ isolable as the nitrate or hexafluorophosphate.⁴

Turning to the remaining compounds, molecular models indicate that [H₂B(pz)₂]⁻ can act only as a bi-

dentate ligand, and the complexes of the form M-[H₂B(pz)₂]₂ give molecular weights and analyses corresponding closely to this formula. They are therefore four-coordinate and either tetrahedral or planar. The evidence on which decisions have been made between the alternatives is summarized below.

Ni[H₂B(pz)₂]₂. The diamagnetism of this compound is strong evidence for its planar structure. This is supported by the electronic spectral data, the longest wave transition being at 21,000 cm⁻¹. Tetrahedral Ni²⁺ complexes, which cannot be diamagnetic within the framework of simple ligand-field theory, show absorption at much longer wavelengths.

Cu[H₂B(pz)₂]₂. This compound is isomorphous with the Ni complex. The d-d transition observed in the electronic spectrum is at too high a frequency to be from a tetrahedral system. Using the electrostatic -4/5 ratio for the splitting due to a tetrahedral field relative to an octahedral field and comparing with the octahedral Δ value, a tetrahedral copper dihydrobis-(1-pyrazolyl)borate would be expected to absorb at about 7000 cm⁻¹. If Jahn-Teller effects are important in the octahedral case, the predicted tetrahedral absorption would be at even longer wavelengths. The longest wavelength absorption in Cu[H₂B(pz)₂]₂ is at 18,500 cm⁻¹.

Co[H₂B(pz)₂]₂ and Zn[H₂B(pz)₂]₂. The proton nmr spectra show all four pyrazolyl residues to be equivalent with the shifts of the cobalt compound being quite different from those for the octahedral complexes. The effective magnetic moment is in the middle of the range for the tetrahedral Co(II). High-spin planar Co(II) cannot be ruled out on the basis of magnetic data, but the complex is isomorphous with Zn[H₂B(pz)₂]₂ and not with Cu[H₂B(pz)₂]₂ and Ni[H₂B(pz)₂]₂. The optical data give strong support to the assignment. All three spin-allowed transitions have been detected, and the splittings and intensities are similar to those for other tetrahedral Co(II) systems in the literature. Four-coordinate Zn(II) complexes are always tetrahedral unless steric requirements make this impossible (e.g., zinc phthalocyanine).

Fe[H₂B(pz)₂]₂ and Mn[H₂B(pz)₂]₂. Optical data for the Fe(II) complex give strong evidence for tetrahedral coordination. Δ for the high-spin octahedral ferrous complexes studied is ~12,500 cm⁻¹,² and so a Δ of ~6000 cm⁻¹ would be expected for high-spin tetrahedral coordination. Absorption corresponding to the ⁵T₂ ← ⁵E transition (separation Δ) is found at 5800 cm⁻¹. The magnetic moments are consistent with the tetrahedral assignment, but high-spin planar structures could not be ruled out on this basis. The change in the sign of the B¹¹ nmr shift on passing from Mn[B(pz)₂]₂ (+1692 cps) and Mn[HB(pz)₂]₂ (+1882 cps) to Mn[H₂B(pz)₂]₂ (-2593 cps) must in any mechanism indicate a change in geometry.

(3) J. P. Jesson, *J. Chem. Phys.*, **45**, 1049 (1966).

(4) S. Trofimenko, unpublished work.

A. Susceptibility Data. The effective magnetic moments of the complexes measured in solution at room temperature and calculated assuming the Curie law is obeyed are given in Table I. Satisfactory measurements of the moments for $\text{Mn}[\text{H}_2\text{B}(\text{pz})_2]_2$ and $\text{Fe}[\text{H}_2\text{B}(\text{pz})_2]_2$ could not be obtained because of the instability of the complexes. Fe^{2+} and Mn^{2+} complexes of structure I ($\text{X} = \text{CH}_3$, $\text{Y} = \text{H}$) are more stable, and room-temperature moments for these compounds are included in the table. We shall consider the magnetic data for each metal in turn, indicating how the information supports the molecular structures which have been assigned to the compounds. It should be emphasized that the moments given are to be viewed as qualitative indicators of the gross molecular structure. The influence of low-symmetry components of the field, corrections for temperature-independent paramagnetism, and possible non-Curie law behavior have been ignored.

Mn^{2+} . High-spin Mn^{2+} has a ${}^6\text{A}_1$ ground state in both octahedral and tetrahedral coordination. This is the only spin sextet of the configuration, and departures from the spin-only value of the moment (5.92) due to spin-orbit mixing of higher states and low symmetry components of the crystal field are expected to be small. The measured moments are consistent with the assignment of a tetrahedral structure to $\text{Mn}[\text{H}_2\text{B}(\text{pz})_2]_2$ and an octahedral structure to $\text{Mn}[\text{HB}(\text{pz})_3]_2$ and $\text{Mn}[\text{B}(\text{pz})_4]_2$. Tetrahedral and octahedral Mn^{2+} cannot, of course, be distinguished on the basis of their magnetic moments.

Fe^{2+} . High-spin octahedral Fe^{2+} has a ${}^6\text{T}_{2g}$ ground state and gives room-temperature moments of about 5.3 BM, which are relatively insensitive to temperature. High-spin tetrahedral Fe^{2+} has a ${}^5\text{E}$ ground state with moments in the 5.1-BM range. A distinction between the two types of coordination for high-spin cases on the basis of their moments is of dubious validity since low-symmetry components of the field can produce appreciable variations in the effective moment.

A clear distinction between tetrahedral and octahedral geometries is possible for low-spin Fe^{2+} since the octahedral low-spin ground state is ${}^1\text{A}_{1g}$, the t_{2g} orbitals being completely occupied, and complexes of this type are, of course, diamagnetic. The low-spin tetrahedral ground state would be ${}^3\text{T}_1$. The diamagnetism of $\text{Fe}[\text{B}(\text{pz})_4]_2$ is then clear evidence for essentially octahedral coordination. Additional evidence is provided by the singlet-quintet spin equilibrium shown by $\text{Fe}[\text{HB}(\text{pz})_3]_2$ and discussed elsewhere.² Octahedral Fe^{2+} is one of the most likely situations for the observation of a spin-free-spin-paired equilibrium, the required mean pairing energy being in the region of 15,000 cm^{-1} and varying according to the degree of reduction of the interelectronic repulsion integrals by covalent bonding of the ligand. Complex II ($\text{X} = \text{Y} = \text{CH}_3$) is completely high spin with a room-temperature moment of 5.22 BM. The moment of 5.2 BM for complex I ($\text{X} = \text{CH}_3$, $\text{Y} = \text{H}$) is consistent with the assignment of tetrahedral geometry.

Co^{2+} . Tetrahedral Co^{2+} has a ${}^4\text{A}_2$ ground state with a moment given approximately by

$$\mu_{\text{obsd}} = 3.87 \left(1 + \frac{4\zeta}{3\Delta} \right)$$

where Δ is the one-electron crystal-field parameter, and

ζ is the single-electron spin-orbit parameter. Because of the possibility of relatively large percentage changes in Δ (Δ for tetrahedral Co^{2+} being in the region 3000 cm^{-1}) and the large spin-orbit parameter ($\zeta = 540 \text{ cm}^{-1}$), μ_{obsd} can cover a quite wide range. Values have been found from ~ 4.2 to ~ 4.9 BM. The upper end of this range overlaps values found for octahedral coordination (4.7–5.4 BM), and the assignment of geometry on the basis of room-temperature moment is not always possible. The fact that $\text{Co}[\text{H}_2\text{B}(\text{pz})_2]_2$ is isomorphous with $\text{Zn}[\text{H}_2\text{B}(\text{pz})_2]_2$ argues strongly for tetrahedral coordination, and the moment of 4.52 BM places it right in the middle of the tetrahedral range.

The high-spin ground state in octahedral coordination is ${}^4\text{T}_{1g}$, and an appreciable temperature dependence of the moment is anticipated. Distortions in the octahedral field can give rise to large anisotropy in the magnetic moment and g -tensor components which would not be found for tetrahedral coordination. Magnetically dilute single-crystal epr measurements in $\text{Co}[\text{HB}(\text{pz})_3]_2$ at 4.2°K give unambiguous evidence for an axially distorted octahedral field.³ The magnetically dilute powder epr of $\text{Co}[\text{HB}(\text{pz})_3]_2$ and $\text{Co}[\text{B}(\text{pz})_4]_2$ are very similar, indicating the same geometry about Co^{2+} . The room-temperature moments of 5.40 and 5.24 BM for $\text{Co}[\text{HB}(\text{pz})_3]_2$ and $\text{Co}[\text{B}(\text{pz})_4]_2$ are good for octahedral coordination.

Ni^{2+} . The zero magnetic moment for $\text{Ni}[\text{H}_2\text{B}(\text{pz})_2]_2$ provides unambiguous evidence for essentially square-planar Ni^{2+} . The electrons are paired owing to the strong antibonding character of the d orbital involved in σ bonding to the square-planar array ($d_{x^2-y^2}$, for a coordinate system in which the x and y axes pass through the nitrogen atoms). $\text{Ni}[\text{H}_2\text{B}(\text{pz})_2]_2$ is isomorphous with $\text{Cu}[\text{H}_2\text{B}(\text{pz})_2]_2$ which must also be planar. Octahedral Ni^{2+} gives rise to a ${}^3\text{A}_{2g}$ ground state. The moment is given approximately by

$$\mu_{\text{eff}} = 2.83 \left(1 + \frac{2\zeta}{\Delta} \right)$$

and should be relatively insensitive to temperature and small departures from octahedral symmetry. Values of 2.9–3.3 BM have been found. Using the free ion value of $\zeta = 650 \text{ cm}^{-1}$, we would have $\Delta = 9400 \text{ cm}^{-1}$. This value is in poor agreement with the value of $\Delta = 12,000 \text{ cm}^{-1}$ found from the optical data. The discrepancy is perhaps not surprising in view of the approximations involved in the formula for the effective moment, and the value of 12,000 cm^{-1} is probably closer to the true value. The room-temperature moments of 3.22 and 3.24 BM for $\text{Ni}[\text{HB}(\text{pz})_3]_2$ and $\text{Ni}[\text{B}(\text{pz})_4]_2$ are consistent with the postulated octahedral geometry.

Cu^{2+} . The ground state for octahedral copper, ${}^2\text{E}_g$, consists of two noninteracting Kramer's doublets, and the moment is relatively insensitive to distortions. Similar moments are therefore found for planar and octahedral environments. Values of ~ 1.9 BM are usually obtained. The measurements on the Cu complexes are less accurate than those for the other metals because of the small nmr shifts involved. Jahn-Teller distortions can be important in these systems.

B. Optical Data. In considering the optical data, it is convenient to discuss the molecules of a given

geometry collectively. After a brief consideration of the zinc complexes, first the planar, then the tetrahedral, and finally the octahedral complexes will be discussed.

1. Zinc Complexes. The transitions in these complexes are probably intraligand in character and set a short wavelength limit for the absorptions in the other complexes which may be assigned to the d-d and charge-transfer transitions involving the metal. The data for the three zinc complexes measured in cyclohexane solution are given in Table II. The possibility

Table II. Ultraviolet Absorption Spectra of Zinc Complexes Measured in Cyclohexane Solution

Compound	λ , $m\mu$	ν , cm^{-1}	ϵ	Comment	Assignment
$Zn(H_2B(pz)_2)_2$	218	45,900	24,000		
	215	46,500	23,000	Shoulder	Intraligand
$Zn(HB(pz)_2)_2$	216	46,300	17,000	Shoulder	
	210	47,600	33,000		Intraligand
	205	48,800	34,000		
$Zn(B(pz)_2)_2$	218	45,900	18,000	Shoulder	
	212	47,200	30,000		Intraligand
	207	48,300	31,000		

that some of the transitions are metal-to-ligand charge transfer is, of course, not completely ruled out, but the wavelengths observed are reasonable for aromatic $\pi^* \leftarrow \pi$ absorption.

2. Planar Complexes. There can be little doubt that there is an essentially planar array of nitrogen atoms about the metal in these complexes. It does not follow, however, that the pyrazole rings and boron atoms, as shown in structure I, are also coplanar. In fact, molecular models indicate that the borons are probably out of the plane of the rings and that the rings may be inclined to one another. Two forms of the molecule $M(H_2B(pz)_2)_2$ could then exist: a "boat" form with both borons up and a "chair" form with one up and one down. With chelates of structure I ($X = CH_3$, $Y = H$ or any other group), only the chair form is possible for steric reasons. The molecular symmetry is therefore less than D_{4h} . However, in the present discussion it will be assumed that only nearest neighbors to the metal need be considered and that the local symmetry is D_{4h} .

The molecular orbital theory of this type of complex has been considered by Gray and Ballhausen⁵ and by Liehr, *et al.*⁶ A complete ligand-field calculation, including spin-orbit effects, has been made by Fenske, *et al.*,⁷ for Pt^{2+} . They find the orbital ordering $d_{xz}, d_{yz} < d_{xy} < d_{x^2-y^2} < d_{z^2}$. The x and y axes pass through the ligand atoms at the corners of a square array. Some confidence may be placed in this ordering for Pt^{2+} , but it could be different when other metals are considered. Gray and Ballhausen⁵ suggest that the lowest unoccupied orbital which is mainly ligand in character,

(5) H. B. Gray and C. J. Ballhausen, *J. Am. Chem. Soc.*, **85**, 260 (1963).

(6) J. R. Permuareddi, A. D. Liehr, and A. W. Adamson, *ibid.*, **85**, 249 (1963).

(7) R. F. Fenske, D. S. Martin, and K. Rudenberg, *Inorg. Chem.*, **1**, 441 (1962).

for systems where the ligand has a π system, will be $a_{2u}(\pi^*)$ and that the long-wavelength charge-transfer transitions in their d^8 complexes involve transfer of an electron from the metal to this orbital. The data and assignments for the two planar pyrazole complexes are given in Table III.

Table III. Electronic Absorption Spectra of Planar Complexes

Compound	λ , $m\mu$	ν , cm^{-1}	ϵ	Comment	Assignment
$Ni(H_2B(pz)_2)_2$	472	21,200	72		$^1A_{1g} \leftarrow ^1A_{1g}$
	277	36,100	1400		$^1B_{1u} \leftarrow ^1A_{1g}$
	247	40,500	15,000	Shoulder	$^1A_{2u} \leftarrow ^1A_{1g}$
	242	41,300	21,000		$^1E_u \leftarrow ^1A_{1g}$
	234 ^a	42,700	15,000	Shoulder	
	219 ^a	45,700	12,000		Ligand ?
$Cu(H_2B(pz)_2)_2$	542	18,450	68		$^3B_{2g} \leftarrow ^3B_{1g}$
	328	30,500	1000		$^3A_{2u} \leftarrow ^3B_{1g}$
	265	37,700	1000		$^3A_{1u} \leftarrow ^3B_{1g}$
	219 ^a	45,700	18,000		
	203 ^a	49,300	20,000		Ligand ?

^a In cyclohexane solution. Others in dichloromethane.

$Ni(H_2B(pz)_2)_2$. The first band, in view of its extinction coefficient, must be assigned to the first d-d transition $(d_{x^2-y^2})(d_{xy}) \leftarrow (d_{xy})^2$. It is somewhat stronger than the corresponding transition in the compounds studied by Gray and Ballhausen. The band is quite symmetrical, and a search to longer wavelengths with more concentrated solutions did not reveal any further absorption (such as the associated singlet-triplet transition). The first charge-transfer transition, $^1B_{1u} \leftarrow ^1A_{1g}$, is orbitally forbidden and is assigned to the absorption at 277 $m\mu$ which has the reasonable extinction coefficient ϵ 1400. The next two charge-transfer transitions are orbitally allowed, and the transition to the 1E_u state was found by Gray and Ballhausen to be the stronger of the two. The assignments in Table III have been completed on this basis. It is possible there is some splitting of the E_u state due to departures from D_{4h} symmetry. Neglecting exchange and Coulomb integrals between electrons centered on different atoms and evaluating those for electrons on the same atom in terms of the Slater-Condon theory for complex atoms, Gray and Ballhausen⁵ found the following energies for the optical transitions.

$$^1A_{2g} \leftarrow ^1A_{1g} \quad \Delta_1 - 35F_4$$

$$^1B_{1u} \leftarrow ^1A_{1g} \quad \Delta E(^1B_{1u})$$

$$^1A_{2u} \leftarrow ^1A_{1g} \quad \Delta E(^1B_{1u}) + \Delta_2 - 20F_2 + 100F_4$$

$$^1E_u \leftarrow ^1A_{1g} \quad \Delta E(^1B_{1u}) + \Delta_2 + \Delta_3 - 15F_2 + 75F_4$$

where Δ_1 , Δ_2 , and Δ_3 are the one-electron splittings $(x^2 - y^2) - (xy)$, $(xy) - (z^2)$, $(z^2) - (xz, yz)$; $\Delta E(^1B_{1u})$ is the energy of the $^1B_{1u} \leftarrow ^1A_{1g}$ transition; and F_2 and F_4 are the Slater-Condon interelectronic repulsion integrals.

Using $F_2 = 10F_4 = 700 \text{ cm}^{-1}$, the assignments in Table III lead to $\Delta_1 = 23,700 \text{ cm}^{-1}$; $\Delta E(^1B_{1u}) = 36,100 \text{ cm}^{-1}$; $\Delta_2 = 11,400 \text{ cm}^{-1}$; and $\Delta_3 \approx 0$.

Table IV. Electronic Absorption Spectra of Tetrahedral Complexes

Compound	λ , m μ	ν , cm ⁻¹	ϵ	Comment	Assignment
Co[H ₂ B(pz) ₂] ₂ in CH ₂ Cl ₂	3120	3,200	7		${}^4T_1 \leftarrow {}^4A_1$
	1220	8,200	97	Well-resolved doublet	${}^4T_1(F) \leftarrow {}^4A_1$
	1070	9,300	92		${}^4T_1(P) \leftarrow {}^4A_1$
	585	17,100	340	Well-resolved triplet	
	552	18,100	406		
	525	19,000	301		
	280	35,700	1,700		
	242*	41,300	5,000		Metal-ligand
	208*	48,100	18,000		Ligand
			16		${}^4T_1 \leftarrow {}^4E$
Fe[H ₂ B(pz) ₂] ₂ (X = CH ₃ , Y = H in CHCl ₃)	1730	5,800	1,500		Metal-ligand
	280*	35,700	12,000		Ligand
	224*	44,600			

* Measured in cyclohexane.

As expected, Δ_1 is by far the largest of the Δ values due to the strongly antibonding character of the σ -bonding $d_{z^2-y^2}$ orbital. The value of Δ_1 is close to that found in $Ni(CN)_4^{2-}$, and the Δ_2 and Δ_3 values are also quite similar. As with most calculations of this type, the results are quite sensitive to the values of F_2 and F_4 chosen (we have used the values selected by Gray and Ballhausen), and so the final parameters, particularly Δ_2 and Δ_3 , are subject to fairly large errors. From the comparison of spectra in planar d^8 complexes in cases where the ligand has no π system with those cases where a π system is present, Gray and Ballhausen were able to establish a pattern for ligand-to-metal and metal-to-ligand charge transfer. They concluded that ligand-to-metal transitions would be separated by $\sim 10,000$ cm⁻¹, while the metal-to-ligand transitions are separated by only 2000–3000 cm⁻¹. The assignments made here are consistent with this scheme.

Cu[H₂B(pz)₂]₂. The assignments in Table III for the copper complex have been made in the same way. The d-d transition $(x^2 - y^2)(xy) \leftarrow (x^2 - y^2)(xy)^2$ is of similar intensity to the corresponding transition in the nickel complex, and again it must be assumed that the remaining d-d transitions are obscured by charge-transfer absorption. For copper, again assuming charge transfer to the low-lying $a_{2u}(\pi^*)$ orbital, the first two charge-transfer transitions are forbidden. The assigned transitions have similar intensity to the forbidden charge-transfer transition in the nickel example. It would be dangerous to assign the absorptions at 219 and 203 m μ to particular metal-to-ligand transitions since they may be intraligand in character. The energy of the d-d transition $(b_{1g})(b_{2g}) \leftarrow (b_{1g})(b_{2g})^2$ is Δ_1 . Denoting the energy of the first charge-transfer transition as $\Delta E({}^2A_{2u})$, an estimate of the interelectronic repulsion correction for the A_{1u} transition is required. The configuration $(b_{2g})(b_{1g})(a_{2u}) \dots$ gives rise to two doublet states and a quartet. The important doublet for our purposes may be written in the form

$$({}^1/a)^{1/2} [\dots (xy)(\bar{a}_{2u})(x^2 - y^2) | - \\ | \dots (\bar{xy})(a_{2u})(x^2 - y^2)]$$

Using the approximation of neglecting repulsion integrals between ao's on different centers, the energy

of the ${}^2A_{1g}$ transition is

$$\Delta E({}^2A_{2u}) = \Delta_1 - 175F_4/2$$

The final parameters for the copper complex are therefore $\Delta_1 = 18,450$ and $\Delta E({}^2A_{2u}) = 30,500$.

The expression for $\Delta E({}^2A_{1u})$ would require $F_4 \sim 20$ cm⁻¹. In view of the approximations involved, this result cannot be viewed as a determination of F_4 , and the true value is almost certainly larger. Δ_1 appears to be significantly lower for Cu than for Ni.

The spectra described above provide strong support for the structures assigned on the basis of the magnetic data and rule out the possibility of tetrahedral coordination in either of the complexes.

3. Tetrahedral Complexes, $M[H_2B(pz)_2]_2$ ($M = Zn^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}$). Data for the Zn^{2+} complex have been presented in Table II. The Fe^{2+} and Mn^{2+} complexes derived from dihydrobis(3,5-dimethyl-1-pyrazolyl)borate were used in the study because of their enhanced stability over the unsubstituted compounds. No d-d transitions were observed for the Mn^{2+} complex for the path lengths and concentrations available. Data for the remaining two complexes are given in Table IV.

Co[H₂B(pz)₂]₂. There are many optical studies of tetrahedral Co(II) complexes in the literature. The most detailed work has been carried out by Ferguson⁸ using low-temperature and polarized-single-crystal techniques. Cotton⁹ has studied a variety of tetrahedral Co(II) compounds both in solution and as mulls. In these studies it has been assumed that the first spin-allowed transition ${}^4T_1 \leftarrow {}^4A_1$ lies in the 3- μ region, outside the spectral range covered, giving a Δ of 3000–4000 cm⁻¹. Transitions to the ${}^4T_1(F)$ and ${}^4T_1(P)$ states then lie at ~ 5500 and $\sim 15,000$ cm⁻¹. Because of the absence of a center of symmetry and consequent mixing of d and p orbitals in these systems, the d-d transitions are commonly 100–200 times more intense than for octahedral coordination. In the present case, the transition in the 3- μ region has been observed by comparing the infrared spectra of $Zn[H_2B(pz)_2]_2$ and $Co[H_2B(pz)_2]_2$ in CCl₄ solution at the same concentration.

(8) J. Ferguson, *J. Chem. Phys.*, **39**, 116 (1961).(9) F. A. Cotton, D. M. L. Goodgame, and M. Goodgame, *J. Am. Chem. Soc.*, **83**, 4690 (1961).

spectra are shown in Figure 1. The sharp vibrational structure and CCl_4 absorption (there was no ncing solvent cell) are quite similar in the two cases, there is an underlying broad absorption in the Co(II) pound due to the ${}^4\text{T}_2 \leftarrow {}^4\text{A}_1$ transition.

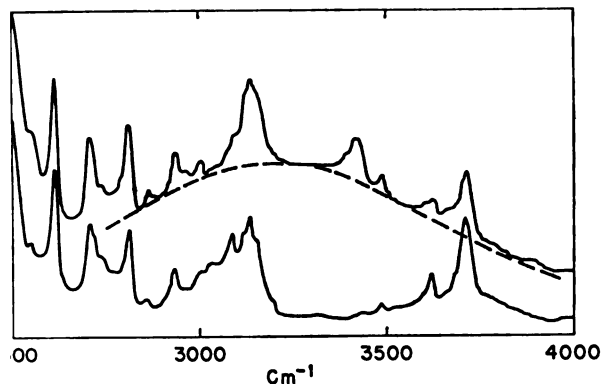


Figure 1. Absorption spectra ($3\ \mu$) of $\text{Zn}[\text{H}_2\text{B}(\text{pz})_2]_2$ and $\text{Co}[\text{H}_2\text{B}(\text{pz})_2]_2$ in CCl_4 .

The spectrum in the 17,000–3500-Å region is shown in Figure 2. Large splittings are observed in the $\text{F} \leftarrow {}^4\text{A}_2$ and ${}^4\text{T}_1(\text{P}) \leftarrow {}^4\text{A}_2$ transitions and are attributed to the effect of spin-orbit coupling and low-symmetry components in the crystal field. Jahn-Teller effects in the excited states are theoretically possible, they are probably small in view of the large spin-orbit contribution. Three well-resolved maxima are found for the ${}^4\text{T}_1(\text{P})$ transition. The ${}^4\text{T}_1$ components probably quite strongly mixed with components of ${}^2\text{G}$ state which occur in the same region, and the splitting observed is quite characteristic of Co^{2+} tetrahedral coordination.^{10–13} The two bidentate ligand residues in $\text{Co}[\text{H}_2\text{B}(\text{pz})_2]_2$ would be expected to give rise to a low-symmetry component in the crystal field of approximately D_{2d} symmetry. It is possible that the well-resolved doublet structure in the transition to the ${}^4\text{T}_1(\text{T})$ state can be accounted for as the splitting $\rightarrow \text{A}_2 + \text{E}$.

Since the ${}^4\text{T}_2 \leftarrow {}^4\text{A}_2$ transition should occur at a frequency $\Delta\ \text{cm}^{-1}$, the infrared measurement indicates $\Delta = 3200\ \text{cm}^{-1}$. However, the transition ${}^4\text{T}_1(\text{F}) \leftarrow {}^4\text{A}_2$ should lie at approximately 1.8Δ , and based on this argument a value of $\Delta \sim 4800\ \text{cm}^{-1}$ is obtained. A possible explanation of this discrepancy is that, in view of the intrinsic weakness of the transition to the ${}^4\text{T}_2$ state, only the transition to the E component is observed, the B_2 component being forbidden. The measured magnetic moment corresponds to a ζ/Δ value of approximately 0.13. Combination of this value with known free ion spin-orbit coupling constant gives $\Delta \sim 4100\ \text{cm}^{-1}$. A further 10% reduction in ζ due to covalency effects would give $\Delta \sim 3700\ \text{cm}^{-1}$. It does, therefore, seem possible to choose between the

alternate Δ values on the basis of the magnetic data. Just as for the planar complexes, it is probable that the boron atoms lie out of the plane of the pyrazole rings, and the rings may be inclined to one another. Two optically isomeric forms of the molecule would be possible, provided there is no rapid N–B–N inversion.

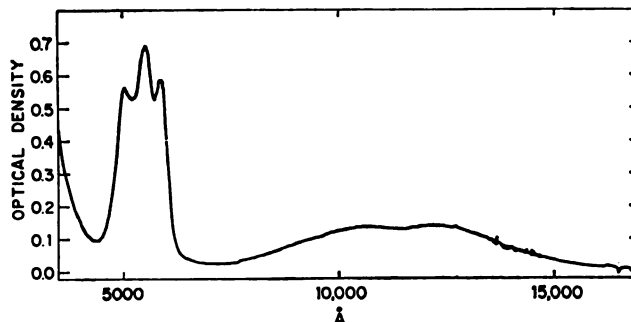


Figure 2. Absorption spectrum of $\text{Co}[\text{H}_2\text{B}(\text{pz})_2]_2$, 3500–17,000 Å, measured in CHCl_3 solution.

$\text{Fe}[\text{H}_2\text{B}(\text{pz})_2]_2$. The tetrahedral ferrous complexes are very easily oxidized in solution. Studies were made with the more stable chelate derived from dihydrobis(3,5-dimethyl-1-pyrazolyl)borate. A single band corresponding to the expected ${}^5\text{T}_2 \leftarrow {}^5\text{E}$ transition is found at $5800\ \text{cm}^{-1}$. The separation of these energy levels is Δ on the crystal-field model, and $\Delta = 5800\ \text{cm}^{-1}$ is very close to $1/3$ the Δ for the octahedral systems ($\sim 12,500\ \text{cm}^{-1}$).²

Tetrahedral Fe^{2+} complexes reported in the literature have no d–d absorption between 500 and $2000\ \text{m}\mu$.^{14,15} It seems unlikely that the ${}^5\text{T}_2 \leftarrow {}^5\text{E}$ transition would be too weak to be observed, and probably Δ is less than $5000\ \text{cm}^{-1}$ for these systems.

4. Octahedral Complexes, $\text{M}[\text{HB}(\text{pz})_2]_2$ and $\text{M}[\text{B}(\text{pz})_4]_2$ ($\text{M} = \text{Zn}^{2+}, \text{Cu}^{2+}, \text{Ni}^{2+}, \text{Co}^{2+}, \text{Mn}^{2+}$). The optical spectra of complexes $\text{M}[\text{HB}(\text{pz})_2]_2$ and $\text{M}[\text{B}(\text{pz})_4]_2$ are almost identical except for the ferrous compounds where a spin equilibrium is present in the first compound. The two types of complex will therefore be considered together. Results have already been given for the Zn complexes (Table II), and the absorption in the octahedral Mn^{2+} complexes was too weak to be detected in the effective concentrations available. Results for a variety of Fe(II) complexes are given in the following paper.³ The results for the remaining complexes are given in Table V.

$\text{Cu}[\text{HB}(\text{pz})_2]_2$ and $\text{Cu}[\text{B}(\text{pz})_4]_2$. Both complexes give one very broad transition in the $16,500\text{-cm}^{-1}$ region which may be assigned to the expected ${}^2\text{T}_{2g} \leftarrow {}^2\text{E}_g$ transition. In both cases extended and very pronounced long-wavelength shoulders are found. There is some evidence of structure in the main absorption. Splittings are expected owing to the trigonal component of the field, spin-orbit coupling, and possible Jahn-Teller distortions. The apparent octahedral splitting parameter Δ , neglecting Jahn-Teller effects, is $\sim 16,000\ \text{cm}^{-1}$, indicating a relatively strong ligand field. There is an increase by a factor of 3 in extinction

(1) D. L. Wood and A. A. Ballman, *Am. Mineralogist*, **51**, 216 (1956).

(2) C. J. Ballhausen and C. K. Jørgensen, *Acta Chem. Scand.*, **9**, (1955).

(3) R. Pappalardo, D. L. Ward, and R. C. Linares, Jr., *J. Chem. Phys.*, **35**, 2041 (1961).

(4) J. Ferguson, *ibid.*, **32**, 528 (1960).

(14) J. T. Donoghue and R. S. Drago, *Inorg. Chem.*, **2**, 1158 (1963).

(15) N. S. Gill, *J. Chem. Soc.*, 3512 (1961).

Table V. Electronic Spectra of Octahedral Complexes

Compound	λ , m μ	ν , cm $^{-1}$	ϵ	Comment	Assignment
Cu[HB(pz) ₃] ₂ in CH ₂ Cl ₂	620	16,100	19	Pronounced long wave tail	${}^3T_{2g} \leftarrow {}^3E_g$
	272	36,700	1,000		Metal-ligand
	210*	47,600	51,000		Ligand
	205*	48,800	51,000		
Cu[B(pz) ₃] ₂ in CH ₂ Cl ₂	595	16,800	60	Pronounced long wave tail	${}^3T_{2g} \leftarrow {}^3E_g$
	307	32,600	600		Metal-ligand
	263	38,000	600		
	215*	46,500	50,000		Ligand
Ni[HB(pz) ₃] ₂ in CH ₂ Cl ₂	849	11,800	4.8	Shoulder	${}^3T_{2g} \leftarrow {}^3A_{2g}$
	760	13,150	2.9		${}^3T_{1g} \leftarrow {}^3A_{2g}$
	570	17,500	3.4	Shoulder	
	522	19,150	4.8	Shoulder	${}^3T_{1g} \leftarrow {}^3A_{2g}$
	450	22,200	0.5		${}^1A_{1g} \leftarrow {}^3A_{2g}$
	339	29,500	7.8		${}^3T_{1g} \leftarrow {}^3A_{2g}$
	210*	47,600	39,000		Ligand
	205*	48,800	39,000		
Ni[B(pz) ₃] ₂ in CHCl ₃	820	12,200	5.2	Shoulder	${}^3T_{2g} \leftarrow {}^3A_{2g}$
	750	13,300	4.0		${}^3T_{1g} \leftarrow {}^3A_{2g}$
	570	17,500	4.3	Shoulder	
	520	19,200	5.8	Shoulder	${}^3T_{1g} \leftarrow {}^3A_{2g}$
	459	21,800	1.5		${}^1A_{1g} \leftarrow {}^3A_{2g}$
	334	29,900	7.7		${}^3T_{1g} \leftarrow {}^3A_{2g}$
	210*	47,600	30,000		Ligand
					Ligand
Co[HB(pz) ₃] ₂ in CH ₂ Cl ₂	1100	9,100	0.4	Shoulder	${}^3E_g \leftarrow {}^3T_{1g}$
	901	11,100	3.4		${}^3T_{2g} \leftarrow {}^3T_{1g}$
	641	15,600	0.1		${}^3T_{1g}, {}^3T_{2g} \leftarrow {}^3T_{1g}$
	515	19,400	1.3		${}^4A_{2g} \leftarrow {}^3T_{1g}$
	459	21,800	13.4		${}^3T_{1g} \leftarrow {}^3T_{1g}$
	284	35,300	1,300		Metal-ligand
	244	41,000	3,900		
	207*	48,300	26,000		Ligand
	202*	49,500	26,000		
					Ligand
Co[B(pz) ₃] ₂ in CHCl ₃	1100	9,000	0.3	Shoulder	${}^3E_g \leftarrow {}^3T_{1g}$
	877	11,400	3.0		${}^3T_{2g} \leftarrow {}^3T_{1g}$
	645	15,500	0.1		${}^3T_{1g}, {}^3T_{2g} \leftarrow {}^3T_{1g}$
	502	19,900	1.5		${}^4A_{2g} \leftarrow {}^3T_{1g}$
	454	22,000	13.1		${}^3T_{1g} \leftarrow {}^3T_{1g}$
	280	35,700	1,500		Metal-ligand
	250*	40,000	3,800		
	210*	47,600	20,000		Ligand
					Ligand

* Measured in cyclohexane solution.

coefficient with the substitution of the fourth pyrazole residue which is perhaps a little surprising. In the corresponding nickel and cobalt complexes there is essentially no change in extinction coefficient on substitution.

Ni[HB(pz)₃]₂ and Ni[B(pz)₃]₂. Calculations have been made for these complexes using the "complete" ligand-field matrices of Liehr and Ballhausen¹⁶ for Ni²⁺ in an octahedral environment. The results must be viewed with some caution since it is probable there is a pronounced trigonal component in the crystal field. The calculated energy scheme as a function of Δ is shown in Figure 3. λ has been taken as -285 cm^{-1} and F_4 as 90 cm^{-1} . The relation $F_2 = 14F_4$ has been assumed. The measured transition frequencies for Ni[HB(pz)₃]₂ are shown in the diagram as horizontal bars, and it is seen that there is good agreement with the calculated values for $\Delta \approx 12,000\text{ cm}^{-1}$. The transition frequencies of Ni[B(pz)₃]₂ are very similar, and Δ must also be close to $12,000\text{ cm}^{-1}$ in this case. The assignments given in Table V are based on this calculation. Jørgensen¹⁷ has suggested that, in Ni(H₂O)₆²⁺,

the doubling of the absorption in the $13,500\text{-cm}^{-1}$ region is due to spin-orbit coupling between ${}^3T_{1g}({}^3F)$ and ${}^1E_g({}^1D)$, giving rise to appreciable intensity for transitions to the latter state. The calculation of Liehr and Ballhausen¹⁶ argues against this since the two states in question do not approach closely for the parameter values they have assumed. The energy scheme, however, depends quite sensitively on the values of F_2 and F_4 chosen, and the Jørgensen assignment cannot be completely ruled out. We have used the same F_2 and F_4 values as Liehr and Ballhausen, and, for the Δ value established for polypyrazolylborates, the 1E state should be close to the ${}^3T_{2g}$ state. This may account for the splitting of the absorption peak. [The spin-orbit splitting in the 3T_2 state is much less than for ${}^3T_1({}^3F)$.]

Co[HB(pz)₃]₂ and Co[B(pz)₃]₂. Most of the data for these compounds have been given in a publication describing paramagnetic resonance absorption in these systems.⁸ Despite the large trigonal component in the crystal field indicated by the resonance data, there are no observable splittings of the orbital triplets in the optical spectrum. Koide¹⁸ has shown that the transition to the ${}^4A_{2g}$ state should be weak. It is a two-electron transition, and his theoretical oscillator strengths are in

(16) A. D. Liehr and C. J. Ballhausen, *Ann. Phys. (N. Y.)*, **6**, 124 (1959).(17) C. K. Jørgensen, *Acta Chem. Scand.*, **9**, 1362 (1955).(18) S. Koide, *Phil. Mag.*, **4**, 243 (1959).

reasonable agreement with those found experimentally for the assignments given. Δ is found to be $\sim 10,000 \text{ cm}^{-1}$.

C. Nuclear Magnetic Resonance Spectra. Proton magnetic resonance data obtained at 30° are given in Table VI. Shifts are in cycles per second from TMS as internal standard. The octahedral Fe(II) complexes are considered in the following paper.³

Table VI. Proton Nuclear Resonance Chemical Shifts

Compound	δ , cps	J, cps	Comment	Assignment
Zn ²⁺ Complexes				
Zn[H ₂ B(pz) ₂] ₂ in CDCl ₃	-463	2.1	Doublet of doublets (0.5 cps)	3- and 5-H
	-453	2.2	Doublet of doublets (0.5 cps)	
	-375	2.1	Triplet	
Zn[HB(pz) ₂] ₂ in CH ₂ Cl ₂	~ -250		Very broad	H ₂ on boron
	-463	2.2	Doublet of doublets (0.6 cps)	3- and 5-H
	-425	1.9	Doublet	
	-361	2.1	Triplet	4-H
	~ -250			H on boron
Zn[B(pz) ₂] ₂ in CDCl ₃	-466	2.4	Doublet	3- and 5-H
	-444	1.6	Doublet	
	-376	2.1	Triplet	
Compound	Shift		Assignment	
Co ²⁺ Complexes				
Co[HB(pz) ₂] ₂ in CDCl ₃	-6875		H on boron	
	-5370		5-H	
	-2430		4-H	
Co[B(pz) ₂] ₂ in CDCl ₃	+6260		3-H	
	-5500		5-H	
	-3630		pz (5)	
	-2270		4-H	
	-1910		pz	
	-1760		pz	
	+6960		3-H	
	(3)(4)			
Co[HB(pz) ₂] ₂ X = CH ₃ , Y = H, in CDCl ₃	-6,450		H on boron	
	-2,670		4-H	
	-2,560		5-Me	
	+4,700		3-Me	
Co[H ₂ B(pz) ₂] ₂ in CDCl ₃	-7,910		H ₂ on boron	
	-2,900		4-H	
	-1,950		5-H	
	+525		3-H	
Co[H ₂ B(pz) ₂] ₂ X = CH ₃ , Y = H, in CDCl ₃	-11,400		H ₂ on boron	
	-3,205		5-Me	
	-2,785		4-H	
	+400		3-Me	
Tetrahedral Fe Complexes				
Fe[H ₂ B(pz) ₂] ₂ in CDCl ₃	-6,935		H ₂ on boron	
	-2,425		4-H	
	-1,370		3-H	
	+480		5-H	
Fe[H ₂ B(pz) ₂] ₂ X = CH ₃ , Y = H, in CDCl ₃	-12,925		H ₂ on boron	
	-3,290		3- and 5-Me	
	-2,695		4-H	
Ni Complexes				
Ni[H ₂ B(pz) ₂] ₂ in CDCl ₃	-470		3-, 4-, 5-H	
	-419			
	-378			
Ni[HB(pz) ₂] ₂ in CDCl ₃	-2,875		3-, 4-, 5-H	
	+560		H on boron	
Ni[B(pz) ₂] ₂ in CDCl ₃	-3,230		3-, 4-, 5-H	
	-2,860			
	-480			
	-439			
	-396			
		pz		

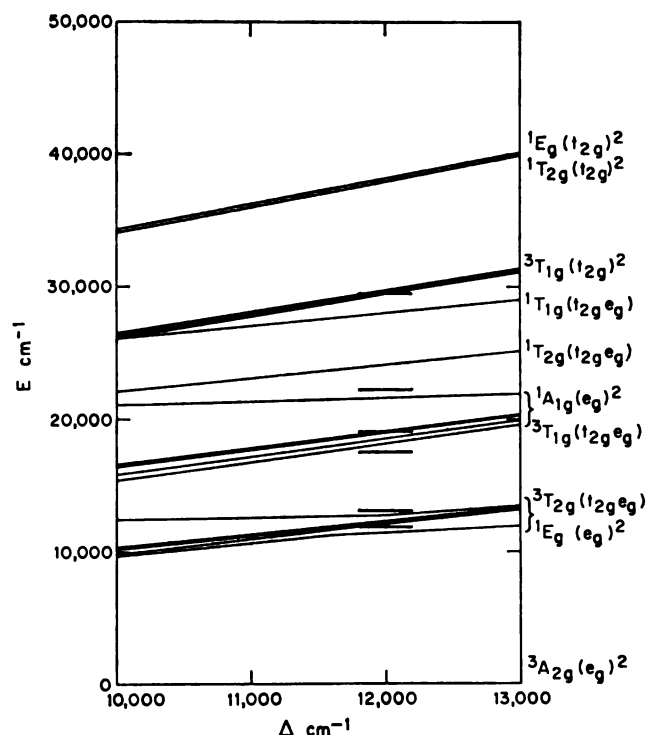


Figure 3. Energy-level diagram for octahedral Ni(II) complexes as a function of Δ . Measured Ni[HB(pz)₂]₂ transitions shown as horizontal bars.

The zinc complexes are, of course, diamagnetic and show well-resolved spin-spin splittings. The resonance of the 4-H is a triplet (see structure I for numbering) and gives an unambiguous assignment. Assignments cannot be made for the 3- and 5-H with the data available. The resonances for the hydrogen on boron are very broad. Their centers have been established by integration. The line widths of nuclear resonance spectra in paramagnetic systems are determined by the effects of dipolar and scalar coupling of the nucleus with the unpaired electrons in the molecule.¹⁹ Appreciable scalar coupling will often broaden the resonances beyond detectability unless the electron spin-lattice relaxation time is very short. For the ions involved in the present study, rapid spin-lattice relaxation is usually found for Co²⁺ and Fe²⁺ in octahedral coordination. (Liquid helium temperatures are usually required for the observation of paramagnetic resonance in these systems.) The Co²⁺ and Fe²⁺ complexes are the only octahedral poly(1-pyrazolyl)borates which give rise to well-resolved nmr spectra. The octahedral Ni²⁺ complexes represent an intermediate case where some information can be obtained from the nmr (liquid nitrogen temperatures are usually needed to observe epr in these systems), and the Cu²⁺ and Mn²⁺ nmr spectra are too broad to provide useful information (epr can be observed at room temperature). Well-resolved proton resonance spectra are also found for the tetrahedral Fe²⁺ and Co²⁺ complexes. The tetrahedral Co²⁺ ground state is orbitally nondegenerate, and the relaxation mechanism must involve coupling of the zero-field splitting to the lattice modes.

Cobalt Complexes. The Co²⁺ complexes provide the most direct structural information since the spectra

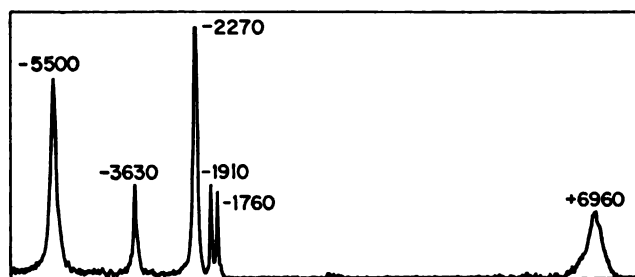
(19) N. Bloembergen, *J. Chem. Phys.*, **27**, 572, 595 (1957).

Table VII. B¹¹ Shifts Relative to Trimethyl Borate External Standard (14.2 Mcps)

	Mn	Fe	Co	Ni	Cu	Zn
M[H ₂ B(pz) ₃] ₂	-2590*	-2130	-5400	+360	+670	+360*
M[HB(pz) ₃] ₂	+1880	+790	-3410	+780	+640	+330
M[B(pz) ₃] ₂	+1690*	+270	-3460*	+940*	+730	+260*

* In CHCl₃ solution; others in CH₂Cl₂.

are not complicated by the presence of a spin equilibrium as is the case for Fe²⁺. The first three Co²⁺ complexes in Table VI are octahedral and are sufficient to establish the assignments given. The assignments have been made on the basis of intensity, the effects of substitution, and from line widths and ease of saturation. In the limit of short electron spin-lattice relaxation times, the nuclear *T*₂ values and hence line widths are usually determined by dipolar terms which depend on the inverse of the sixth power of the distance of the proton from the electronic dipole, and so protons closest to the metal have the greatest half-widths. Direct evidence for the tridentate nature of the HB(pz)₃⁻ and B(pz)₃⁻ ligands is provided by comparison of the nmr spectra of Co[HB(pz)₃]₂ and Co[B(pz)₃]₂. In the former complex the six pyrazolyl residues giving rise to three separate proton resonances are all equivalent. The proton resonance spectrum of Co[B(pz)₃]₂ is shown in Figure 4. The addition of the fourth pyrazolyl resi-

Figure 4. Proton resonance spectrum of Co[B(pz)₃]₂ in CDCl₃. Shifts from TMS at 60 Mcps.

due gives rise to three new resonances of one-third the intensity of the main three resonances, and, of course, the resonance due to the proton on boron is no longer present. Assignments for the tetrahedral complexes Co[H₂B(pz)₃]₂ and I (M = Co, X = CH₃, Y = H), given in Table VI, have been made in the same way.

The isotropic shifts in the octahedral compounds are determined predominantly by pseudo-contact interactions. A detailed analysis of these shifts together with complementary epr data will be published elsewhere.²⁰

Ni²⁺ Complexes. Results for the Ni²⁺ complexes are given in Table VI. Ni[H₂B(pz)₃]₂, which is diamagnetic, gives resonances in roughly the same positions as those of the zinc complexes or of the free ligand. In Ni[HB(pz)₃]₂ only one resonance is observed due to the three ring protons. In Ni[B(pz)₃]₂ the resonance for the ring protons splits into two components, and it

seems likely that the third resonance is also present in this grouping. The resonance due to H on boron is replaced by three resonances in essentially the positions for a free pyrazole residue, showing there is effectively no spin delocalization to this ring. Any appreciable dipolar shift is also ruled out. This is in harmony with the fact that the ground state is ³A₂, and the electronic moment would be expected to be isotropic.

Boron Nuclear Resonances. B¹¹ resonance shifts measured from trimethyl borate as an external standard at 14.2 Mcps are given in Table VII. Susceptibility corrections have been applied to the shifts. The Zn complexes provide diamagnetic reference points. For the M[HB(pz)₃]₂ and M[B(pz)₃]₂ complexes of the same metal the shifts are approximately the same except for the Fe²⁺ case where the spin equilibrium is present. The shifts for the M[H₂B(pz)₃]₂ systems are in general quite different, the large low-field shifts in the Mn and Fe complexes providing additional evidence for the assumed geometrical differences.

Discussion

The magnitude of Δ for a given metal ion determines the position of a ligand in the spectrochemical series. Jørgensen²¹ has suggested that Δ may be represented as a product of two factors, one for the ligand and one for the central ion.

$$\Delta = f(\text{ligand}) \times g(\text{central ion})$$

The position of a ligand in the nephelauxetic series is determined by the reduction of the interelectronic repulsion integrals from the values in the free ion, the parameter β being defined by

$$B(\text{complex}) = \beta B(\text{free ion})$$

Again Jørgensen has suggested that this parameter may be split into a quantity characteristic of the ligand and one characteristic of the metal

$$1 - \beta = hk$$

where *h* refers to the ligand and *k* to the metal.

Values of Δ, *B*, and β for the complexes studied are given in Table VIII. *B* values for the free ion are given in parentheses. Values of the corresponding quantities for the hexaquo ions are given beneath the octahedral parameters for comparison. For the octahedral Ni(II) complexes the calculated transitions, using the undistorted octahedral model, are in very good agreement

(20) J. P. Jesson, to be published.

(21) C. K. Jørgensen, *Discussions Faraday Soc.*, 26, 110 (1958).

the experimental values (see Figure 3). All the t states are reproduced closely. The high-spin for Co(II) are not reproduced so well. This is probably due to the effect of the trigonal component field perturbing the positions of the 4A_2 and ${}^4T_1({}^4P)$ states which lie close together. In the Ni(II) all the high-spin states are well separated. In

VIII. Spectral Parameters for High-Spin Octahedral and Tetrahedral Complexes^a

	Octahedral				Tetrahedral	
	Fe	Co	Ni	Cu	Fe	Co
	12,500	10,000	12,000	16,000	5800	4500
	...	830 (980)	850 (1040)
	...	0.85	0.82
O)	10,400	7,900	8,500	12,600		
O)	...	880	890	...		
O)	...	0.90	0.89	...		

^a Δ and B values in cm^{-1} .

finding Δ and B for the Ni(II) case, we have used results of the ligand-field calculation which indicates 12,000 cm^{-1} and the relationship

$$\delta(T_1) = (225B^2 - 18B\Delta + \Delta^2)^{1/2}$$

$\delta(T_1)$ is the separation between the two T_1 states. The relevant parameters for establishing the position of hydrotris(1-pyrazolyl)borate ligand in the spectrochemical and nephelauxetic series using the Ni(II) are then $\Delta = 12,000 \text{ cm}^{-1}$ and $\beta = 0.82$. These lead to the final quantities $f = 1.35$ and $h = 1.5$. The h value is quite sensitive to $\delta(T_1)$, and, because of the small splittings of the ${}^3T_1({}^3F)$ state, $\delta(T_1)$ cannot be estimated accurately. The h value should therefore be accepted with some reservation. A value of $\delta(T_1) = 10,000 \text{ cm}^{-1}$ has been used in the calculation. The B value is reasonably close to that assumed in the original γ level calculation ($F_2 = 14F_4$; $F_4 = 90$ corresponds to $B = 810 \text{ cm}^{-1}$). $h = 1.5$ gives the ligand the same position in the nephelauxetic series as methylenediamine, which is not unreasonable. The f of 1.35 places the anion at about the same position in the spectrochemical series as *o*-phenanthroline. It should be noted that the ferrous complex of *o*-phenanthroline is low spin, as are some of the poly(1-pyrazolyl)borates.

The Δ value for the octahedral Co(II) complexes has been taken from a previous publication² and was obtained as a best fit to the spectrum using matrices for octahedral potential. The Δ value obtained is quite different from the 4T_1 - 4A_2 separation, and, as pointed out above, this difference is probably due to the 4A_2 - 4T_1 interaction under the low symmetry component field. B has been calculated from the estimated separation in the complex² ($= 15B$).

The Δ value for Cu^{2+} is, of course, uncorrected for Jahn-Teller effect, and the "true" Δ is probably somewhat lower. The effects of the trigonal component field are probably comparable to any Jahn-Teller effect and have also been neglected. There is considerable uncertainty in the value of Δ given for Co(II) in tetrahedral coordination. The Δ values for the tetra-

hedral complexes are quite close to $4/9$ times the Δ for the octahedral cases.

The nuclear resonance shifts in the paramagnetic systems relative to the corresponding diamagnetic species must be ascribed to either dipolar or scalar coupling between the electron and nuclear spins. A scalar contribution to the shift requires unpaired spin density in a σ orbital on the proton in question. Four separate mechanisms giving rise to resonance shifts may be identified: (1) delocalization in the π system through $d\pi$ - $p\pi$ bonding with polarization of the spin in the σ orbital on the proton by unpaired $p\pi$ spin density, (2) delocalization in the σ system, (3) polarization of metal-ligand bonding orbitals by unpaired spin in metal orbitals of a different symmetry, and (4) the pseudo-contact or dipolar interaction.

It is apparent that the interpretation of these shifts can be a matter of some complexity, and a complete analysis is not possible with the present state of the art. Usually firm conclusions can only be obtained when one of the mechanisms predominates. With the exception of the shifts in the octahedral Co(II) complexes, which are determined largely by the pseudo-contact effect, this is apparently not the case for the present series of compounds. However, the following observations can be made for the data in this paper.

In the complex $\text{Ni}[\text{B}(\text{pz})_4]_2$, the proton resonances in the pyrazolyl residue not bonded to the metal are close to those for the diamagnetic zinc complex. The ground state for this complex is 3A_2 , and even quite large trigonal distortions in the crystal field would not be expected to give rise to large g -tensor anisotropies. Dipolar contributions to the shifts are therefore expected to be negligible. The scalar contribution to the shifts on the fourth pyrazolyl residue must also be negligible, indicating that the saturated boron atom is effective in insulating the terminal substituent from the unpaired spin on the metal. The fourth pyrazolyl residue in the corresponding Co^{2+} complex shows large downfield shifts. The ground state here is 4T_1 , and large anisotropies in the electron moment have been shown to arise from the trigonal component in the field. The shifts in the fourth pyrazolyl residue are therefore due to the dipolar coupling between the proton and electron moments.

An appreciable dipolar contribution for the octahedral ferrous system is also anticipated. This expectation receives some support from the shift to high field of the H on boron in the hydrotris(3,4,5-trimethyl-1-pyrazolyl)borates and hydrotris(3,5-dimethyl-1-pyrazolyl)borates.² It is, however, still possible that the shift could arise from spin polarization through the boron. Unfortunately, the $\text{Fe}[\text{B}(\text{pz})_4]_2$ compound, which would give the best test of this point, is diamagnetic. If the high-field shift of the terminal proton is due to the dipolar interaction, the over-all anisotropy for the Fe^{2+} system is indicated to be of the opposite sign to that for Co^{2+} where the proton on boron shifts to low field. Interpretations involving the protons attached directly to boron should be viewed with caution since large shifts are found for these protons in the tetrahedral cobaltous complexes where little g anisotropy is expected.

In conclusion, it may be stated that the optical and magnetic properties of this series of compounds fall

into a consistent pattern. The nmr shifts of the paramagnetic compounds on the other hand do not show pronounced regularities even in such a series of closely related compounds, and it is apparent that several of the possible mechanisms for producing these shifts are combining to give a complex pattern.

Experimental Section

A. Susceptibility Measurements. Susceptibility measurements have been made in solution using an nmr method.²² Measurements were made in CHCl_3 or CH_2Cl_2 depending on the solubility. The effective moments have been calculated using room-temperature data and assuming the Curie law is obeyed. The assumption is reasonable for all cases except the octahedrally coordinated Co complexes where a pronounced temperature dependence of effective moment is anticipated. The accuracy of the measurements varies because of the differing solubilities and susceptibilities involved. The variation of susceptibility with temperature could not be meas-

ured with sufficient accuracy to permit a meaningful verification of the Curie law behavior because of the limited temperature range which could be investigated.

B. Optical Measurements. Optical absorption studies were made in the region 17,000 to 2000 Å using a Cary 14 recording spectrophotometer. Measurements at short wavelengths were made in hexane solution, and the remaining measurements were made in chloroform or dichloromethane. Infrared spectra were obtained using a Perkin-Elmer Model 21 spectrophotometer.

C. Nmr Spectra. The nmr spectra were recorded using a Varian HR-60 spectrometer for proton resonance studies of the paramagnetic species and an A-60 for the diamagnetic species. A 14.2-Mcps radiofrequency unit and probe were used for the boron studies. Measurements were made in deuteriochloroform except as noted. The proton shifts are measured *vs.* tetramethylsilane as an internal standard. The boron shifts are measured *vs.* trimethyl borate as an external standard.

D. Synthesis of Compounds. The synthesis of transition metal complexes with unsubstituted poly(1-pyrazolyl)borates²³ and poly(1-pyrazolyl)borates containing substituents on carbon or boron²⁴ will be published elsewhere.

(23) S. Trofimenko, *J. Am. Chem. Soc.*, **89**, 3165 (1967).

(24) Part IV: S. Trofimenko, submitted for publication.

(22) D. F. Evans, *J. Chem. Soc.*, 2003 (1959).

Spin Equilibria in Octahedral Iron(II) Poly(1-pyrazolyl)borates

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Abstract: The Fe^{2+} complexes based on the hydrotris(1-pyrazolyl)borate ligand provide an example of a "spin equilibrium" between high- and low-spin forms. Fully high-spin, fully low-spin, and complexes of intermediate spin can be produced by appropriate substitution. Optical spectra, susceptibility data, and magnetic resonance experiments leading to the characterization of these equilibria are presented.

The possibility of the occurrence of a thermally accessible electronic state of different multiplicity from the ground state has long been recognized for d^4 , d^5 , d^6 , and d^7 ions in octahedral environments.¹ The experimental realization of an equilibrium of this type is determined by the availability of a complex for which the low-spin and high-spin ground states are separated by only a few hundred reciprocal centimeters. Since the energies involved in changes in chemical binding are in general much larger than this, the requirement is very restrictive and accounts for the fact that there are few, if any, well-documented cases of equilibria of this type.

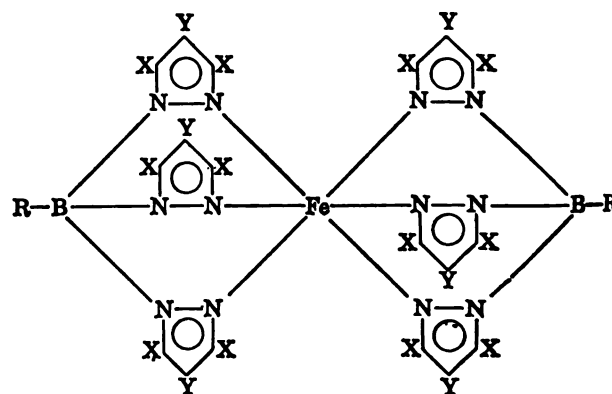
For the d^5 and d^6 configurations, the susceptibility may be taken as the population weighted-average of the susceptibilities of the two terms of different multiplicity. For d^4 and d^7 the situation is more complicated as the spin-orbit coupling connects the two states involved. The presence of low-symmetry components in the crystal field is another factor which must also be considered.

The most favorable case for an unambiguous experimental observation of this type of equilibrium is the

(1) L. E. Orgel, 10th Conseil Institute Chemie Solvay, Brussels, 1956.

d^6 configuration where the low-spin system is diamagnetic and the change in the number of unpaired electrons is four.

The ferrous compounds of structures I–V present such an unambiguous example of a system in which both high- and low-spin ground states are thermally ac-



I, R = 1-pyrazolyl (pz); X = Y = H
 II, R = C_6H_5 ; X = Y = H
 III, R = H; X = Y = H
 IV, R = H; X = CH_3 ; Y = H
 V, R = H; X = Y = CH_3

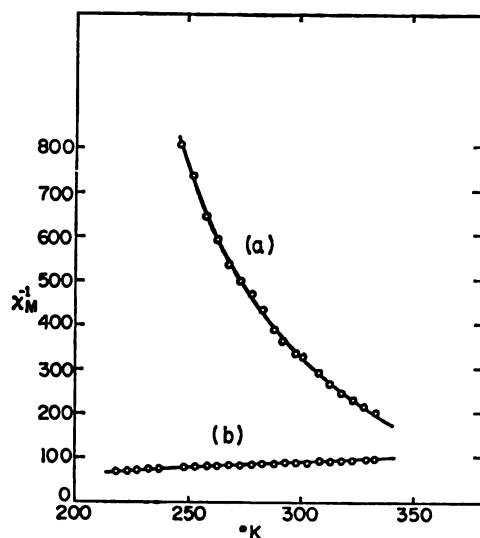


Figure 1. Plot of reciprocal molar susceptibility against temperature: (a) compound III in CH_2Cl_2 , (b) compound V in CHCl_3 .

sible, without change of molecular geometry. (A possible difference could arise due to a Jahn-Teller distortion in the high-spin state. As indicated in the discussion the large trigonal component in the crystal field leaves an orbital singlet lowest in the high-spin state, and Jahn-Teller effects will probably be small. There will, of course, be a difference in Fe-N bond lengths in the two states.)

Minor changes in molecular structure give rise to very diamagnetic low-spin compounds, fully paramagnetic high-spin compounds (μ_{eff} at room temperature ~ 5.2 BM), and compounds for which the moment is intermediate and strongly temperature dependent. The diamagnetic or partially diamagnetic complexes are deeply colored magenta compounds, while the fully paramagnetic compounds are pale green, almost colorless.

Other possible examples of anomalous magnetic behavior close to the crossover point have been reported by Stoufer, *et al.*, for $\text{Co}^{2+}(\text{d}^7)$,² Ewald, *et al.*, for $\text{Cr}^{3+}(\text{d}^3)$,³ and Melson and Busch⁴ for $\text{Ni}^{2+}(\text{d}^8)$. More recently a convincing example for $\text{Fe}^{2+}(\text{d}^6)$ has been reported by König and Madaya.⁵

Magnetic Susceptibilities

The room-temperature moments for some of these complexes measured in solution by an nmr method, together with their molecular weights, are listed in Table I. (The molecular weights were measured in chloroform using the vapor-pressure osmometer technique.) It is clear from these molecular weights that we are dealing with monomeric species. The rigid tridentate character of the ligand eliminates the possibility of a

(a) R. C. Stoufer, D. H. Busch, and W. B. Hadley, *J. Am. Chem. Soc.*, **83**, 3732 (1961); (b) R. C. Stoufer, D. W. Smith, E. A. Clevenger, T. E. Norris, *Inorg. Chem.*, **5**, 1167 (1966); (c) J. G. Schmidt, W. S. , and R. C. Stoufer, *ibid.*, **6**, 268 (1967).

(d) A. H. Ewald, R. L. Martin, I. G. Ross, and A. H. White, *Proc. Soc. (London)*, A280, 235 (1964).

(e) G. A. Melson and D. H. Busch, *J. Am. Chem. Soc.*, **86**, 4830 (1964).

(f) E. König and K. Madaya, *Chem. Commun.*, **3**, 61 (1966).

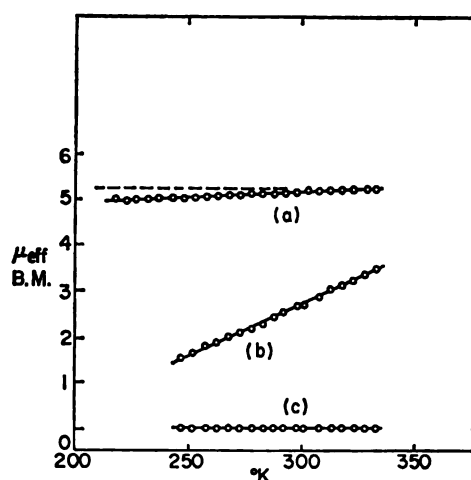


Figure 2. Plot of effective magnetic moment against temperature: (a) compound V in CHCl_3 , (b) compound III in CH_2Cl_2 , (c) compound I in CHCl_3 .

conformational equilibrium of the type which has been reported for four-coordinate $\text{Ni}(\text{II})$ chelates such as nickel(II) N,N' -dimethylaminotroponeimine.⁶

Table I. Room-Temperature Moments and Molecular Weights of Octahedral Iron(II) Poly(1-pyrazolyl)borates

Compound	Moment, BM	Molecular weight	
		Calcd	Measured
I	~ 0	614	614
II	~ 0	634	630
III	2.71*	481	479
IV	5.03	650	647
V	5.22	734	716

* Measured in CH_2Cl_2 because of solubility. All others measured in CHCl_3 .

The data of Table I show that the first two and last two complexes have moments corresponding essentially to fully low-spin and fully high-spin systems, respectively, and that the remaining complex bis[hydrotris(1-pyrazolyl)borate]iron(II) has an intermediate moment. If this arises from a spin equilibrium it should be strongly temperature dependent. This latter prediction is substantiated by the data shown in Figures 1 and 2. Figure 1 shows plots of the reciprocal molar susceptibility against temperature for the complexes III and V. The diamagnetic compounds cannot, of course, be included in this plot. Compound IV shows essentially the same behavior as V. Figure 2 shows a plot of the effective moments against temperature for complexes I, III, and V, complex I being diamagnetic at all temperatures studied. It appears there is some reduction in the effective moment of complex V with decreasing temperature, possibly indicating some favoring of the diamagnetic form. The moment is close to 5.2 BM at room temperature and about 5.0 BM at the lower temperatures. However, an alternative explanation could be that the 6E_g component of the split $^6T_{2g}$

(6) D. R. Eaton, W. D. Phillips, and D. J. Caldwell, *J. Am. Chem. Soc.*, **85**, 397 (1963).

ground state lies lowest and that the temperature dependence of the effective moment is due to varying populations of the sublevels in the E state. The behavior of complex III, though, is only interpretable in terms of a spin equilibrium. The variation of the effective moment with temperature is as nearly intermediate between the high-spin and low-spin cases as one could expect to realize. Several other complexes have also been studied. The compound with $R = X = H$, $Y = i\text{-Pr}$ showed intermediate behavior analogous to complex III, and the compound with $R = n\text{-Bu}$, $X = Y = H$ proved to be diamagnetic.

Optical Spectra

The positions of absorption maxima and the extinction coefficients for these Fe(II) complexes are given in Table II. Results for compound II have been

Table II. Electron Spectra of Octahedral Iron(II) Poly(1-pyrazolyl)borates

Compound	λ , m μ	ν , cm $^{-1}$	ϵ	Assignment
I in CHCl ₃	529	18,900	90	${}^1T_{1g}({}^1I) \leftarrow {}^1A_{1g}$
	342	29,200	13,700	Metal-to-ligand charge transfer
	318	31,400	8,600	
	286	35,000	4,000	
	207*	48,300	20,000	Ligand
III in CH ₂ Cl ₂	535	18,700	57	${}^1T_{1g}({}^1I) \leftarrow {}^1A_{1g}$
	337	29,700	12,100	Metal-to-ligand charge transfer
	322	31,100	8,200	
	288	34,700	5,400	
	206*	48,500	25,000	Ligand
IV in CHCl ₃	800	12,500	3.2	${}^6E_g \leftarrow {}^6T_{2g}$
	220*	45,400	34,000	
V in C ₆ H ₆	800	12,500	3.2	${}^6E_g \leftarrow {}^6T_{2g}$
	225*	44,400	39,000	

* Measured in cyclohexane.

omitted as the spectrum is closely similar to those of complexes I and III. The relatively small extinction coefficient of the absorption at $\sim 19,000\text{ cm}^{-1}$ in complex III indicates that it is probably a d-d transition, and since this band is also found in the fully diamagnetic molecule I it must be a singlet-singlet transition. We assign the absorption to the expected ${}^1T_{1g}({}^1I) \leftarrow {}^1A_{1g}$ transition. It might be noted that complex III is almost completely diamagnetic at room temperature in the solid state. Mössbauer and magnetic susceptibility studies have shown that the same general type of behavior with temperature is observed in the solid as is found in solution. However, the equilibrium has shifted in favor of the diamagnetic form.⁷

The absorption spectra and appearance of complexes IV and V are similar to those of hydrated ferrous salts. Only one d-d transition of any intensity is observed, and as indicated in Table II this is assigned to the ${}^6E_g \leftarrow {}^6T_{2g}$ transition. In the hydrated ferrous salts this transition usually shows a pronounced doubling which has been ascribed to either Jahn-Teller distortions or to low-symmetry components in the crystal field.⁸ In the

present case the band is quite symmetrical and shows no evidence of splitting. The transition should occur at a frequency Δ , showing that $\Delta \approx 12,500\text{ cm}^{-1}$ for the high-spin systems. Δ is the octahedral splitting parameter.

The reason for the dramatic color change from pale green to deep magenta on going from fully high-spin to fully low-spin compounds is now clear. The first d-d transition occurs at a much shorter wavelength for the spin-paired compound. This is to be anticipated on the basis of a simple crystal-field calculation, as is shown in the Discussion. The singlet-singlet transition is 20-30 times more intense than the quintet-quintet. This is probably due to intensity borrowing from nearby charge-transfer absorption in the former case. For the high-spin systems, the d-d transition is well separated from the charge-transfer absorption. The charge-transfer absorption is at considerably shorter wavelengths in the high-spin systems. These high-spin chelates all have methyl substituents, and the shift may be ascribed to the hyperconjugative effect of these groups. Hyperconjugation raises the energy of the highest filled ligand π orbital. Thus the ionization potentials of alkyl-substituted ethylenes are lower than that of ethylene. Calculations indicate that the lowest antibonding π orbital is also raised in energy by alkyl substitution, but by a smaller amount so that the energy gap is decreased. This is supported by the red shift in the long wave absorption in ethylene on alkyl substitution. Thus the lowest unfilled ligand orbital is expected to occur at higher energies in the high-spin complexes than in the low-spin complexes. The energies of the d orbitals are unlikely to be grossly different in the high-spin and low-spin complexes. The large blue shift observed on passing from low spin to high spin is therefore consistent with the assignment of these bands to metal-to-ligand charge-transfer transitions.

Nuclear Magnetic Resonance Spectra

Nmr assignments for the octahedral ferrous complexes are complicated by the high-spin-low-spin equilibrium. The resonances for the 4-H proton in the parent complex and the 3,5-dimethyl complex, which are in essentially the same positions for the Co^{2+} derivatives,⁹ are very different for the Fe^{2+} case since a large proportion of the parent complex is in the diamagnetic state. Assignments have been made mainly on the basis of line intensities and widths, although the effect of substitution can be utilized by comparing complexes IV and V. Chemical shifts at 30° and assignments for the octahedral Fe(II) complexes are given in Table III.

It is clear that the nmr data are in qualitative agreement with the conclusions from the susceptibility data. Thus the resonances in compounds I and II are in the positions anticipated for diamagnetic complexes, the positions of the resonances for the 3-, 4-, and 5-H on the pyrazolyl groups being close to those for the corresponding zinc complexes.⁹ Complex III shows intermediate shifts which are compatible with the assumed spin equilibrium, and much larger shifts are observed for the fully paramagnetic complexes IV and V. More direct evidence for the spin equilibrium in complex

(7) J. P. Jesson and J. F. Weiher, *J. Chem. Phys.*, **46**, 1955 (1967).

(8) F. A. Cotton and M. D. Meyers, *J. Am. Chem. Soc.*, **82**, 5023 (1960).

(9) J. P. Jesson, S. Trofimenko, and D. R. Eaton, *ibid.*, **89**, 3148 (1967).

e III. 60-Mcps Nmr Data for Octahedral Fe(II) Complexes*

Compound	Shift, mμ	Assignment
I	-486	3-, 4-, 5-H
	-433	
	-397	
II	-474	3-, 4-, 5-H
	-425	
	-379	
	-491	<i>p</i> -H
	-457	<i>o</i> - and <i>m</i> -H
	-430	
III	-815	3-, 4-, 5-H
	-815	
	-480	
IV	+240	H on boron
	-2870	4-H
	-2350	3-CH ₃
	-770	5-CH ₃
V	+2570	H on boron
	-2330	3-CH ₃
	-820	5-CH ₃
	-570	4-CH ₃
	+2625	H on boron

Shifts measured from TMS as internal standard.

is provided by the temperature dependence of the shifts. The temperature dependence of the shifts of complexes IV and V (see Figure 3b and c) show the normal Curie-type behavior expected in paramagnetic complexes. Complex III, however (Figure 3a), shows the anomalous type of behavior, the shifts converging toward diamagnetic positions as the temperature is lowered.

Discussion

An approximate estimate of the magnitude of the octahedral splitting parameter Δ required to induce spin pairing may be obtained by equating the first-order expressions for the energies of the electronic states involved, using the strong-field scheme. The Δ found in this way is equal to the mean-pairing energy π . Griffiths¹⁰ has found expressions for the mean pair-energies in these configurations and obtained the following approximate conditions for the occurrence of the low-spin form (in cm⁻¹).

$$\begin{aligned} d^5 \Delta &> 7.5B + 5C \approx 24,000 \\ d^6 \Delta &> 2.5B + 4C \approx 16,400 (12,500) \\ d^7 \Delta &> 7B + 4C \approx 20,000 (10,000) \end{aligned} \quad (1)$$

The values after the expressions have been calculated using $B = 800$ and $C = 4.5B = 3600$ cm⁻¹. The numbers in parentheses are the Δ values estimated from spectra of the octahedral high-spin iron(II) and cobalt(II) poly(1-pyrazolyl)borates.⁹ It can be seen that spin pairing is more easily achieved for the d⁶ than the d⁵ or d⁷ configurations.

The absorption at 12,500 cm⁻¹ in complexes IV and V has been assigned to the transition ${}^6E_g \rightarrow {}^6T_{2g}$ which simple crystal-field theory has an energy $\Delta(\text{hs}) = 500$ cm⁻¹ (hs = high spin). However, as Ewald, et al.,³ have pointed out, because of the expected in-

(*) J. S. Griffiths, *J. Inorg. Nucl. Chem.*, **2**, 1 (1956).

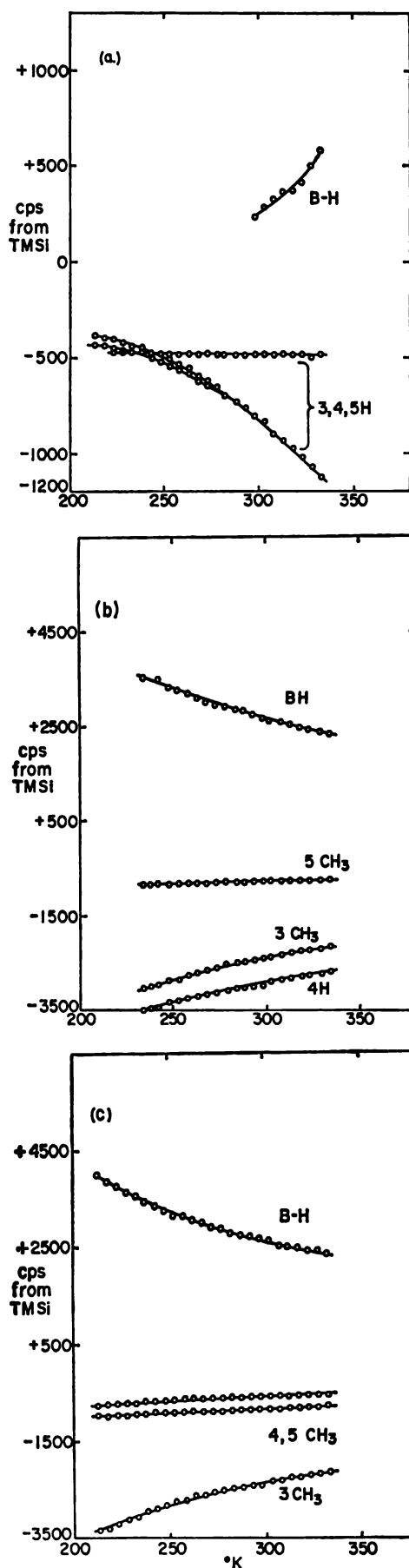


Figure 3. Proton resonance spectra of octahedral ferrous complexes as a function of temperature measured in CDCl₃ (shifts from TMS at 60 Mcps): (a) compound III, (b) compound IV, (c) compound V.

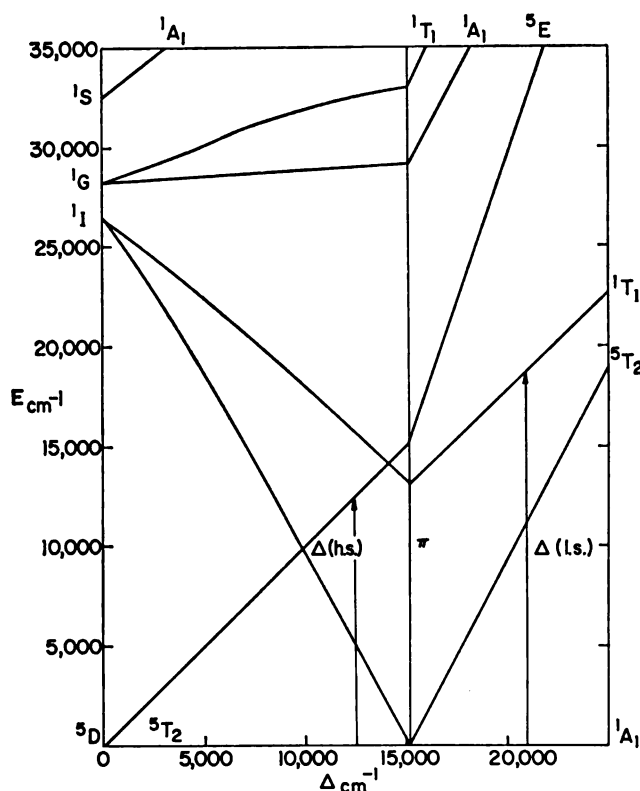


Figure 4. Tanabe diagram for d^4 configuration. Only the quintet states and the ${}^1T_{1g}$ and ${}^1A_{1g}$ states below 35,000 cm^{-1} have been included. The positions of the experimentally observed high-spin transition and first low-spin transition are indicated in the figure; $B = 800$ and $C = 3600 \text{ cm}^{-1}$.

crease in bond lengths on transferring an electron from the t_{2g} orbitals (nonbonding) to the e_g orbitals (antibonding), the Δ values for the high- and low-spin states in their equilibrium geometries will be different, and one has the approximate condition

$$\Delta(\text{hs}) < \pi < \Delta(\text{ls}) \quad (2)$$

the Δ values referring to the equilibrium situations ($\text{ls} = \text{low spin}$).

Robinson, *et al.*,¹¹ have made an estimate of the critical $\Delta(\text{hs})$ value for crossover to the low-spin form by comparison of a series of iron(II) and the corresponding nickel(II) complexes. They note that the ratio $\Delta_{\text{Fe}^{2+}}/\Delta_{\text{Ni}^{2+}} = 1.11 \pm 0.07$ for a series of five complexes. The weakest ligand which produced spin pairing in the iron(II) complexes gave an extrapolated $\Delta(\text{hs}) \approx 13,400 \text{ cm}^{-1}$. The strongest ligand which did not give spin pairing has $\Delta(\text{hs}) = 11,600 \text{ cm}^{-1}$. It was therefore estimated that the critical value of $\Delta(\text{hs})$ is $12,500 \pm 800 \text{ cm}^{-1}$, in remarkably good agreement with the value found from the iron poly(1-pyrazolyl)borates. Some variation in the critical value of $\Delta(\text{hs})$ is possible since the mean pairing energy π depends on the interelectronic repulsion parameters (B and C) which themselves vary with the degree of covalent bonding in the complexes.

The relevant electronic levels of d^4 as a function of crystal-field strength Δ , for octahedral coordination, are shown in Figure 4. The levels were calculated us-

ing the matrices of Tanabe and Sugano¹² with $B = 800$ and $C = 3600 \text{ cm}^{-1}$. The choice of values for B and C is based on the following considerations. The free ion value of B for Fe^{2+} ($\sim 940 \text{ cm}^{-1}$) is somewhat lower than the values for Co^{2+} ($\sim 980 \text{ cm}^{-1}$) and Ni^{2+} ($\sim 1040 \text{ cm}^{-1}$).¹³ It seems likely that the value in the complex will also be lower. Values of B of ~ 830 and ~ 850 were found for the corresponding Co(II) and Ni(II) complexes. A value of $B = 800 \text{ cm}^{-1}$ for the Fe(II) complexes is therefore reasonable. The assumption $C = 4.5B = 3600 \text{ cm}^{-1}$ leads to a mean pairing energy of $\pi \approx 16,400 \text{ cm}^{-1}$ from eq 1. The crossover point " π " in the full calculations is seen to be $\sim 15,000 \text{ cm}^{-1}$ rather than the value of $16,400 \text{ cm}^{-1}$ given by the approximate formula. The difference is due to the interaction between the four 1A_1 states of the configuration, which has been neglected in the simple formulas.

The positions of the first high-spin and first low-spin transitions are marked on Figure 4, occurring at $\Delta(\text{hs}) = 12,500 \text{ cm}^{-1}$ and $\Delta(\text{ls}) = 21,000 \text{ cm}^{-1}$. In view of the neglect of the low-symmetry component of the field, the uncertainty in the values of the interelectronic repulsion integrals, and the fact that they are assumed to have the same value for high- and low-spin compounds, there may be considerable error in the $\Delta(\text{ls})$ value. In the iron(III) dithiocarbamates, Ewald, *et al.*,³ found that their electronic spectral data gave a quite low value for $\Delta(\text{hs}) \approx 12,800 \text{ cm}^{-1}$. This value is even lower than Δ for $\text{Fe(H}_2\text{O)}_6^{2+}$. A similar situation was noted in the Co(II) complexes of Stouffer, *et al.*² The results of Ewald, *et al.*,³ were rationalized in terms of a very large nephelauxetic effect with $B(\text{complex})/B(\text{free ion}) = \beta \approx 0.47$. Values of β and Δ could not be obtained directly from electronic spectral data and were estimated by comparison of optical data for other dithiocarbamates with the corresponding hexaaquo complexes.

In the present case $\Delta(\text{hs})$ is already considerably larger than $\Delta[\text{Fe(H}_2\text{O)}_6^{2+}]$, $\sim 10,400 \text{ cm}^{-1}$. The β value, on the basis of our assumption that the reduction in B is similar to that found in the Co(II) and Ni(II) cases,⁹ is ~ 0.85 .

It is anticipated that in the complex $\text{Fe[HB(pz)}_3\text{)]}_2$ which has D_{3d} symmetry, there will be a large trigonal component in the crystal field. Such a trigonal component has been established for $\text{Co[HB(pz)}_3\text{)]}_2$, and it has been shown that the splitting of the ${}^4T_{1g}$ ground state is approximately 2000 cm^{-1} with the orbital doublet lying lowest.¹⁴ It is also anticipated that the orbital splitting of the ${}^5T_{2g}$ state in $\text{Fe[HB(pz)}_3\text{)]}_2$ due to this trigonal component will have the opposite sign to that of the Co(II) complex, giving an orbital singlet as the lowest component.¹⁵ This follows from simple one-electron theory since the high-spin d^7 system has a single hole in the t_{2g} shell, and the high-spin d^6 ground state is degenerate owing to a single electron in the t_{2g} shell. However, it has been suggested that the inclusion of Coulomb and exchange interactions can reverse the sign of the ground-state splitting for Co^{2+} .¹⁶ In addition the assumption that the low-symmetry

(12) Y. Tanabe and S. Sugano, *J. Phys. Soc. Japan*, **9**, 753 (1954).

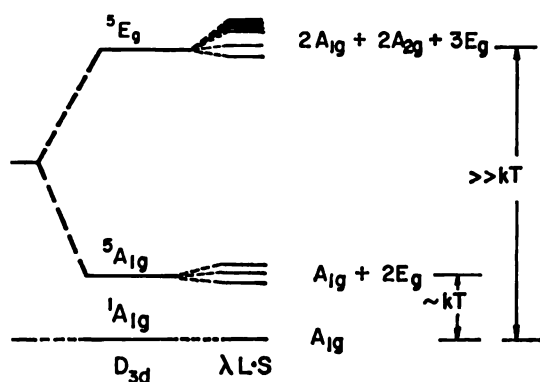
(13) J. S. Griffiths, "The Theory of Transition Metal Ions," Cambridge University Press, London, 1961.

(14) J. P. Jesson, *J. Chem. Phys.*, **45**, 1049 (1966).

(15) J. H. van Vleck, *Discussions Faraday Soc.*, **26**, 96 (1958).

(16) P. K. Baltzer, private communication.

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Level scheme for ground-state manifold of $\text{Fe}[\text{HB}(\text{pz})_3]_2$.

ent of the crystal field is of the same form for Fe^{2+} and Fe^{3+} cases may not be completely justified. Since the orbital degeneracy of the ground state is not taken into account in the interpretation of the susceptibility data, the final evidence bearing on this point will be forthcoming.

Magnetic resonance experiments for Fe^{2+} and Fe^{3+} in the cadmium chloride lattice give the following

$$\begin{array}{lll} \text{Fe}^{2+} & g_{\parallel} = 7.4 & g_{\perp} = 0? \\ \text{Fe}^{3+} & g_{\parallel} = 3.06 & g_{\perp} = 4.98 \end{array}$$

Results have been obtained in this laboratory for Fe^{2+} ions in MgTiO_3 .

$$\begin{array}{lll} \text{Fe}^{2+} & g_{\parallel} \approx 12 & g_{\perp} = 0? \\ \text{Fe}^{3+} & g_{\parallel} = 2.78 & g_{\perp} = 5.02 \end{array}$$

Measurements were made on powders at 4.2°K, and there is considerable uncertainty in the g_{\parallel} value due to the breadth of the absorption. In contrast, the Co^{2+} results show unambiguously that a singlet lies lowest in the split ground state.¹⁸ The corresponding treatment for the ${}^6\text{T}_{2g}$ state of Fe^{2+} given by Griffiths.¹³ g_{\parallel} varies from about 4 depending on the magnitude and sign of the component in the crystal field. $g_{\perp} = 0$. Values between 7 and 10 correspond to the orbital doublet, suggesting that this is the case for the distorted MgTiO_3 systems. This interpretation could be related in the even-electron Fe^{2+} system by the effect of rhombic components in the crystal fields. Ideal structures for the two cases demand axial symmetry about the metal in the host.

The substitution of the Fe^{2+} impurity could introduce slight rhombic components into the fields. It is difficult to say whether the distortions would be large enough to reverse the assignment. Thus the magnetic resonance data do seem to indicate that ground-state splittings for Fe^{2+} and Co^{2+} in the octahedral field are of the opposite sign, and for the discussion we shall therefore assume that the splitting of the orbital triplet in the ferrous poly(1-pyrazolyl)borates is large and leaves an orbital singlet.

¹⁸ Orton, *Rept. Progr. Phys.*, 22, 204 (1959).

¹⁹ Bragg and M. H. L. Pryce, *Proc. Roy. Soc. (London)*, 1951).

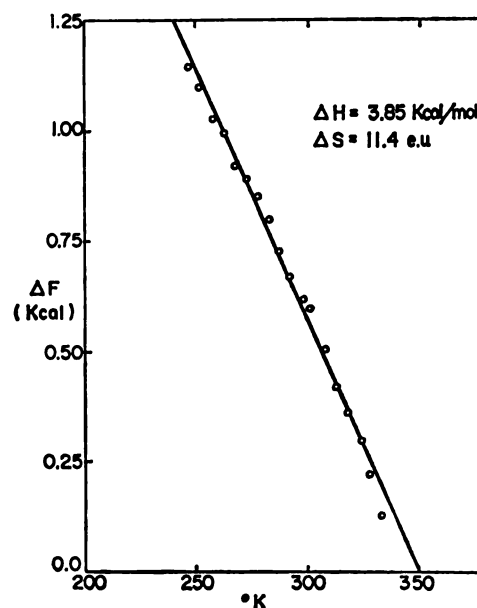


Figure 6. Plot of free energy against temperature for spin equilibrium in $\text{Fe}[\text{HB}(\text{pz})_3]_2$.

A schematic energy level diagram based on this assumption is shown in Figure 5. The spin equilibrium involves the ${}^5\text{A}_{1g}$ and ${}^1\text{A}_{1g}$ states. Diagrams such as Figure 5 must be viewed with caution when temperature studies are involved since the level scheme may be a fairly sensitive function of temperature. If ${}^5\text{A}_{1g} \leftrightarrow {}^1\text{A}_{1g}$ separation varies approximately linearly with temperature, the effect will appear as an entropy term when the free energy of the equilibrium is considered. Such an effect can also be produced by differences in the vibrational partition functions for the high-spin and low-spin states.³ In a previous paper it was suggested⁶ that an appreciable entropy term in the apparent free energy for an equilibrium of this type would argue for a geometrical difference between the species involved. The arguments given above, however, suggest that this is not the only possible origin of the term.

Splitting of the ${}^5\text{A}_{1g}$ state due to spin-orbit effects and the low-symmetry component of the field will be of the order of tens of wavenumbers, and for our purposes the state will behave as a simple spin quintet with $g \sim 2$. g will be slightly larger than 2 owing to spin-orbit mixing from excited states, and a value of 2.13 is obtained from the moment of the fully paramagnetic complex.

The susceptibility of the system as a function of temperature is then given by

$$\chi_M = \frac{Ng^2\beta^2S(S+1)}{3kT} [e^{\Delta G/RT} + 1]^{-1} \quad (3)$$

ΔG being the molar free-energy change in the process. The expression may be written in terms of the effective moments as

$$\Delta G = RT \ln \left[\frac{\mu_{\infty}^2}{\mu^2} - 1 \right] \quad (4)$$

where μ_{∞} is the moment for the fully paramagnetic form, and this is taken as 5.22 BM from the moment of V.

In Figure 6 the free-energy change for the spin equilibrium in $\text{Fe}[\text{HB}(\text{pz})_3]_2$ is plotted against temperature, giving $\Delta H = 3.85$ kcal/mole and $\Delta S = 11.4$ eu. If our assumptions about the energy level scheme are correct, the entropy term of 11.4 eu will contain a contribution $R \ln 5 = 3.2$ eu due to the spin degeneracy of the quintet state but no contribution from orbital degeneracy. The remaining 8.2 eu must be accounted for in terms of a temperature dependence of the effective crystal field, variable solvation effects, and differences in the vibrational partition functions between the two states.

There are two possible mechanisms for the paramagnetic shifts observed in the nuclear resonance spectra. Spin delocalization to the ligand can result in a Fermi contact interaction, the shifts being given by an expression of the form

$$\Delta\nu_i = -a_i \frac{2\pi g\beta\nu S(S+1)}{3kT\gamma} \quad (5)$$

where a_i is in cycles per second. The expression is based on the assumption of a Curie law magnetic behavior of the ground state, a situation which is seldom if ever realized in paramagnetic compounds showing well-resolved nmr spectra.

The second mechanism involves the dipolar coupling of the electron and nuclear magnetic moments and gives a net shift for the nuclear resonances in solution only if the electron moment is anisotropic. With the limiting assumption of a Curie law situation, an expression of the form

$$\Delta\nu = -\frac{1}{15}\nu \left(\frac{3\cos^2\theta - 1}{r_i} \right) \frac{\beta^2 S(S+1)}{3kT} [g_{\parallel} - g_{\perp}] [3g_{\parallel} + 4g_{\perp}] \quad (6)$$

is derived. The additional assumption has been made, in averaging over the tumbling motion, that the spin-

lattice relaxation time is short relative to the correlation time for tumbling. This situation is likely to apply to cases where well-resolved nmr spectra are observed since we have the criterion $T_1^{-1} \gg a_i$, required for sharp spectra, T_1 being the electron spin-lattice relaxation time and a_i the electron-nuclear hyperfine coupling constant.

If either or both types of interaction are present, the shifts are inversely proportional to temperature for the paramagnetic species. The diamagnetic-paramagnetic equilibrium can be allowed for by the factor $[e^{\Delta G/RT} + 1]^{-1}$ as in the susceptibility equations. Quite large anisotropies can be induced in the $^5\text{T}_2$ ground state by low-symmetry components in the field,¹² and it would be unwarranted to assume that the observed shifts are due only to the scalar interaction. In addition to the departures from the simple $1/T$ behavior due to the spin equilibrium, departures can also be produced by non-Curie law behavior. Differences in g -tensor components and hyperfine coupling constants for the split levels of the ground state would require a more complicated Boltzmann averaging, giving a relatively complex temperature dependence.

In view of the limitations imposed on the formulas and the difficulty in establishing the proton shifts for the fully paramagnetic system, the data do not seem to merit analysis in terms of an enthalpy and entropy change for the equilibrium.

Experimental Section

The epr measurements were made using a Varian 100-kcps X-band spectrometer equipped with a 12-in. magnet having a fixed 1.75-in. gap. Field measurements were made using a Harvey Wells FC-502 gaussmeter and CMC 709C frequency counter. Frequency measurements were made with a Hewlett-Packard X5332A frequency meter. A quartz helium finger was used to maintain the samples at 4.2°K.

Other experimental techniques used have been described in a previous paper.⁹

Organic and Biological Chemistry

Boron-Pyrazole Chemistry. I. Pyrazaboles

S. Trofimenko

Contribution No. 1238 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898.

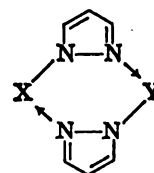
Received January 5, 1967

Abstract: Boranes and borane complexes react cleanly with pyrazoles giving rise to nondissociable dimers of 1-borylpyrazoles. These compounds represent a new, remarkably stable class of boron heterocycles and have been named pyrazaboles. One-step syntheses of representative pyrazaboles are described and their properties are discussed.

In 1924 Morgan and Tunstall¹ found that a BF_2 group can replace the hydrogen bridge in acetylacetone, benzoylacetone, and dibenzoylmethane. The stability of the products has been attributed to coordination of the BF_2 group with the second heteroatom. At that time other examples of a BR_2 group ($\text{R} = \text{Cl}$, alkoxy, alkyl, aryl; $\text{R}_2 = o$ -phenylenedioxy) replacing the chelated proton in enolizable β -diketones,²⁻¹² β -keto esters,^{9b,10,13} β -ketocarboxamides,¹⁴ etoimines,^{9b,10,15} 8-hydroxyquinoline,^{10,12,16-19} binide,²⁰ 1-amino-7-imino-1,3,5-cycloheptatrienes,²¹ dimethylglyoxime)nickel²² and -cobalt,²³ as well as cellaneous chelating agents with N and O termin-^{24,25} have appeared. The notion that a BR_2 group, when bonded to one heteroatom of a chelating agent and coordinated to the other, resembles in some ways a metal ion is implicit in the above results and has been mentioned by several of the authors. It is further supported by the finding that BF_2 -bridged acetylacetone

undergoes electrophilic substitution reactions²⁶ akin to those of transition metal acetylacetonates for which quasi-aromaticity has been invoked.²⁷

In all these compounds the BR_2 group forms an intramolecular bridge. We were interested in constructing resonance-stabilized cyclic structures of high symmetry based on *intermolecular* BR_2 bridges. Pyrazole was selected for this purpose since its geometry was known to favor formation of hydrogen-bonded dimers²⁸ and since both its cationic and anionic forms possess C_{2v} symmetry.²⁹ In addition this heterocyclic nucleus has great hydrolytic and oxidative stability. With pyrazole dimer as the starting point, it was assumed that this entity could be bridged by any binary combination chosen from (a) hydrogen, (b) transition metal ion, and (c) BR_2 group, the interchangeability of these in chelating systems having been amply demonstrated. Structures I-VI were arrived at in this fashion. Of these, the first two are known examples of pyrazole dimer and



I, $\text{X}=\text{H}$; $\text{Y}=\text{H}$

II, $\text{X}=\text{M}$; $\text{Y}=\text{M}$

III, $\text{X}=\text{BR}_2$; $\text{Y}=\text{BR}_2$

IV, $\text{X}=\text{BR}_2$; $\text{Y}=\text{H}$

V, $\text{X}=\text{BR}_2$; $\text{Y}=\text{M}$

VI, $\text{X}=\text{M}$; $\text{Y}=\text{H}$

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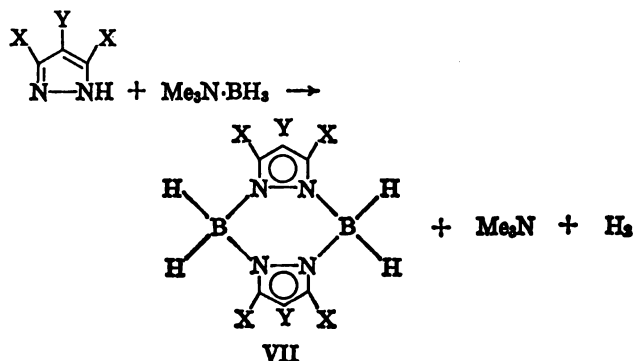
(29) See, for instance, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 45.

transition metal compounds with pyrazole,³⁰ respectively. Compounds IV and V are hydrogen and metal poly(1-pyrazolyl)borates³¹ and are dealt with elsewhere.³²

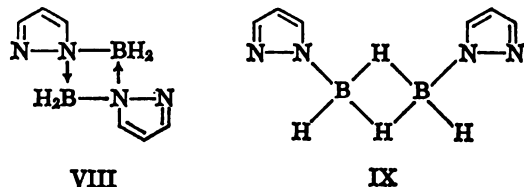
This paper is concerned with compounds of type III which, because of their unusual features, stability, and wealth of derivatives, were given the trivial name "pyrazabole" with numbering as shown in structure X.

Results and Discussion

Refluxing equimolar amounts of pyrazole and trimethylamine borane in toluene resulted in rapid evolution of hydrogen and trimethylamine (eq 1, X = Y = H). A crystalline, sublimable solid of camphoraceous odor, mp 80–81°, was isolated in good yield. It was a dimer of 1-dihydroborylpyrazole as established by elemental analysis, molecular weight determination, the presence of a strong BH₂ multiplet around 2400–2500 cm⁻¹ in the infrared, and the degradation of this compound by boiling hydrochloric acid to pyrazole and boric acid.



Of the three *a priori* possible structures, VII (X = Y = H), VIII, and IX, one would immediately tend to select VII for electronic and steric reasons.³³ Support for this structure was obtained from H¹ nmr which had



only two C–H peaks: a doublet at τ 2.49 and a triplet at τ 3.83 ($J = 2.0$ cps) in a 2:1 ratio. This is obviously incompatible with structures VIII and IX, both of which should display spectra characteristic of asymmetrically substituted pyrazole.³⁴ The nmr spectrum of pyraza-

(30) M. Inoue, M. Kishita, and M. Kubo, *Inorg. Chem.*, **4**, 627 (1965).

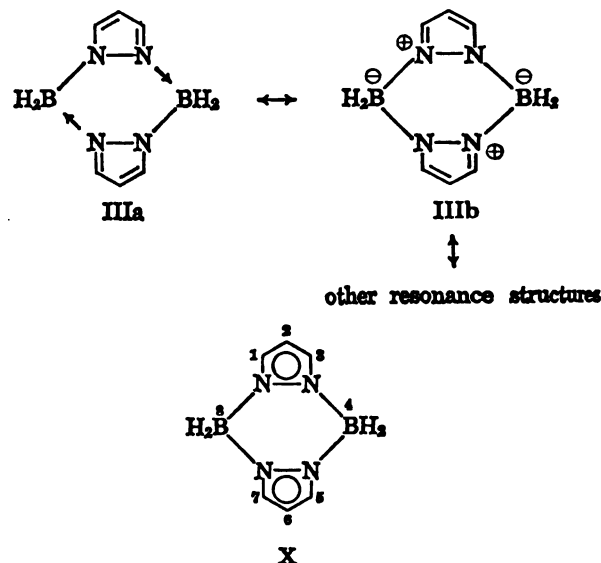
(31) S. Trofimenko, *J. Am. Chem. Soc.*, **88**, 1842 (1966).

(32) S. Trofimenko, *ibid.*, **89**, 3170 (1967).

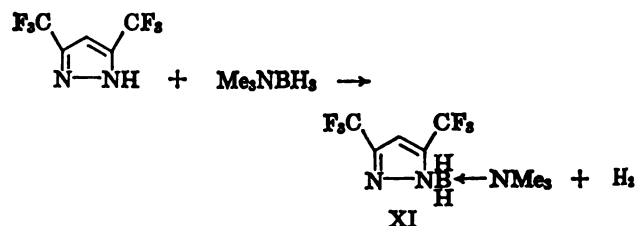
(33) As far as VIII is concerned, no precedent is known for electron donation by the substituted nitrogen in 1-alkylpyrazoles. Reactions such as quaternization invariably take place at the 2 position, thus maintaining resonance in the pyrazole ring which would otherwise be lost. Values for the resonance energy of pyrazole range, depending on the method used, were from 27 to 41 kcal/mole: H. Zimmerman and H. Geisenfelder, *Z. Elektrochem.*, **65**, 368 (1961); A. F. Bedford, P. B. Edmondson, and C. T. Mortimer, *J. Chem. Soc.*, 2927 (1962). Moreover, VII should be favored over VIII by some additional 26 kcal/mole from strain considerations, using the thermochemical strain energy for cyclobutane of 26.2 kcal/mole: S. Kaarsemaker and J. Coops, *Rec. Trav. Chim.*, **71**, 261 (1952). With regard to IX, no precedent is known for a simple aminoborane containing hydrogen bridges; such bridges are always broken in the presence of donor atoms.

(34) Proton nmr was shown to be a reliable and discriminating tool for establishing the type of substitution in pyrazole. See, for instance, L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966), and

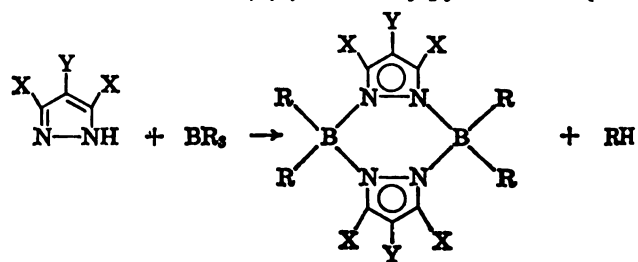
bole indicates equivalence of positions 1, 3, 5, 7. This spectroscopic equivalence persists in all pyrazabole derivatives and is indicative of a structure such as X containing tetrahedral boron in a symmetrical environment. This structure would contain positive charges delocalized in the ligand and negative charges on boron much like the analogous β -diketonates, which is consistent with the inertness of pyrazabole to sodium hydroxide and other nucleophiles.³⁵



When substituted pyrazoles were used instead of pyrazole, the reaction proceeded analogously and C-substituted pyrazaboles were obtained (Table I). Pyrazoles with strong electron-withdrawing substituents reacted at a slower rate, commensurate with the reduced nucleophilicity of the 2-nitrogen. In the case of 3,5-bis(trifluoromethyl)pyrazole the product was trimethylamine 3,5-bis(trifluoromethyl)pyrazol-1-ylborane (XI), which could be distilled without decomposition. 1,3,5,7-Tetrakis(trifluoromethyl)pyrazabole (as well as 1,2,3,5,6,7-hexabromopyrazabole) was prepared by using tetrahydrofuran–borane complex instead of trimethylamine borane.



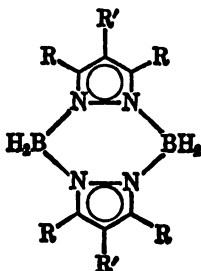
Trialkylboranes react with pyrazoles on heating to 120–150° with evolution of the appropriate hydrocarbon and formation of 4,4,8,8-tetraalkylpyrazaboles (Table



references cited therein, as well as V. F. Bystrov, I. I. Grandberg, and G. I. Sharova, *Zh. Obshch. Khim.*, **35**, 293 (1965).

(35) Part III: S. Trofimenko, submitted for publication.

Table I. Compounds of Structure



R	R'	Mp, °C	Yield, %	C, %		H, %		N, %		X, %		H ¹ nmr ^a	B ¹¹ nmr ^a	Miscellany
				Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found			
H	H	80–81 ^a	90	45.2	45.4	6.27	6.09	35.1	35.1	B, 13.5 Mol wt, 160	B, 13.7 Mol wt, 166	d, 2.49 (2) t, 3.83 (1) (J = 2.0 cps)	t, 27.1 (J = 108 cps)	Ultraviolet, end absorption 213 mμ (ε 1130)
H	Cl	119–120 ^b	74	31.4	31.3	3.49	3.49	24.2	24.2			s, 2.43		
H	Br	144–145 ^b	99	22.6	22.8	2.54	2.51	17.6	17.7	Mol wt, 318	Mol wt, 313	s, 2.40	t, 27.6 (J = 94 cps)	Ultraviolet, λ _{max} 233 mμ (ε 7060)
H	CH ₃	81–82 ^a	70	51.1	51.6		7.46		7.46			s, 2.64 (2) s, 7.95 (3)		
H	CN	290–300 dec	95	45.8	46.6	3.81	3.98	40.0	39.8			s, 0.95	t, unresolved 27.3	Ultraviolet, end absorption only; infrared, 2500 and 2470 cm ⁻¹ (BH ₂), 2260 cm ⁻¹ (CN)
H	NO ₂	202–203	96	28.8	29.4	3.20	3.12					s, 1.15		Photosensitive, turns orange on exposure to light
H	CF(CF ₃) ₂	49–50 ^a Bp 70–78 (2 mm)	66	29.0	29.5	1.61	1.88			Mol wt, 496	Mol wt, 526	s, 1.91	t, unresolved 27.2	Very unpleasant, penetrating odor
CH ₃	H	184–185 ^c	58	55.6	55.8	8.33	8.38	25.9	25.9	Mol wt, 216	Mol wt, 210		t, 31.2 (J = 103 cps)	
C ₆ H ₅	H	203 ^d sinters 232–242 dec	29	77.6	77.6	5.70	5.69	12.1	12.3					Ultraviolet, λ _{max} 248 mμ (ε 53,000)
CF ₃	H	88–89 ^a	93	27.8	27.7	1.37	1.58	12.9	12.8	F, 52.8 Mol wt, 432	F, 53.3 Mol wt, 489		t, unresolved 27.7	
CH ₃	CH ₃	173–174 ^c	99	59.0	59.2	9.02	9.06	22.9	23.1			s, 7.67 (2) s, 8.10 (1)		
Br	Br	280 ^d sinters 285–290 dec	90	11.3	11.0	0.63	0.50	8.83	8.78					

^a Recrystallized from hexane. ^b Recrystallized from heptane. ^c Recrystallized from toluene. ^d Recrystallized from xylene. ^e Distilled. / Molecular weights determined osmotically in chloroform. High volatility of perfluoroalkylpyrazaboles would lead to high values. ^a The H¹ nmr data show multiplicity, chemical shift in τ, and relative areas. The B¹¹ nmr data are given in parts per million and referred to external methyl borate

II), while triphenylborane yields 4,4,8,8-tetraphenylpyrazabole.

All pyrazaboles thus prepared are colorless, sublimable solids except for 4,4,8,8-tetrabutylpyrazabole which is a liquid. They are unaffected by air and water and have been stored for over 3 years without any apparent deterioration, although 2,6-dinitropyrazabole is photosensitive.

Such extraordinary stability is even more noteworthy if one considers that none of the other chelating systems has yielded isolable BH₂-bridged species despite several attempts at their preparation.^{12,22} This stability (thermodynamic as well as kinetic) may be rationalized as follows. (A) Molecular models²⁶ show that the nitrogen and boron atoms (the prospective targets of electrophilic and nucleophilic attack, respectively) in pyrazabole are much better shielded than the BR₂ group and the corresponding heteroatoms in, for instance, analogous acetylacetone derivatives. The im-

portance of steric factors in B–N coordination chemistry is well known.²⁷ (B) While there are four nonexcited resonance structures based on charge separation in BR₂-bridged acetylacetone, there are 16 structures such as IIIa in pyrazabole with attendant stabilization of the ground state. (C) The pyrazole nucleus is much more resistant to reduction than an enolizable 1,3-dione system.

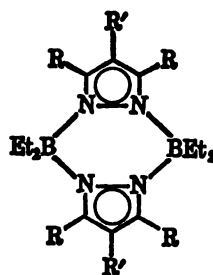
A characteristic feature in the infrared spectra of B-unsubstituted pyrazaboles is the strong absorption due to BH stretch (Figure 1). It is most complex in pyrazabole itself and consists of peaks at 2470, 2430, 2410, 2370, 2310, 2280, 2250, and 2240 cm⁻¹. The strongest peak is at 2470 cm⁻¹, and the remaining ones are of gradually decreasing intensity, except for the 2310, 2280 cm⁻¹ pair where the higher frequency peak is the weaker of the two.²⁸ Most C-substituted pyrazaboles have a strong sharp doublet in the 2400–

(37) T. D. Coyle and F. G. A. Stone, *Progr. Boron Chem.*, **1**, 132 (1964), and references cited therein.

(38) This spectrum was measured in Nujol mull. The BH₂ band remained complex even in CCl₄ solution: 2440 (s), 2415 (s), 2345 (m), 2280 (w), 2265 (w), and 2220 (w) cm⁻¹. This complexity of the BH stretch is inconsistent with a planar model of essentially D_{2h} symmetry and supports a puckered structure as indicated by molecular models.

(36) While Stuart–Breigleb models may not give an accurate picture of the molecular structure, they are useful in supplying qualitative data. An unstrained model of pyrazabole is puckered in the boat form, whereas one would expect the molecule to be planar if coplanarity of the B–N bonds and tetrahedral angles around boron are preserved. Such a model may be also constructed, but it entails considerable strain.

Table II. Compounds of Structure



R	R'	Mp, °C	Yield, %	C, % Calcd	C, % Found	H, % Calcd	H, % Found	X, % Calcd	X, % Found	H ¹ nmr ^f	B ¹¹ nmr ^f
H	H	106-107 ^a	94	61.8	61.7	9.56	9.35	B, 7.94	B, 7.90	d, 2.41 (2) t, 3.60 (1) m, 9.5 (10) (<i>J</i> = 2.3 cps)	s, +16.1
H	Cl	117-118 ^a	85	49.0	49.3	7.00	7.18	N, 16.9	N, 16.5	s, 2.38 (1) m, 9.4 (5)	s, +15.0
H	Br	127-128 ^a	95	39.1	39.0	5.59	5.91	Br, 37.2 Mol wt, 430	Br, 37.2 Mol wt, 447 ^e	s, 2.32 (1) m, 9.4 (5)	s, +15.6
H	CN	264-265 ^b	93	59.7	60.0	7.46	7.41	N, 26.1	N, 26.0	s, 1.97 (1) m, 9.4 (5)	s, +15.4
H	NO ₂	186-189 ^b dec	46	46.4	45.0	6.63	6.70	N, 23.2	N, 23.9	s, 1.70 (1) m, 9.3 (5)	
CH ₃	H	156-157 ^c	86	65.8	65.9	10.4	10.6			s, 4.03 (1) s, 7.60 (6) m, 9.08-9.75 (10)	s, +13.8
CH ₃	CH ₃	173-174 ^c	99	67.4	67.4	10.7	10.7	N, 15.7	N, 15.9	s, 7.57 (6) s, 7.88 (3) m, 9.4 (10)	s, +14.3
Br	Br	~210 dec	94	22.5	23.0	2.68	2.79			q, 8.73 (2) t, 9.52 (3) (<i>J</i> = 8.0 cps)	
H	CF(CF ₃) ₂	63-64 ^d	69	39.5	39.5	3.95	3.96	N, 9.21	N, 9.79		

^a Recrystallized from ethanol. ^b Recrystallized from xylene. ^c Recrystallized from heptane. ^d Distilled, bp 94-98° (4.5 mm). ^e Molecular weights determined osmotically in chloroform. ^f The H¹ nmr spectra show: multiplicity, chemical shift in τ , and relative areas. The B¹¹ nmr data are given in parts per million and referred to external methyl borate.

2500-cm⁻¹ range, separated by 10-100 cm⁻¹, and additional weaker and less well-defined bands in the 2250-2400-cm⁻¹ range. Other functional groups attached to carbon in pyrazaboles absorb normally. For instance,

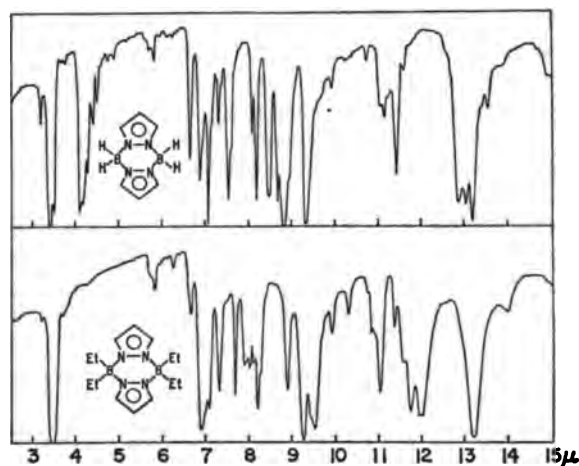


Figure 1. Infrared spectra of pyrazabole and 4,4,8,8-tetraethylpyrazabole.

2,6-pyrazaboledicarbonitrile contains the CN band at 2260 cm⁻¹, as does 4-pyrazolecarbonitrile. Many 4,4,8,8-tetraethylpyrazaboles have characteristic strong

absorption in the 840-880-cm⁻¹ range and a weaker band at about 910 cm⁻¹.

The H¹ nmr spectra of pyrazaboles were most useful in structure assignment. They invariably indicated equivalence of the 1,3,5,7 and 2,6 positions, respectively. The chemical shift of the 1,3,5,7-hydrogens in 2,6-disubstituted pyrazaboles ranges from τ 0.95 (Y = CN) to 2.64 (Y = CH₃) and seems to parallel the inductive effect of the substituents. The same trend is noted, but to a lesser extent, in 2,6-disubstituted 4,4,8,8-tetraethylpyrazaboles. Ethyl groups in the latter compounds appear as a relatively narrow triplet (half-height width 10-12 cps) around τ 9.30-9.40, the methylene hydrogens coinciding with the methyl group (Figure 2). In 1,3,5,7-tetramethyl-4,4,8,8-tetraethylpyrazabole and 1,2,3,5,6,7-hexamethyl-4,4,8,8-tetraethylpyrazabole, the methylene and methyl peaks appear as an ill-defined multiplet in the τ 9.0-9.8 range. 1,2,3,5,6,7-Hexabromo-4,4,8,8-tetraethylpyrazabole is the only compound having the normal quadruplet-triplet pattern for its ethyl groups. The hydrogens of the BH₂ group in pyrazaboles appear as an exceedingly broad (300 cps) band, but their presence and ratio to other hydrogens is easily established by integration.

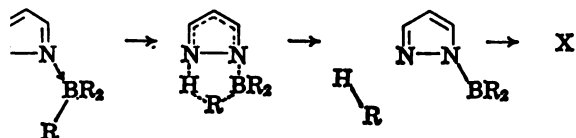
The B¹¹ nmr spectra of pyrazaboles show the expected 1:2:1 triplet in the 27-31-ppm range.³⁹ In some cases

(39) This is close to the range reported for trimethylamine borane: D. F. Gaines and R. Schaefer, *J. Am. Chem. Soc.*, **86**, 1505 (1964).

are well resolved with coupling constants around cps; in others the triplets are ill defined. In 8-tetraethylpyrazaboles the boron resonance appears as a singlet in the 15–17-ppm range, which is 13 ppm higher than for the BEt_2 -bridged acetylates,⁶ but about 18 ppm lower than in tetraethyl- e^- ion.⁴⁰

With regard to the mechanism of pyrazabole formation two situations may be distinguished. Before considering these, one should note that the geometry of the molecule is favorable to a cyclic five-center transition

If one assumes coordination at the 2 position to precede any bond breaking, the 1-hydrogen should be sufficiently close to an R group to permit intramolecular departure of RH . Such proximity may be indicated from the facile formation of a pyrazole formaldehyde adduct⁴² possessing an intramolecular hydrogen



and the ease of intramolecular quaternization of 1-(2,3-dibromopropyl)pyrazole.⁴³ The reaction scheme as shown above is the most plausible path for trialkylboranes, triarylboranes, and tetrahydrofuran where uncontested B–N coordination takes place, as manifested by heat evolution and dissolving pyrazoles suspended in xylene upon addition of trialkylborane. The 1-dialkylboronpyrazole fragment apart from dimerizing, reacts with pyrazole to form a pyrazabole. It has been shown,³⁵ however, that hydrogen poly(pyrazolyl)borates disproportionate irreversibly at elevated temperatures to pyrazaboles and pyrazole. Moreover, the electrophilicity of a BR_2 group ought to be less than that of pyrazole hydrogen, and hence the probable formation of IV is of minor significance. The molecular activation by coordination suggested here has its analogy in the reaction of boranes with carboxylic acids, the mechanism of which has been discussed by Brown⁴⁴ and confirmed by Toporcer, Green, and Green.⁴⁵ While the transition state in the 1-pyrazole reaction involves a five-membered ring, the electrons are relayed along pyrazole's π system in that sense an eight-membered ring is involved in the transition state.

A different situation obviously exists when pyrazoles with trimethylamine borane where a strong donor molecule is involved. Probably an equilibrium involving trimethylamine 1-pyrazolylborane is established, the reaction being driven to completion by removal of trimethylamine from the system and irreversible formation of a pyrazabole.

The reaction of 1,2,4-triazole with triethylborane and the analogous 4,4,8,8-tetraethyl-*sym*-triazabole. This compound was obtained in lower yield than the corresponding pyrazabole, which is not surprising

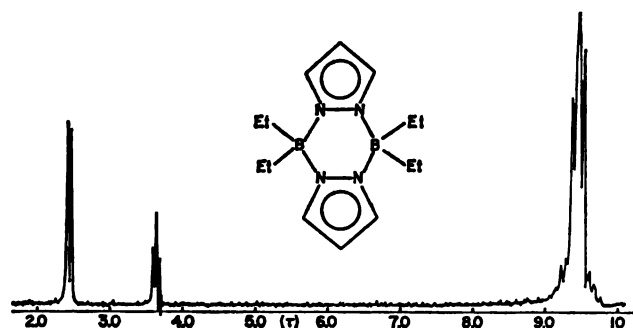


Figure 2. Nmr spectrum of 4,4,8,8-tetraethylpyrazabole.

in view of the additional nitrogen atom than can interact in the coordinating stage of the reaction.

Experimental Section

Pyrazole, 3,5-dimethylpyrazole, 1,2,4-triazole, triethylborane, tributylborane, triphenylborane, and trimethylamine borane are commercially available. They were used without further purification. 4-Chloropyrazole,⁴⁶ 4-bromopyrazole,⁴⁷ 4-methylpyrazole,⁴⁸ 4-pyrazolecarbonitrile,⁴⁹ 4-nitropyrazole,⁵⁰ 3,4,5-trimethylpyrazole,⁵¹ and 3,4,5-tribromopyrazole⁵² were prepared by published methods.

General Method for Preparing Pyrazaboles. Equimolar amounts of the appropriate pyrazole and trimethylamine borane were refluxed in toluene (about 1 l./mole). The emanating gases were conducted through a -80° trap to a wet-test meter or other suitable volumetric device. The progress of the reaction was followed by measuring the amount of hydrogen evolved. In most instances the reaction was complete within a few hours. The solvent was distilled under aspirator vacuum, and the residue was purified by recrystallization and sublimation (see Table I). In the cases of 3,5-bis(trifluoromethyl)pyrazole and 3,4,5-tribromopyrazole, their tetrahydrofuran solutions were added, under nitrogen, to an equivalent amount of borane in tetrahydrofuran. The theoretical amount of hydrogen was evolved rapidly. The solutions were then processed as above.

General Method for Preparing 4,4,8,8-Tetraethylpyrazaboles. Equimolar amounts of the appropriate pyrazole and triethylborane were stirred and refluxed in xylene (about 1 l./mole) until the theoretical amount of ethane, as measured by a wet-test meter, was evolved. The solvent was evaporated and the residue purified by recrystallization and sublimation (see Table II).

4,4,8,8-Tetraethylpyrazabole. A mixture of 13.6 g of pyrazole and 50 ml of tributylborane (both 0.2 mole) was stirred and refluxed in 250 ml of xylene until about 5 l. of butane was evolved. The solvent was evaporated at reduced pressure, and the residual oil was distilled *in vacuo*. There was obtained 34.2 g (89.0%) of material, bp 190° (4.6 mm), n_D^{20} 1.4948. *Anal.* Calcd for $\text{C}_{12}\text{H}_{16}\text{B}_2\text{N}_4$: C, 68.8; H, 10.9. Found: C, 69.0; H, 10.9.

The nmr spectrum consists of a doublet at τ 2.42 ($J = 2.5$ cps), a triplet at 3.62 ($J = 2.5$ cps), and a multiplet around 9.2 in 2:1:18 ratio.

4,4,8,8-Tetraphenylpyrazabole. A mixture of 22.6 g (0.0935 mole) of triphenylborane and 68 g (1.0 mole) of pyrazole was heated to reflux until benzene ceased to distill. The melt was poured into 800 ml of water and stirred for 2 days. The mixture was filtered, and the solid was air dried and recrystallized from 200 ml of boiling toluene. It was washed with ether and air dried. There was obtained 15.7 g (72.4%) of a material melting at 273 – 274° . *Anal.* Calcd for $\text{C}_{28}\text{H}_{18}\text{B}_2\text{N}_4$: C, 77.6; H, 5.60; N, 12.0. Found: C, 77.9; H, 5.40; N, 11.6.

3,5-Bis(trifluoromethyl)pyrazole. A. Adduct of 1,1,1,5,5,5-Hexafluoropentane-2,4-dione with Hydrazine. 1,1,1,5,5,5-Hexafluoropentane-2,4-dione (208 g, 1.00 mole) was added slowly at

R. J. Thompson and J. C. Davis, Jr., *Inorg. Chem.*, **4**, 1464 (1965). The bond angles and distances in pyrazole have not been deter-

R. Hüttel and P. Jochum, *Ber.*, **85**, 820 (1952).

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H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, 1962, p 66.

L. H. Toporcer, R. E. Dessy, and W. I. E. Green, *J. Am. Chem. Soc.*, **87**, 1237 (1965).

(46) R. Hüttel, O. Schafer, and G. Welzel, *Ann.*, **598**, 186 (1956).

(47) E. Buchner and M. Fritsch, *Ann.*, **273**, 256 (1893).

(48) V. T. Klimko, T. V. Protopenova, and A. P. Skoldinov, *Zh. Obshch. Khim.*, **31**, 170 (1960).

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(50) R. Hüttel, F. Büchele, and P. Jochum, *Ber.*, **88**, 1577 (1955).

(51) R. v. Rothenburg, *J. Prakt. Chem.*, **[2]** **52**, 45 (1895).

(52) R. Hüttel, H. Wagner, and P. Jochum, *Ann.*, **593**, 179 (1955).

5° to a solution of 60 g (1.2 moles) of hydrazine hydrate in 1.5 l. of ethanol. The solution was evaporated at 40° (20 mm), yielding a white solid which was recrystallized from toluene. Two crops, 148 and 15 g, were obtained for a total yield of 72%. The material was purified further by sublimation and melted at 133–135°. *Anal.* Calcd for $C_5H_5F_3N_2O_2$: C, 25.0; H, 2.50; F, 47.5. Found: C, 24.9; H, 2.73; F, 47.5.

B. The above product (173 g, 0.72 mole) was melted and heated with stirring as water distilled slowly. After cessation of water evolution, the temperature rose and a material boiling at 147–149° (1 atm) came over and solidified. It melted at 84°, had an unpleasant, pungent odor, and sublimed with great ease. *Anal.* Calcd for $C_5H_5F_3N_3$: C, 29.4; H, 0.98; F, 56.0; mol wt, 204. Found: C, 29.5; H, 1.20; F, 56.2; mol wt (cryoscopic in benzene), 208.

Trimethylamine 3,5-Bis(trifluoromethyl)pyrazol-1-ylborane. A mixture of 3,5-bis(trifluoromethyl)pyrazole (20.4 g, 0.100 mole) and trimethylamine borane (7.3 g, 0.10 mole) was refluxed over-

night in 150 ml of toluene. The solvent was distilled at atmospheric pressure leaving an oil. On vacuum distillation there was obtained 21.4 g (78%) of product, bp 88° (1 mm). *Anal.* Calcd for $C_5H_5BF_6N_3$: C, 34.9; H, 4.37; F, 41.5; N, 15.3. Found: C, 35.2; H, 4.47; F, 42.2; N, 15.2.

The infrared spectrum has a BH_3 multiplet in the 2500-cm^{-1} region. The nmr spectrum shows two singlets at τ 3.12 and 7.41 with relative intensity of about 1:9.

4,4,8,8-Tetraethyl-*sym*-triazabole. A mixture of 13.8 g of 1,2,4-triazole and 28 ml of triethylborane (both 0.2 mole) in 250 ml of xylene was stirred and refluxed overnight. The solution was evaporated to dryness, and the residue was sublimed *in vacuo*. The product was obtained, after recrystallization from heptane and resublimation, in 14-g (50%) yield. It melts at 163–164°. *Anal.* Calcd for $C_{13}H_{14}B_2N_4$: C, 52.5; H, 8.77; N, 30.7. Found: C, 52.5; H, 8.66; N, 31.2.

The nmr spectrum has a single sharp peak at τ 1.74 and a multiplet around τ 9.35 with relative intensities 1:5.

Boron-Pyrazole Chemistry. II. Poly(1-pyrazolyl)borates

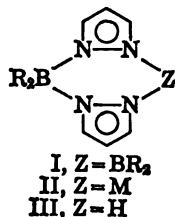
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Abstract: Alkali metal dihydrobis(1-pyrazolyl)borates, hydrotris(1-pyrazolyl)borates, and tetrakis(1-pyrazolyl)borates have been prepared from alkali metal borohydrides and pyrazole. The first two are parent compounds, each representing a new class of chelating agents. Dihydrobis(1-pyrazolyl)borates are uninegative bidentate ligands and react with divalent transition metal ions forming square-planar or tetrahedral chelates, while hydrotris(1-pyrazolyl)borates are uninegative tridentates yielding octahedral coordination compounds. A study of the solvent and cation dependence in the nmr spectra of poly(1-pyrazolyl)borate ions permitted assignment of the 3-H and 5-H doublets. All alkali metal poly(1-pyrazolyl)borates can be converted to isolable free acids of moderate stability. The synthesis and properties of representative compounds are described.

It has been shown recently^{1,2} that when a BR_2 group acts as a bridging unit between two pyrazole nuclei, several new classes of boron compounds are obtained, depending on the nature of the second bridging unit.³ When that unit, Z, is BR_2 , then the resulting structure is a pyrazabole (I). When Z is a metal or onium ion, the compound belongs to the class of poly(1-pyrazolyl)borates (II). Finally, when Z is a hydrogen bridge, we have the corresponding free acid (III).



Pyrazaboles (I) are neutral heterocycles that may be regarded as dimers of an intermediate dihydroboryl-pyrazole (for $R = H$) fragment. On the other hand,

poly(1-pyrazolyl)borates belong to the class of uninegative tetrasubstituted boron compounds which hitherto have been known only as salts. Of these, there are only a few examples of $[BR_nR'_4-n]^-$ species containing a B–N bond, N being an amino, pyrrolyl, or indolyl group. None of these has displayed any unusual properties.⁴⁻⁸

By contrast, poly(1-pyrazolyl)borates not only exhibit remarkable hydrolytic and oxidative stability but are excellent chelating agents for a wide range of transition metals and provide for the first time examples of isolable, albeit hydrated, free acids, $H[BR_nR'_4-n]$. This paper is concerned with the synthesis and properties of the two parent ligands, dihydrobis(1-pyrazolyl)borates⁹ and hydrotris(1-pyrazolyl)borates,⁹ and their free acids and diverse salts and chelates derived therefrom. Although tetrakis(1-pyrazolyl)borates⁹ are, in terms of coordinating ability, merely a substituted variant of tris(1-pyrazolyl)borates, they will be covered

(1) S. Trofimenko, *J. Am. Chem. Soc.*, **88**, 1842 (1966).

(2) S. Trofimenko, *ibid.*, **89**, 3165 (1967).

(3) One could, of course, view this field from the aspect of a bidentate pyrazolyl group acting as a bridge between two BR_2 groups or between BR_2 and a metal ion. Analogies in the former case are numerous with hydrogen, dialkylamino, alkylmercapto, and other groups acting as bridges. To the latter belong the few examples of hydrogen-bridged metal borohydrides: B. D. James, R. K. Nanda, and M. G. H. Wattbridge, *J. Chem. Soc., Sect. A*, 182 (1966), and references cited therein.

(4) C. A. Kraus and W. W. Hawes, *J. Am. Chem. Soc.*, **55**, 2776 (1933).

(5) C. A. Kraus, *Nucleus*, **13**, 213 (1936).

(6) J. E. Smith and C. A. Kraus, *J. Am. Chem. Soc.*, **73**, 2751 (1951).

(7) H. S. Turner and R. J. Warne, *Proc. Chem. Soc.*, 69 (1962).

(8) V. A. Sazonova and V. I. Karpov, *Zh. Obshch. Khim.*, **33**, 3313 (1963).

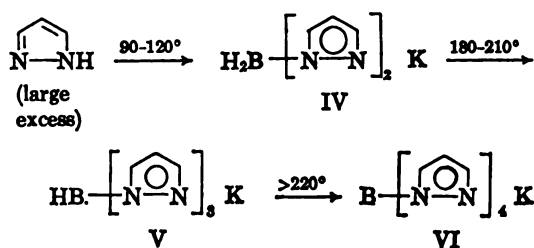
(9) For the sake of brevity the dihydrobis(1-pyrazolyl)borate, hydrotris(1-pyrazolyl)borate, and tetrakis(1-pyrazolyl)borate ions will be written as $H_2B(pz)_2^-$, $HB(pz)_3^-$, and $B(pz)_4^-$, respectively, "pz" denoting the 1-pyrazolyl fragment.

aper since they are preparatively related to the 1 they also fit the $[H_nB(pz)_4 - n]^-$ formula.

and Discussion

potassium borohydride is added to an excess n pyrazole, evolution of hydrogen commences. ues smoothly at 90–120° and comes, essentially, when 2 equiv of hydrogen has been evolved. ing the melt into toluene, the salt IV, mp 171–precipitated in 74% yield. This salt may be lized from anisole.

the other hand, the above reaction mixture is urther, a third equivalent of hydrogen is evolved 10°, and the salt V can be isolated in 80% t can be recrystallized from anisole and melts 189°. Finally, on prolonged heating above



fourth equivalent of hydrogen is evolved, and VI can be isolated in 98% yield. It melts, after lization from ethanol, at 230–231°.

ructure of IV is consistent with the following: chiometry of hydrogen evolution, elemental the infrared spectrum which shows a strong tch multiplet resembling that of pyrazole at 50 cm^{-1} , and the H^1 nmr spectrum which shows e pyrazole hydrogens as doublets at τ 2.42 (3 cps) and 2.49 ($J = 2.2$ cps) and a triplet at $\tau = 2.0$ cps in a 1:1:1 ratio. The signal arising I_2 hydrogens is broad and cannot be discerned, number of boron-bonded hydrogens can be ed as two by integration in the τ 3–9 range.

nmr spectrum consists of a triplet ($J = 96$ itered at +25.7 ppm.¹⁰

ure V was established in similar fashion. The tch appeared as a single peak at about 2470 The H^1 nmr spectrum in D_2O showed three ie to CH hydrogens as doublets at τ 2.43 ($J =$ and 2.82 ($J = 2.2$ cps) and a triplet at τ 3.85 :3 ratio. The BH hydrogen of intensity 1 was y integration over the range τ 3–9. The B^{11} ctrum had a doublet ($J = 105$ cps) at +19.6

alt $\text{KB}(pz)_4$ showed no BH band in the infrared l three nmr peaks (in D_2O): doublets at $\tau \sim 1.7$ cps) and 2.62 ($J = 2.3$ cps) and an ill- triplet at τ 3.67 in a 1:1:1 ratio. The B^{11} nmr n consisted of a sharp singlet at +17.3 ppm.

roton nmr spectra of $\text{H}_2\text{B}(pz)_2^-$, $\text{HB}(pz)_3^-$, and ions show that all the pyrazolyl residues in each identical. The triplet (resolvable into a set of ing doublets) was readily assigned to the 4-H. other hand, the data available were insufficient n the $J_{2,3}$ and $J_{1,8}$ doublets.¹¹ In a similar 1 pertaining to 1-acyl-substituted pyrazoles,

e B^{11} nmr spectra were determined at 19.2 Mc, and the chemi- ere referred to external trimethyl borate. e 3,5 splitting of ~ 0.6 cps is not always discernible.

Williams¹² concluded, by unambiguously blocking the 5 position, that the 5-H appears at *lower* field and that it has the *higher* coupling constant of the two. The above conclusions were corroborated later and extended to 1-alkylpyrazoles by other authors.¹³

Since there was no basis to assume *a priori* that these conclusions could be equally well applied to poly-(1-pyrazolyl)borates, and especially since boron is known to change the appearance of signals arising from well-known groups in unpredictable fashion,¹⁴ the problem of assigning the 3-H and 5-H doublets in poly(1-pyrazolyl)borate ions had to be solved independently.

The approach chosen entailed studying the effect of changing the solvent and/or cation on the chemical shifts in $M[H_nB(pz)_4 - n]$ salts. It was assumed that in solvents where ionization is suppressed and ion-pairing or, in the extreme case, chelation¹⁵ of the cation takes place, the environment of the "outer," 3-H, would change more significantly than that of the "inner," 5-H, and suitable changes in their chemical shifts would be observed. In order to separate the differential solvent effect from the over-all solvent effect, the position of the 4-H was used as an internal standard, and changes in the distance ($\Delta_{2,3}$ and $\Delta_{1,8}$) of the two doublets $J_{2,3}$ and $J_{1,8}$ from it were measured in cycles per second. It was established that in a given system $\Delta_{2,3}$ and $\Delta_{1,8}$ are relatively independent of concentration.

When $\Delta_{2,3}$ and $\Delta_{1,8}$ were measured in water for a series of $\text{MB}(pz)_4$ salts ($M = \text{Li}, \text{Na}, \text{K}, \text{Cs}$, and Me_4N), values of 62 ± 1 and 82 ± 1 cps, respectively, were obtained, which is consistent with complete separation of the ions. The situation changed dramatically upon switching to acetone as solvent. There $\Delta_{1,8}$ remained relatively constant at 84 ± 2 cps, but $\Delta_{2,3}$ proved to be strongly cation dependent, and values of 45 (Li), 55 (Na), 65 (K), 72 (Cs), and 76 cps (Me_4N) were obtained. The same effect was observed in dimethylformamide and dimethyl sulfoxide. There $\Delta_{1,8}$ varied over 6–7 cps in going from the Li to the Me_4N salt, while $\Delta_{2,3}$ ranged over 30 and 38 cps, respectively.

A similar situation prevails in $M[\text{HB}(pz)_3]$ salts. There, too, $\Delta_{2,3}$ and $\Delta_{1,8}$ are relatively invariant in water (65 ± 2 and 83 ± 2 cps, respectively). On switching to acetone $\Delta_{1,8}$ remains at 84 ± 2 cps while $\Delta_{2,3}$ is again cation dependent with values of 98 (Li), 97 (Na), 93 (K), 84 (Cs), and 80 cps (Me_4N). This behavior is also noted in other solvents such as dimethylformamide, dimethyl sulfoxide, and acetonitrile, where $\Delta_{1,8}$ remains relatively constant at 83 ± 3 cps, while $\Delta_{2,3}$ values range over 12–17 cps. Since in all of these cases the $J_{2,3}$ doublet appears at either higher or lower field than the $J_{1,8}$ doublet, the hazard involved in assigning the 3- and 5-hydrogens in unsymmetrical pyrazoles on the basis of their chemical shifts alone becomes immediately obvious.

If the cation is held constant but the solvent varied,

(12) J. K. Williams, *J. Org. Chem.*, **29**, 1377 (1964).

(13) L. G. Tensmeyer and C. Ainsworth, *ibid.* **31**, 1878 (1966); I. L. Finar and E. F. Mooney, *Spectrochim. Acta*, **20**, 1269 (1964).

(14) For instance, the B-ethyl group may appear as a singlet or a triplet around τ 9 rather than the well-known triplet-quadruplet pattern: L. H. Toporcer, R. E. Dessy, and S. I. E. Green, *Inorg. Chem.*, **4**, 1649 (1965).

(15) Formation of very tight ion pairs in systems capable of chelate formation has been demonstrated: H. E. Zaugg and A. D. Schaefer, *J. Am. Chem. Soc.*, **87**, 1857 (1965), and references cited therein.

Table I. Compounds of Structure $M[H_2B(pz)_2]_2$

Color	M	Mp, °C	% yield	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	M, % Calcd	M, % Found	Mol wt Calcd	Mol wt Found
White	Mn	Darkens 155, ^a 162 dec	56	41.3	42.7	4.58	4.72						
White (greenish tinge)	Fe	~130 ^a dec	52	41.2	41.9	4.58	4.82	32.0	32.2				
Violet	Co	163–164 ^b	87	40.8	41.1	4.53	4.61			16.7	16.6		
Orange	Ni	181–182 ^c	92	40.8	40.7	4.54	4.60	31.7	31.1	16.7	16.7	352	337 ^d
Lilac	Cu	134–135 ^c	84	40.3	40.6	4.48	4.77			17.8	17.7	357	367 ^e
White	Zn	161–162 ^b	90	40.1	39.8	4.46	4.37	31.2	30.6				

^a Sublimed. ^b Recrystallized from heptane. ^c Recrystallized from toluene. ^d Ebullioscopic in benzene. ^e Ebullioscopic in methylene chloride.

the same behavior is observed. For instance, for $LiHB(pz)_3$, $\Delta_{1,8}$ is 84 and 86 cps in water and acetone, respectively, while the corresponding $\Delta_{2,2}$ values are 64 and 98 cps. Intermediate values for $\Delta_{2,2}$ may be obtained by using water–acetone mixtures as solvent. Analogous, if less dramatic, results were obtained with other cation or solvent combinations as well as with the $M[H_2B(pz)_2]_2$ salts.

These results show clearly that the chemical shift of the $J_{2,2}$ doublet is much more cation and solvent dependent than that of the $J_{1,8}$ doublet. On this basis, the former is assigned to the 3-H and the latter to the 5-H.

When sodium or lithium borohydrides are used instead of potassium borohydride, the corresponding sodium and lithium poly(1-pyrazolyl)borates are obtained. It is noteworthy that $LiHB(pz)_3$, $LiB(pz)_4$, and $NaHB(pz)_3$ can be sublimed *in vacuo* without decomposition.

The oxidative and hydrolytic stability of poly(1-pyrazolyl)borates increases with decreasing number of hydrogens attached to boron. Thus, $H_2B(pz)_2^-$ is oxidized instantaneously by aqueous permanganate, $HB(pz)_3$ is oxidized slowly, while $B(pz)_4^-$ remains unaffected under these conditions. This trend is also corroborated by polarographic studies. The same order of stability is observed with regard to storage of their solutions: $B(pz)_4^-$ can be stored for long periods of time in solution without noticeable deterioration, while $HB(pz)_3^-$ is stored less well, and $H_2B(pz)_2^-$ solutions have to be used within a few days. In the solid state, however, all three salts can be stored for years at room temperature exposed to air and light.

Careful acidification of aqueous solutions of IV, V, and VI with acetic acid yields the corresponding free acids as water-insoluble solids. This is the first known instance of a stable free acid derived from a $[BR_nR'_4-n]^-$ species being isolated,¹⁶ and it underscores the importance of chelation as a stabilizing factor.

The exact structure of these free acids has not been determined. They may be ion pairs or have a "chelated proton" structure. They are hydrated to varying degrees. Analysis of the free acid derived from $KH_2B(pz)_2$ fits best $H[H_2B(pz)_2]_2 \cdot 4H_2O$, which is in accord with

(16) The ions $[BR_nR'_4-n]^-$ are extremely sensitive to aqueous acid: R. Damico, *J. Org. Chem.*, **29**, 1971 (1964). Even in the case of relatively stable $B(C_6H_5)_4^-$, no evidence for the existence of a viable $HB(C_6H_5)_4$ species was found: J. H. Cooper and R. E. Powell, *J. Am. Chem. Soc.*, **85**, 1590 (1963). On the other hand, the preparation of $H[(C_6H_5)_2B(OH)_2]$, mp –35 to –33°, has been claimed: B. M. Mikhailov and V. A. Vaver, *Dokl. Akad. Nauk SSSR*, **102**, 531 (1955).

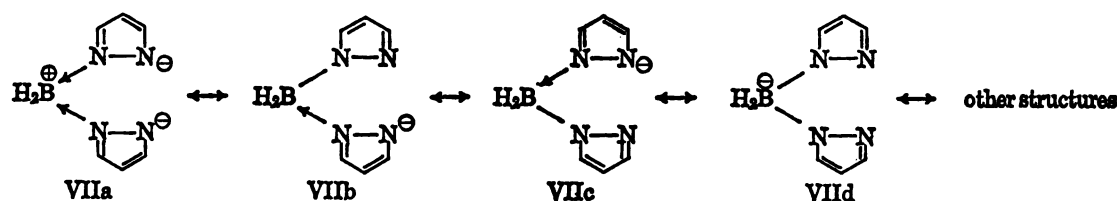
data pertaining to hydration of a proton extracted into organic solvents.¹⁷ On the other hand, $HB(pz)_3$ is essentially anhydrous. That these solids do indeed contain the intact $[H_nB(pz)_4-n]^-$ ion is indicated by the fact that they can be reconverted to salts with the same or different cation by titration with an alkali or onium hydroxide. Moreover, the free acids do react readily with transition metal ions giving the same chelates as those obtained from the salts. In fact, precipitation of $M[H_nB(pz)_4-n]_2$ chelates is often carried out advantageously slightly on the acid side to avoid coprecipitation of transition metal hydroxides. The free acid derived from $KHB(pz)_3$ is the least stable of the three and could not be recrystallized. Nevertheless, it too could be converted to $HB(pz)_3^-$ salts by titration with metal or onium hydroxides. All the free acids have infrared spectra generally similar to those of the salts from which they were derived. They all have broad absorption around 2000–3000 cm^{-1} , and area characteristic of intramolecular hydrogen bonding.

Coordination compounds derived from $H_2B(pz)_2^-$, $HB(pz)_3^-$, $B(pz)_4^-$, and divalent first-row transition metal ions can be prepared readily by metathesis. Since the compounds $M[H_2B(pz)_2]_2$ and $M[HB(pz)_3]_2$ are of different structural types, they will be discussed separately.

Chelates of Mn^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} are precipitated immediately when aqueous solutions of $KH_2B(pz)_2$ and the appropriate metal ion are mixed. Similarly, the compounds $M[H_2B(pz)_2]_2$ are precipitated when M is Pb^{2+} or Cd^{2+} , but not when M is Mg^{2+} , Ca^{2+} , Sr^{2+} , or Ba^{2+} . Ag^+ , Pd^{2+} , and Hg^{2+} ions are reduced to the free metals. Compounds $M[H_2B(pz)_2]_2$ are extractable with organic solvents, particularly well with methylene chloride. They are stable to air and moisture and can be stored in the solid state for years without decomposition, with the exception of the unstable, air-sensitive $Mn[H_2B(pz)_2]_2$ and $Fe[H_2B(pz)_2]_2$. Most of them can be sublimed *in vacuo*, although sublimation is at times accompanied by decomposition to diverse products, mainly metal pyrazolide, pyrazole, and $M[HB(pz)_3]_2$. For this reason purification by recrystallization or by chromatography is preferred. Properties of $M[H_2B(pz)_2]_2$ compounds are summarized in Table I. Their structures were determined as follows.

From *a priori* consideration of contributing structures of the $H_2B(pz)_2^-$ ion, it is apparent that significant contributions are to be expected from structures VIIb and c.

(17) M. I. Tocher, D. C. Whitney, and R. M. Diamond, *J. Phys. Chem.*, **68**, 368 (1964), and references cited therein.



structures have electronic and geometric features: a negative charge and an available electron pair at the termini of the N-N-B-N-N sequence which can exchange places by way of resonance) similar to those of the anion derived from an imine 1,3-dicarbonyl compound or its imine.

Hence, as a first approximation, structures analogous to metal acetylacetonates would be expected. It should be noted, however, that (a) the 3-CH group is close to the metal atom, thus shielding it, especially in tetrahedral chelates, and (b) both nitrogen atoms in pyrazole are involved in bond formation or coordination and hence are expected to be unreactive. These reasons favor formation of associated species, such as dimers, encountered in various nickel(II) and cobalt(II) complexes,¹⁸ would not be anticipated. Indeed, all $M[H_2B(pz)_2]_2$ compounds show no evidence of self-association or planar-tetrahedral equilibrium and are monomeric.

Infrared spectra of $Mn[H_2B(pz)_2]_2$, $Fe[H_2B(pz)_2]_2$, $Co[H_2B(pz)_2]_2$, $Ni[H_2B(pz)_2]_2$, $Cu[H_2B(pz)_2]_2$, and $Zn[H_2B(pz)_2]_2$ are all very similar. Closer examination of these spectra can be divided into two groups, the spectra within each group being identical. The first group (A) belong to $Ni[H_2B(pz)_2]_2$ and $Cu[H_2B(pz)_2]_2$; to the other (B), $Mn[H_2B(pz)_2]_2$, $Fe[H_2B(pz)_2]_2$, $Co[H_2B(pz)_2]_2$, and $Zn[H_2B(pz)_2]_2$. There are regions of the spectrum where differences are apparent.

(1) the fine structure in the BH_2 stretch region (around 1060 cm^{-1}) where the second strongest band in group B is resolved into a doublet, compared with group A where the band around 1060 cm^{-1} is a doublet in group B and a singlet in group A; and (3) the $850\text{--}950\text{ cm}^{-1}$ region is distinctly different in each group.

Since the same ligand is involved in all these compounds, the differences in ionic radii of the metal ions are comparable, and the observed spectral differences are ascribed to differences in molecular geometry. Since zinc forms exclusively tetrahedral complexes, group B must consist of tetrahedral chelates while those of group A are expected to be square planar. In accord with this, $Ni[H_2B(pz)_2]_2$ is orange-red and diamagnetic. The BH_2 group in the infrared spectra of $Ni[H_2B(pz)_2]_2$ and $Cu[H_2B(pz)_2]_2$ is more similar to that of pyrazabole, which is consistent with molecular models which indicate a tetrahedral environment of the BH_2 in the above compounds resembles that found in pyrazabole rather than in chelates from group B.

The nmr spectra of the diamagnetic chelates $Ni[H_2B(pz)_2]_2$ and $Zn[H_2B(pz)_2]_2$ each consisted of two singlets and a triplet (made up of two overlapping singlets) in a 1:1:1 ratio. They were at τ 2.38 ($J = 1$), 3.17 (2.1), and 3.87 (2.1) for $Ni[H_2B(pz)_2]_2$ and τ 2.29 ($J = 2.3\text{ cps}$), 2.46 (2.3 cps), and 3.80

(2.3 cps) for $Zn[H_2B(pz)_2]_2$ again implying fundamentally different molecular geometries.

Definitive evidence for the structure of all these chelates was obtained from magnetic data, electronic spectra, and nmr studies of the paramagnetic chelates.¹⁹

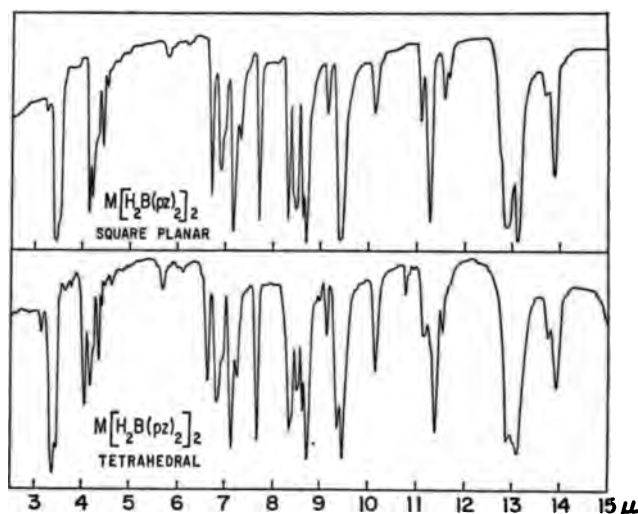


Figure 1. Infrared spectra of $M[H_2B(pz)_2]_2$ compounds.

Compounds of structure $M[HB(pz)_2]_2$ are precipitated immediately upon mixing solutions of an alkali or onium hydrotris(1-pyrazolyl)borate and of a divalent transition metal ion. In addition, such compounds are also precipitated with Mg^{2+} , Pb^{2+} , Cd^{2+} , and Pd^{2+} ions. Using Ag^+ ion, the compound $AgHB(pz)_2$ is obtained. The Ag as well as the Pd compounds decompose readily on heating with formation of the free metal. Besides Mg^{2+} , Ca^{2+} is also precipitated by the $HB(pz)_2^-$ ion but from more concentrated solutions. The solubility in water of alkaline earth hydrotris(1-polypyrazolyl)borates increases in the order $Mg \ll Ca < Sr < Ba$. The strontium and barium compounds are salt-like and, like the alkali salts, may serve as starting materials for the preparation of transition metal compounds. The calcium compound behaves in some ways like a salt and in others like a chelate, although $Mg[HB(pz)_2]_2$ behaves like one of the transition metal compounds in terms of physical properties. Despite their high solubility in water, $Sr[HB(pz)_2]_2$ and $Ba[HB(pz)_2]_2$ can be extracted with organic solvents, e.g., methylene chloride, and $Sr[HB(pz)_2]_2$ can be sublimed *in vacuo* without decomposition.

The transition metal compounds $M[HB(pz)_2]_2$ are all high-melting solids, sublimable *in vacuo*. They are sparingly soluble in polar solvents such as alcohols or acetone but dissolve readily in halocarbons and aromatic hydrocarbons from which they may be conven-

¹⁸ For instance, F. A. Cotton and R. C. Elder, *Inorg. Chem.*, **4**, 59; G. J. Bullen, R. Mason, and P. Pauling, *Nature*, **189**, 1, and references cited therein.

¹⁹ J. P. Jesson, S. Trofimenko, and D. Eaton, *J. Am. Chem. Soc.*, **89**, 3148 (1967).

Table II. Compounds of Structure $M[HB(pz)_3]_2$

Color	M	Mp, °C	% yield	C, % Calcd	% Found	H, % Calcd	% Found	N, % Calcd	% Found	M, % Calcd	% Found	Mol wt Calcd	Found
White	Mg ^a	284-285	71	48.0	48.3	4.45	4.40						
White	Ca	269-271	92	46.9	46.9	4.29	4.53	36.1	35.7				
White	Mn	283-284	100	44.9	45.1	4.17	4.33			11.4	10.9	481	496
Wine-red	Fe	265-269	96	44.9	45.1	4.16	4.24			11.6	11.7	482	479 ^b
Yellow	Co	277-278	93	44.6	44.8	4.13	4.21			12.2	12.0		
Lilac	Ni	280-281	100	44.6	44.6	4.13	3.92			12.1	11.9		
Blue	Cu	245-247	96	44.2	44.2	4.08	4.18						
White	Zn	282-284	94	44.0	44.4	4.08	4.38			13.3	13.3		
White	Cd	285-286	75	40.2	40.0	3.72	3.64	31.2	31.3				
White	Pb	220-222	93	34.1	33.9	3.16	3.34	26.5	26.5	32.7	32.7		

^a All samples were recrystallized from toluene. ^b By vapor-pressure osmometry in chloroform.

iently recrystallized. Some properties of $M[HB(pz)_3]_2$ are summarized in Table II.

Nothing has been said thus far about the structure of these compounds. Since chelates $M[H_2B(pz)_2]_2$ are, in terms of geometry and symmetry, similar to transition metal acetylacetonates or to the BR_2 -bridged bis-(dimethylglyoxime)nickel(II)²⁰ and its cobalt analog,²¹ one might expect a similar structure in $M[HB(pz)_3]_2$ compounds except for the 1-pyrazolyl group replacing a hydrogen. That this is not the case became apparent.

For one thing, the colors of the iron, cobalt, nickel, and copper compounds are all different from those in the corresponding $M[H_2B(pz)_2]_2$ compounds and essentially identical with those of the corresponding complexes with the isosteric and isoelectronic ligand, 1,1,1-tripyrzolylmethane.²² Molecular models²³ show that the 2-nitrogen of the third pyrazolyl group is in such close proximity to the metal ion that it can form a coordinate bond with it, thus giving rise to a compact structure of D_{3d} symmetry.

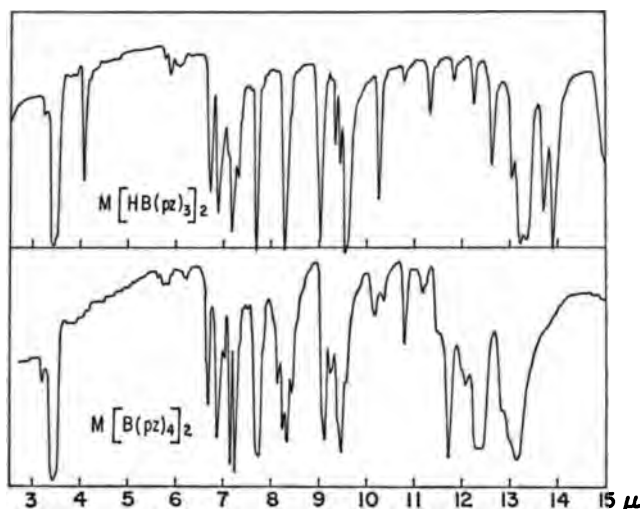


Figure 2. Infrared spectra of $M[HB(pz)_3]_2$ and $M[B(pz)_4]_2$ compounds.

Compounds $M[HB(pz)_3]_2$ have the simplest infrared spectra (Figure 2) among poly(1-pyrazolyl)borates, all containing a BH singlet.²⁴ The $Cu[HB(pz)_3]_2$ is sig-

(20) G. N. Schrauzer, *Ber.*, **95**, 1438 (1962).

(21) G. N. Schrauzer, *J. Am. Chem. Soc.*, **88**, 3738 (1966).

(22) S. Trofimenko, unpublished results.

(23) While the exact dimensions of the pyrazole ring are not known, the Stuart-Briegleb models provide a good qualitative picture of the molecular structure.

nificantly different in having several of the peaks that are singlets in other $M[HB(pz)_3]_2$ compounds appear as doublets. The nmr spectra of $M[HB(pz)_3]_2$ compounds discern only one kind of pyrazolyl group. The octahedral nature of these compounds is also confirmed by electronic spectra, magnetic data, and nmr studies of paramagnetic compounds.¹⁹ An interesting case of spin equilibrium between high- and low-spin forms has been found in $Fe[HB(pz)_3]_2$.²⁵

Compounds $M[B(pz)_4]_2$, which have the same octahedrally coordinated structure around the metal ion as $M[HB(pz)_3]_2$, are, nevertheless, in some ways different. They are prepared by metathesis and have the same colors as their $M[HB(pz)_3]_2$ counterparts. They, too, are sublimable but are higher melting, more thermally stable, and less soluble in organic solvents. However, the presence of two additional 1-pyrazolyl groups per molecule makes $M[B(pz)_4]_2$ compounds soluble in aqueous mineral acids from which they can be recovered on basification. In addition to divalent first-row transition metal ions, Cd^{2+} , Pd^{2+} , Hg^{2+} , and Ag^+ are precipitated, and of these all but the silver compound can be purified by recrystallization. In the alkaline earth group Mg^{2+} is precipitated readily, Ca^{2+} less readily, and Sr^{2+} and Ba^{2+} are too soluble to be precipitated except from very concentrated solutions. The infrared spectra of all $M[B(pz)_4]_2$ compounds are similar (Figure 2) and devoid of BH absorption. Their properties are shown in Table III.

Convincing proof that one of the four 1-pyrazolyl groups attached to boron is different from the other three is provided by the nmr spectrum of the paramagnetic $Co[B(pz)_4]_2$ compound where protons due to three identical and one different 1-pyrazolyl groups per ligand are discerned, the signals covering a range of over 12,000 cycles due to spin-contact interactions.¹⁹

At this point it is pertinent to touch on the mechanism of the reaction of pyrazole with the tetrahedral borohydride ion. While some work has been done in the area of displacement reactions on tetrahedral boron,²⁶ mainly relating to solvolytic and displacement reactions of borane complexes, the situation is by no means as clear as in the case of substitution on carbon.

(24) At higher resolution this is seen to consist of two peaks at 2460 and 2474 cm^{-1} assigned, on the basis of their intensities, to the BH stretch of the B^{11} and B^{10} isotopes.

(25) J. P. Jesson, S. Trofimenko, and D. R. Eaton, *J. Am. Chem. Soc.*, **89**, 3158 (1967).

(26) G. E. Ryschkievitch and E. R. Birnbaum, *Inorg. Chem.*, **4**, 575 (1965); *J. Phys. Chem.*, **65**, 1087 (1961); M. F. Hawthorne, W. L. Budde, and D. Walnisky, *J. Am. Chem. Soc.*, **86**, 5337 (1964); M. F. Hawthorne and W. L. Budde, *ibid.*, **86**, 5337 (1964).

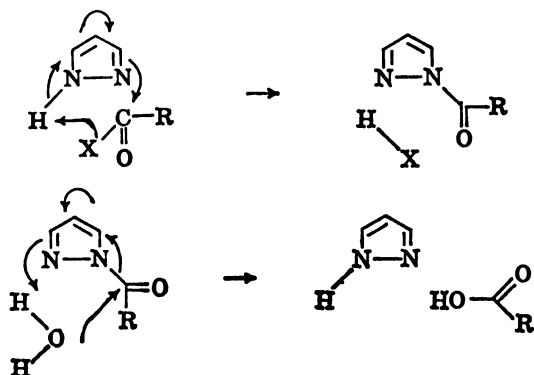
ble III. Compounds of Structure $M[B(pz)_3]$

Color	M	Mp, °C	Yield, %	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	M, % Calcd	M, % Found	Mol wt Calcd	Mol wt Found
White	Mg	358–359 ^a	71	49.6	49.2	4.13	3.79			4.18	4.10		
White	Ca	310–311 ^a	80	48.1	48.0	4.02	4.06	37.5	37.5				
White	Sr	343–346 dec ^b	60	44.6	44.1	3.72	3.91	34.7	34.1				
White	Ba	316–318 ^c	72	41.4	39.8 ^d	3.45	4.08	32.2	30.8				
White	Mn	342–343 ^a	88	47.0	47.2	3.92	3.85			8.95	8.93	613	643 ^e
Pale wine-red	Fe	352–360 dec ^a	86	46.9	47.1	3.91	4.04	36.5	35.9	9.12	9.05	614	614 ^f
												3.52 % B	3.75 % B
Yellow	Co	364–365 ^a	88	46.8	46.8	3.89	3.91	36.3	36.4	9.57	9.59		
Lilac	Ni	371–372 ^a	88	46.8	47.1	3.89	4.22			9.49	9.48		
Blue	Cu	310–312 ^a	86	47.1	46.6	4.11	3.86			10.2	10.4		
White	Zn	322–323 ^a	92	46.2	46.3	3.85	3.62			10.5	10.5		
White	Cd	328–329 ^a	75	43.0	43.1	3.58	3.61	33.4	33.1				
White	Pb	230–232 ^a	79	37.6	37.5	3.14	3.13	29.3	28.9	27.1	27.0		
White	Hg	216–220	71	37.9	37.5	3.16	3.66	29.5	28.7				

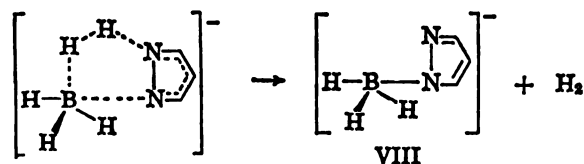
^a Recrystallized from toluene. ^b Sublimed. ^c Recrystallized from water. ^d Calculated for dihydrate: C, 39.4; H, 3.82; N, 30.6. ^e Bullioscopic in toluene. ^f Osmometric in chloroform.

In our case, the reaction of borohydride ion with razole is thought to proceed in a manner that comes some features of SN1 and SN2 reactions. This mechanism is probably also operating in the reaction trimethylamine borane with pyrazole.

The main feature of this mechanism is a cyclic low-energy transition state with a geometry resembling at in SN2 substitution. However, while in SN2 actions the departing and the attacking groups are at the apices of a trigonal bipyramid, in the case of razole and borohydride ion the evolution of hydrogen proceeds concertedly through a cyclic five-center transition state²⁷ and involves equatorial rather than apical



hydrogen. Here, both B–N bond forming and B–H

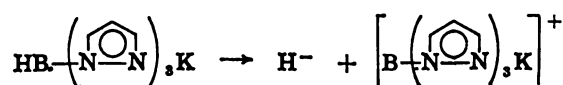


and breaking are facilitated by the “push–pull” effect of razole approaching as a 1,3 dipole. The intermediate III could then again undergo the same type of reaction to reach a resonance-stabilized form as the potassium salt IV. Alternatively, the same stage could be reached by coordination of 1-dihydroborylpyrazole obtained from VIII *via* loss of hydride ion) with

(27) This cyclic five-center transition state is probably characteristic all pyrazole reactions with dipolarophiles AB; it is just as applicable *e.g.*, acylation of pyrazoles as to hydrolysis of acylpyrazoles.

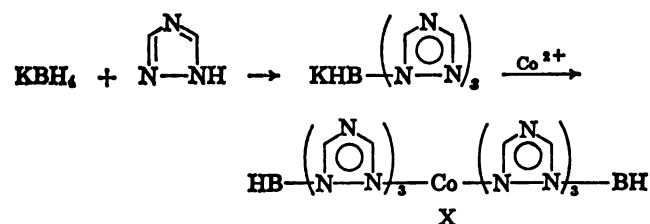
pyrazole, present in large excess, to yield the free acid $H[H_2B(pz)_3]$ directly. This acid, in a basic medium, would be converted to the $[H_2B(pz)_3]^-$ ion, as the potassium chelate. It should be noted that there is no noticeable break in hydrogen evolution until two pyrazole molecules per BH_4^- have reacted. The third pyrazolyl group is attached less readily, probably for steric reasons, and also because of possible orientation of the noncoordinating nitrogen in the transition state toward the potassium ion rather than toward the hydrogen to be eliminated.

The fourth pyrazolyl group is introduced very slowly as, by now, the access to the boron atom is quite obstructed. Possibly, a direct SN1, dissociation may occur with the slow step being followed by rapid reac-



tion of IX with pyrazole or pyrazolide ion.

When potassium borohydride is heated in excess 1,2,4-triazole, the hydrotris(1,2,4-triazol-1-yl)borate ion is formed, as proved by the formation of compound X when the reaction product was treated with Co^{3+} ion. This compound is yellow just like $Co[HB(pz)_3]_3$. In contrast to $Co[HB(pz)_3]_3$, however, it is soluble in and can be recrystallized from water. This solubility is attributable to the presence of six additional nitrogens in the molecule.



Experimental Section

Potassium Dihydrobis(1-pyrazolyl)borate. Potassium borohydride (54 g, 1 mole) was mixed with 272 g (4 moles) of pyrazole in a 1-l. flask attached through an air condenser to a gas meter. The pyrazole was carefully melted by means of an oil bath at 90°. When the contents of the flask was sufficiently molten to allow magnetic stirring, the mixture was stirred and heated at tempera-

tures not exceeding 115°. Potassium borohydride dissolved slowly with evolution of hydrogen, and the progress of the reaction was followed on the gas meter. After 20 hr, 2 moles (ca. 50 l.) of hydrogen had evolved and only a few small particles of KBH_4 were still floating in the melt. These were removed mechanically. The melt was poured into 500 ml of toluene; the resulting mixture was stirred until it cooled to room temperature and was then filtered. The filter cake was washed twice with 150-ml portions of hot toluene and then air-dried, yielding 137 g (74%) of a solid, mp 171–172°. The analytical sample was recrystallized from anisole. The infrared spectrum of the product has a complex BH pattern at 2250–2420 cm^{-1} . *Anal.* Calcd for $\text{C}_6\text{H}_5\text{BN}_4\text{K}$: C, 38.7; H, 4.30; N, 30.1. Found: C, 38.9; H, 4.36; N, 29.9.

Potassium Hydrotris(1-pyrazolyl)borate. A mixture of 272 g (4.0 moles) of pyrazole and 54 g (1.0 mole) of potassium borohydride was heated with stirring in a 1-l. flask, connected *via* an air-cooled condenser to a gas meter, until about 75 l. (3 moles) of hydrogen had been evolved. The melt was poured slowly into 600 ml of stirred toluene, whereupon a solid precipitated. The mixture was filtered and the product was washed with hot toluene, then with hexane, and air-dried. There was obtained 190 g (79%) of white solid, mp 185–190°. The solid was recrystallized from anisole and obtained as fine needles, mp 188–189°. *Anal.* Calcd for $\text{C}_6\text{H}_5\text{BN}_4\text{K}$: C, 42.8; H, 3.97; N, 33.3. Found: C, 42.9; H, 4.23; N, 33.4.

Lithium Hydrotris(1-pyrazolyl)borate. This compound was prepared by the above method and obtained, after recrystallization from toluene, as needles, mp 264–265°. It is readily sublimable at 240° (2 mm). *Anal.* Calcd for $\text{C}_6\text{H}_5\text{BLiN}_4$: C, 49.1; H, 4.55; N, 38.2. Found: C, 48.8; H, 4.84; N, 38.2. This lithium salt is very soluble in water, acetone, alcohols, and tetrahydrofuran, moderately soluble in chloroform, and sparingly soluble in cold toluene.

Sodium Hydrotris(1-pyrazolyl)borate. This compound was prepared by the above method and obtained in 91% yield. It was purified by recrystallization from 1,2-dimethoxyethane and then by sublimation at 210–215° (2 mm), mp 222–223°. *Anal.* Calcd for $\text{C}_6\text{H}_5\text{BN}_4\text{Na}$: C, 45.7; H, 4.24; N, 35.5. Found: C, 45.5; H, 4.26; N, 35.2.

Potassium Tetrakis(1-pyrazolyl)borate. Potassium borohydride (54 g, 1 mole) and pyrazole (340 g, 5 moles) were heated together until about 100 l. of hydrogen (4 moles) was evolved. The melt was cooled until it became viscous and then was poured into 1.5 l. of stirred toluene. The mixture was filtered and the cake washed with successive portions of hot toluene, benzene, and ether. The solid was air-dried to give 310 g (98% yield). The analytical sample was recrystallized from ethanol and dried at 130° (2 mm), mp 253–254. *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{BKN}_8$: C, 45.3; H, 3.78; N, 35.2. Found: C, 45.1; H, 3.79; N, 35.2.

Preparation of Poly(1-pyrazolyl)borate Salts by Neutralization of the Free Acids. General Procedure. The free acids were prepared by adding an equimolar amount of acetic acid to a fairly concentrated aqueous solution of the appropriate potassium poly(1-pyrazolyl)borate. The precipitated free acid was isolated by filtration and washed thoroughly with water. It was then stirred with a stoichiometric amount of the appropriate alkali metal or quaternary ammonium hydroxide with additional methanol, as necessary, to effect homogeneity. The solutions were decolorized with Darco and evaporated at reduced pressure. The solid residues were recrystallized from an appropriate solvent, usually with substantial solubility losses.

Tetramethylammonium Tetrakis(1-pyrazolyl)borate. This compound was recrystallized from 1,2-dimethoxyethane and obtained in 93% yield. It decomposes with evolution of trimethylamine at 219–220°. *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{BN}_8$: C, 54.4; H, 6.81; N, 35.7. Found: C, 54.4; H, 7.02; N, 36.0. The nmr spectrum (D_2O) has doublets at τ 2.33 ($J < 2.0$ cps) and 2.62 (~ 2.3), a triplet at 3.67 (~ 1.9), and a singlet at 6.92 in exactly a 1:1:1:3 ratio.

Lithium Tetrakis(1-pyrazolyl)borate. This compound was obtained in 89% yield and was recrystallized from water. It was purified further by sublimation at 300° (2 mm), mp 394–395°. *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{BLiN}_8$: C, 50.3; H, 4.19; N, 39.2. Found: C, 50.3; H, 4.36; N, 38.8. The nmr (D_2O) has an unresolved doublet at τ 2.26, a doublet ($J \sim 2.2$ cps) at τ 2.58, and an unresolved triplet at τ 3.60 in a 1:1:1 ratio.

Sodium Tetrakis(1-pyrazolyl)borate. This compound was obtained in 80% yield after recrystallization from ethanol, mp 238–239°. *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_8\text{Na}$: C, 47.7; H, 3.97; N, 37.1. Found: C, 47.0; H, 3.87; N, 36.3.

Cesium Tetrakis(1-pyrazolyl)borate. This salt was obtained in 47% yield after recrystallization from ethanol, mp 243–244°. *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{BCsN}_8$: C, 35.0; H, 2.92; N, 27.2. Found: C, 34.9; H, 2.85; N, 26.6.

Tetramethylammonium Dihydrobis(1-pyrazolyl)borate. This salt was obtained in 58% yield after recrystallization from 1,2-dimethoxyethane, mp 107–108°. *Anal.* Calcd for $\text{C}_{10}\text{H}_{10}\text{BN}_6$: C, 54.2; H, 9.05; N, 31.7. Found: C, 54.0; H, 9.44; N, 31.3.

Tetramethylammonium Hydrotris(1-pyrazolyl)borate. This compound was obtained in 46% yield after recrystallization from 1,2-dimethoxyethane, mp 96–97°. *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{BN}_7$: C, 54.4; H, 7.67; N, 34.1. Found: C, 53.9; H, 7.38; N, 33.5.

Hydrogen Dihydrobis(1-pyrazolyl)borate. To a solution of 19 g (0.1 mole) of $\text{KH}_2\text{B(pz)}_2$ in 200 ml of water was added 6.0 g (0.1 mole) of acetic acid. The precipitated solid was filtered, washed with water, and obtained, after air-drying, in 15.3-g yield.

Recrystallization from chloroform gave white crystals, mp 128–129°, with gas evolution. *Anal.* Calcd for $\text{C}_6\text{H}_5\text{BN}_4$ (anhydrous acid): C, 48.7; H, 6.08; N, 37.9. Calcd for $\text{C}_6\text{H}_5\text{BN}_4\text{O}$ (tetrahydrate): C, 32.7; H, 7.73; N, 25.5. Found: C, 33.6; H, 5.95; N, 25.5. The infrared spectrum of this material had, apart from the complex BH₂ sketch, broad and intense absorption characteristic of intramolecular hydrogen bonding at 1700–3000 cm^{-1} .

Hydrogen Hydrotris(1-pyrazolyl)borate. This compound was prepared as above and obtained as a solid which decomposed on attempted recrystallization.

Hydrogen Tetrakis(1-pyrazolyl)borate. To a stirred solution of 159 g (0.5 mole) of potassium tetrakis(1-pyrazolyl)borate in 1 l. of water was added 30 g (0.5 mole) of acetic acid. The precipitated solid was separated by filtration, washed thoroughly with water and then ethanol, and air-dried overnight. It was purified further by dissolution in a minimum amount of methylene chloride and concentration under reduced pressure at 30–35° to a thick slurry. It was stirred with 500 ml of ether and filtered, and the solid was dried in a stream of warm nitrogen. There was obtained 27 g of material, mp 70–71°. *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{BN}_8$: C, 51.4; H, 4.64; N, 40.0. Found: C, 52.1; H, 4.69; N, 40.4.

Preparation of Metal Dihydrobis(1-pyrazolyl)borates. Compounds of this type were prepared by adding an aqueous solution of 1 equiv of the appropriate metal ion to an aqueous solution of 2 equiv of potassium dihydrobis(1-pyrazolyl)borate. The chelates precipitated immediately. In the case of the air-sensitive chelates of Mn(II) and Fe(II), the addition and subsequent manipulations had to be done in an inert atmosphere. The products were isolated either by filtration or by extraction with methylene chloride. While they could be sublimed with care, such sublimation was at times attended by pyrolysis to metal pyrazolide and pyrazabole, hence recrystallization from toluene or heptane was preferred. The properties of metal dihydrobis(1-pyrazolyl)borates are summarized in Table I.

Preparation of Metal Hydrotris(1-pyrazolyl)borates. Compounds of this type were prepared by adding a solution of 1 equiv of the appropriate metal ion to a stirred solution of 2 equiv of potassium hydrotris(1-pyrazolyl)borate. The precipitated product was either extracted with methylene chloride or filtered and purified further by recrystallization from xylene and/or sublimation. Some products were purified by chromatography on acid-washed alumina. The properties of metal hydrotris(1-pyrazolyl)borates are listed in Table II.

Preparation of Metal Tetrakis(1-pyrazolyl)borates. These compounds were prepared as described above. Metal tetrakis(1-pyrazolyl)borates were, as a rule, less soluble than the tris analogs; hence, filtration was preferred to extraction. The properties of metal tetrakis(1-pyrazolyl)borates are summarized in Table III.

Hydrotris(1,2,4-triazol-1-yl)boratecobalt(II). A mixture of 5.4 g of potassium borohydride and 27 g of 1,2,4-triazole (0.1 and 0.4 mole, respectively) was heated until 7.5 l. (0.3 mole) of hydrogen was evolved. The melt was dissolved in 800 ml of hot water (90°) and was treated with 100 ml of 0.5 M cobaltous acetate solution. A precipitate formed which was insoluble in methylene chloride and was recrystallized from 800 ml of boiling water to give 3.9 g (16% yield) of well-shaped yellow crystals. The material darkens from 390° up but is still solid at 450°. *Anal.* Calcd for $\text{C}_3\text{H}_3\text{N}_3\text{B}_2\text{CoN}_3$: C, 29.3; H, 2.85; N, 51.3. Found: C, 29.5; H, 2.93; N, 51.4.

Polarographic Studies. All the samples were dissolved in acetonitrile, except for the iron compounds which were dissolved in dimethyl sulfoxide. The solutions were 0.1 M in tetrabutylammonium perchlorate, used as supporting electrolyte. The dropping mercury electrode *vs.* sec was used with $\text{Cu}(\text{H}_2\text{B(pz)}_2)_2$, CuB

(pz)₃, Co[H₂B(pz)₃]₂, and Co[HB(pz)₃]₂. The rotating platinum electrode *vs.* sce was used for Fe[HB(pz)₃]₂ and Fe[B(pz)₃]₂.

Both Cu[H₂B(pz)₃]₂ and Cu[B(pz)₃]₂ were found to undergo reversible one-electron reduction at about $E_{1/2} = 0.29$ v. The cobalt compounds, Co[H₂B(pz)₃]₂ and Co[HB(pz)₃]₂, were oxidized (one electron) at +0.2 and -0.09 v, respectively. Co[HB(pz)₃]₂ underwent a two-electron reduction at -2.13 v, while its Fe(II)

counterpart could not be reduced in the +0.34- to -2.75-v range. Fe[HB(pz)₃]₂ and Fe[B(pz)₃]₂ underwent one-electron oxidation at +0.27 and 0.37 v, respectively.

Acknowledgment. The author wishes to thank Miss Lucille E. Williams who carried out the polarographic studies.

Cyanonitrene. Reaction with Saturated Hydrocarbons¹

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Contribution No. 1288 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898.

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Abstract: Cyanonitrene was generated thermally from cyanogen azide, and its intermediacy in reactions with saturated hydrocarbons was established by means of isotopic labeling. The nitrene exhibits pronounced selectivity in insertions into C-H bonds, which in the absence of a solvent occur in a stereospecific manner. Mechanisms are discussed.

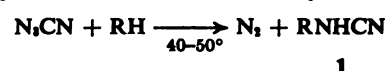
In contrast to the well-documented chemistry of carbenes,³ their nitrogen counterparts (nitrenes)⁴ have received serious attention by organic chemists only recently.⁵ In 1962, Barton and Morgan⁶ reported the first examples of intramolecular C-H insertions⁷ of alkyl nitrenes to afford either five- or three-membered rings, and Lwowski and Mattingly⁸ presented the first case of an intermolecular insertion⁷ in the reaction of carbethoxynitrene with cyclohexane.

The recent synthesis of cyanogen azide (N₃CN)⁹ has provided a direct route for the generation of the highly symmetrical molecule NCN, "cyanonitrene." In the present paper we report on the thermal generation of NCN and on the mechanism of its reactions with saturated hydrocarbons.

Results and Discussion

Unlike most organic azides which require temperatures in excess of 100° for fragmentation to the corresponding nitrenes,⁴ cyanogen azide smoothly evolves nitrogen when heated to 40–50°. Kinetics have not been studied in detail but the rate of nitrogen evolution appears to be first order in dilute solutions. In addition the rate of nitrogen evolution depends on the polarity of the solvent employed, being more rapid in nonpolar media (hydrocarbons) than in polar media (ethyl acetate, acetonitrile). These facts are consistent

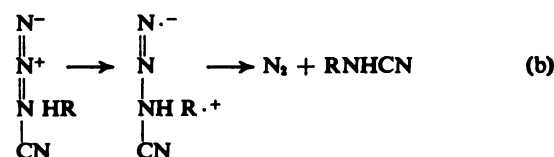
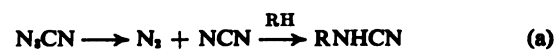
with unimolecular fragmentation of the highly polar azide to two nonpolar species. When the decomposition of the azide is conducted in a paraffinic hydrocarbon, alkylcyanamides **1** are formed in yields of 55–70%.



For example, thermolysis of a 1% solution of N₃CN¹⁰ in cyclohexane at 50° afforded cyclohexylcyanamide (**1**, R = C₆H₁₁) in 57% yield. The product showed strong infrared absorption at 3200 (NH) and 2210 (C≡N) and nmr signals at τ 4.3 (doublet, 1 H), 7.0 (multiplet, 1 H), and 7.9–9.0 (multiplet, 10 H); cyclohexylcyanamide was characterized by hydrolysis to cyclohexylurea on boiling with 10% sulfuric acid.

Isotopic Labeling Experiments. In photolytic or thermolytic reactions of azides with saturated hydrocarbons to yield insertion products, a likely mechanism involves unimolecular fragmentation of the azide to the corresponding nitrene and nitrogen followed by insertion⁷ of the nitrene into C-H bonds. Although this is the most reasonable sequence of events, there usually is no unequivocal experimental evidence excluding an alternative mechanism in which the azide itself reacts with the hydrocarbon. The two possible mechanisms are depicted in Scheme I.¹¹

Scheme I



(1) This work was described in preliminary form: A. G. Anastassiou, H. E. Simmons, and F. D. Marsh, *J. Am. Chem. Soc.*, **87**, 2296 (1965).

(2) To whom inquiries may be addressed at the Department of Chemistry, Syracuse University, Syracuse, N. Y. 13210.

(3) For an excellent account see W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964.

(4) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).

(5) The term nitrene is used here to indicate a monovalent nitrogen species which adds to double bonds and inserts into C-H bonds.

(6) D. H. R. Barton and L. R. Morgan, Jr., *J. Chem. Soc.*, 622 (1962). See, however, D. H. R. Barton and A. N. Starratt, *J. Chem. Soc.*, 2444 (1965).

(7) The term insertion is used here to indicate end result rather than mechanistic detail.

(8) W. Lwowski and T. W. Mattingly, Jr., *Tetrahedron Letters*, 277 (1962).

(9) F. D. Marsh and M. E. Hermes, *J. Am. Chem. Soc.*, **86**, 4506 (1964).

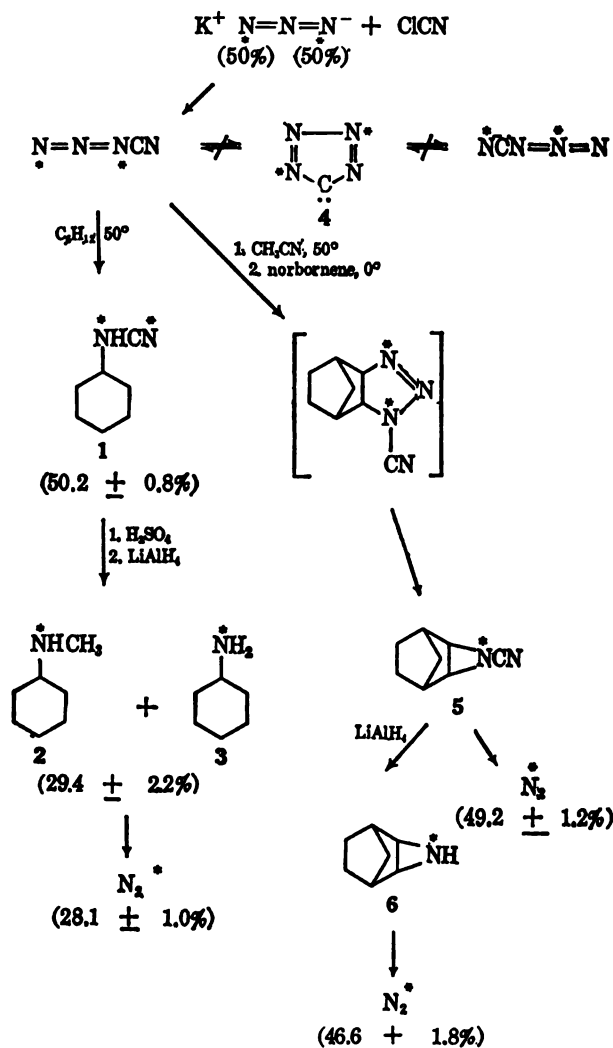
(10) This experiment was first carried out by Dr. F. D. Marsh.

(11) In Scheme Ib the dipolar intermediate is supposed to be associated with singlet N₃CN and the diradical species with triplet N₃CN. Thus, abstraction of hydrogen might occur as either hydride ion or as a hydrogen atom.

An unambiguous distinction between paths a and b should be possible in principle by isotopic labeling experiments. Theory suggests that the lowest singlet and triplet states of NCN are linear. Symmetry demands that the two nitrogen atoms of NCN are equivalent, whereas no such equivalence can be achieved in path b. To elucidate this point we studied the insertion reaction employing appropriately labeled N_3CN .

The procedure used is shown in Scheme II. The degree of isotopic enrichment at the various stages was

Scheme II



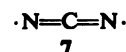
determined mass spectrometrically employing the natural abundances of the same materials prepared in parallel experiments but starting with unenriched potassium azide. The results of these experiments are clearly consistent with the intermediacy of *free* cyanonitrile in which the two nitrogen atoms are chemically indistinguishable.¹² The possibility that scrambling of the label occurs prior to decomposition of the azide, perhaps through a rapid prereaction equilibrium between a cyclic form 4 and two equivalent but differently tagged linear forms of N_3CN , was tested by allowing the azide to decompose partially in acetonitrile and then adding norbornene.⁹ The virtual identity of the amount of label in 5 and its subsequent hydrolysis product 6 pre-

(12) The small excess label in amines 2 and 3 (28.7% ^{15}N instead of the theoretical value of 25.0%) is probably at least partly due to an isotopic bias of the insertion, *i.e.*, a slight preference of the ^{15}N site over the ^{14}N site of NCN to undergo reaction.

cludes the occurrence of any significant prereaction scrambling.

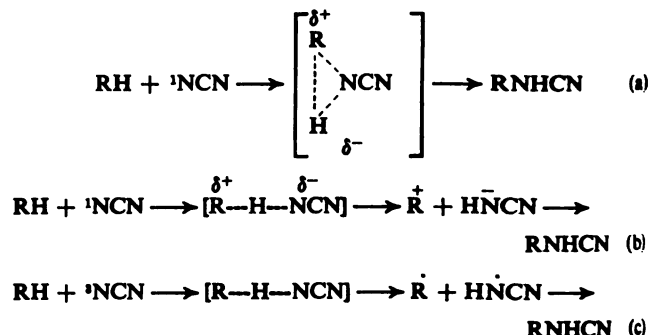
Electronic Structure of NCN. Cyanonitrile has ten bonding electrons. Simple valence theory predicts the lowest energy electronic configuration for cylindrically symmetrical NCN to be $\dots 2\sigma_g^2 2\sigma_u^2 1\pi_u^4 1\pi_g^2$, where π_g^2 could be $\pi_g^2(x)$, $\pi_g^2(y)$, or $\pi_g^1(x)\pi_g^1(y)$. Therefore, we have a situation where two electrons have to be distributed among two degenerate molecular orbitals. According to multiplet theory such an arrangement should give rise to one triplet and three singlet states: $^3\Sigma_g^-$, $^1\Sigma_g^+[\dots \pi_g^1(x)\pi_g^1(y)]$; and two $^1\Delta_g[\dots \pi_g^1(x)$ and $\dots \pi_g^1(y)]$. Electron repulsion considerations suggest that the triplet should be lowest in energy and hence represent the ground state.

Theory was verified by a number of recent spectroscopic studies involving flash photolysis,^{13,14} electron paramagnetic resonance,¹⁵ and matrix isolation¹⁶ experiments. The results of all these investigations point strongly to $^3\Sigma_g^-$ as the ground state. Support for this conclusion was also provided recently by flash photolysis experiments in which N_3CN was photolyzed in the absence of an inert gas diluent.¹⁷ Under these conditions the originally observed species was the $^1\Delta_g$ singlet which decayed to $^3\Sigma_g^-$ at a measurable rate. Further information concerning the structure of NCN derives from a vibrational analysis¹⁸ of its ultraviolet spectrum which afforded a carbon-nitrogen distance very close to that of a C=N bond, suggesting structure 7 as a good representation for the ground state.



Selectivity of the Insertion Reaction. The mild conditions employed in the present work for the generation of NCN suggest that it is produced in a low-energy electronic state. It is reasonable to assume that reacting NCN would be in the lowest electronic state of a given multiplicity, since radiationless decay is usually extremely rapid compared to diffusion. Hence, only the $^3\Sigma_g^-$, $^1\Sigma_g^+$, and $^1\Delta_g$ states need concern us here. For these low-lying states the three distinct modes of reaction shown in Scheme III are formally possible.¹¹

Scheme III



(13) G. Herzberg and D. N. Travis, *Can. J. Phys.*, **42**, 1658 (1964).

(14) G. J. Pontrelli and A. G. Anastassiou, *J. Chem. Phys.*, **42**, 3735 (1965).

(15) E. Wasserman, L. Barash, and W. A. Yager, *J. Am. Chem. Soc.*, **87**, 2075 (1965).

(16) D. E. Milligan, M. E. Jacox, and A. M. Bass, *J. Chem. Phys.*, **43**, 3149 (1965).

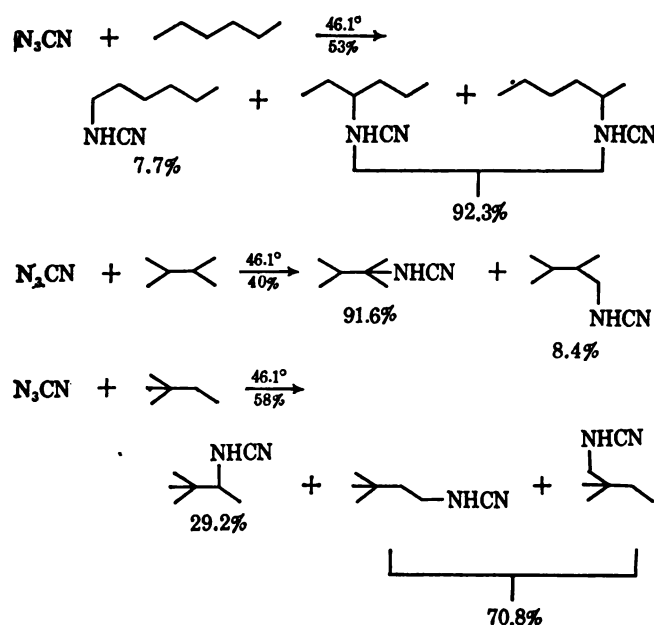
(17) H. W. Kroto, *ibid.*, **44**, 831 (1966).

(18) This is correct only for the low-energy states considered here in which the reactive electrons are roughly isoenergetic. In higher excited electronic states the distinction between singlets and triplets is

Of these, (a) and (c) represent the commonly considered one-step and two-step mechanisms for singlet and triplet species, respectively. Path b becomes a distinct possibility only with highly electrophilic species such as NCN which possess a vacant low-energy bonding MO, e.g., π_g , of $^1\Delta_g$.

To obtain information about the mechanism of the insertion, we determined the selectivity of the reaction with various types of C-H links both in intramolecular and intermolecular competition experiments. In the intramolecular competition experiments, N_2CN was thermolyzed at 46.1° in *neat* *n*-hexane, 2,3-dimethylbutane, and 2,2-dimethylbutane to afford the corresponding alkylcyanamides in the yields and relative amounts indicated in Scheme IV. The proportions of the various products were determined from the nmr spectra of the crude mixtures (see Product Analysis).

Scheme IV



The product distributions in Scheme IV are given as relative rates in Table I (A). The pronounced selectivity of NCN indicated by these results suggests that

Table I.^a Reactivity of Cyanonitrene with C-H Bonds of Saturated Hydrocarbons at $46.1 \pm 0.1^\circ$

A			B		
HC	H	Affinity	HC	H	Affinity
2,3-Dimethylbutane	Prim	1.0	<i>n</i> -Hexane	Sec (α)	1.62
	Tert	67.0		Sec (β)	1.30
<i>n</i> -Hexane	Prim	1.0	Cyclohexane	Sec	1.00
	Sec	9.0		Sec	1.21
2,2-Dimethylbutane	Prim	1.0	Cycloheptane	Sec	1.2 \pm 0.1
	Sec	14.8		Sec	

^a Values are corrected for statistical factors.

appreciable C-H bond rupture occurs in the transition state, but does not provide any relevant information concerning the details of the bond-breaking process which could enable us to decide among the possible reaction

reactions does not appear to be as well defined. For a discussion of this point see A. G. Anastassiou, *J. Am. Chem. Soc.*, **89**, 3184 (1967).

paths. Of the three rate-limiting transition states shown in brackets in Scheme III, only (b) closely resembles that of an S_N1 process with hydride ion partly bound to NCN acting as the leaving group. At first glance it appears that the discrimination of NCN for the various types of hydrogen is far too low for such a process.¹⁹ However, this comparison is not strictly correct, since we may be witnessing a duality of mechanism akin to that observed in solvolytic displacements. For example, singlet NCN could be reacting by path a with primary C-H bonds, by path b with tertiary C-H bonds, and by a combination of paths a and b with secondary C-H bonds. Therefore, in order to distinguish among the three possible alternatives, it was necessary to devise additional experiments. It is known that in saturated carbocycles the rate of formation of an incipient carbonium ion is a sensitive function of ring size. For example, cyclooctyl tosylate and cycloheptyl tosylate solvolyze, respectively, >286 and 31 times as rapidly as cyclohexyl tosylate, which in turn is roughly as reactive as isopropyl tosylate.²⁰ These rate differences are commonly attributed²⁰ to the required hybridization changes involved in the incipient formation of carbonium ions, which occur more readily in the cyclooctyl and cycloheptyl systems than in the cyclohexyl system. This information coupled with the fact that of the three mechanisms in Scheme III only (b) requires any drastic hybridization changes²¹ suggested that a determination of the relative ease with which NCN reacts with the C-H bonds of various cycloalkanes may provide significant information concerning the occurrence or absence of mechanism b. Furthermore, the comparison of the results ought to be free of the ambiguity introduced by a possible duality of mechanism since the C-H bonds involved are all of the same type.

We have carried out intermolecular competition experiments and have found virtually no difference in reactivity among the methylene hydrogens of *n*-hexane, cyclohexane, cycloheptane, and cyclooctane. The results are collected in Table I (B). We interpret the observed lack of discrimination of NCN for the methylene groups of the three monocycles to mean that, at least in the absence of a solvent, secondary and certainly the less reactive primary C-H bonds do not react by a hydride-abstraction process such as that indicated in Scheme IIIb. These experiments do not, of course, provide any information concerning the mode of reaction of tertiary C-H bonds. Hydride abstraction here should be more favorable than with the other types of C-H bonds because of the production of a more stable tertiary cation.

Additional support for the nonoccurrence of mechanism b was obtained in the following manner. If an ion pair is produced, the carbonium ion might be amenable to skeletal rearrangement if it is of appropriate structure. Carbonium ion 8 is particularly susceptible to skeletal reorganization to ion 9, e.g., both

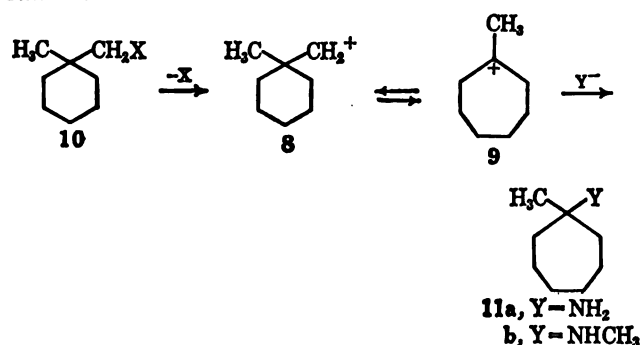
(19) Larger rate differences are usually observed in S_N1 processes. For example, *t*-butyl bromide solvolyzes ca. 10^7 times as fast as isopropyl bromide: L. C. Bateman and E. D. Hughes, *J. Chem. Soc.*, 945 (1940).

(20) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 95.

(21) This statement rests on the assumption that (1) little rehybridization is necessary in the three-center process a, and (2) the commonly accepted view that alkyl radicals are not subject to any stringent hybridization requirements.

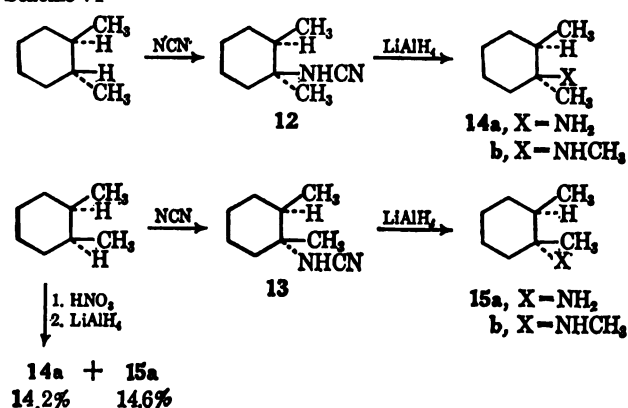
oxidative decarboxylation²² of acid **10** ($X = \text{COOH}$) and nitrous acid deamination of the corresponding amine **10**, ($X = \text{NH}_2$)²³ yield **11** as the major product and material with intact skeleton is not produced (Scheme V). In the present work, cyanogen azide was thermolyzed in 1,1-dimethylcyclohexane and the crude cyanamide mixture was converted to the corresponding amino and methylamino compounds with excess lithium hydride. Gas-liquid partition chromatographic (glpc) analysis established the absence (<2%) of the amines **11** ($Y = \text{NH}_2, \text{NHCN}_2$).^{24,25}

Scheme V



Stereochemistry of the Insertion Reaction. In principle, the direct insertion mechanism (a) and that involving hydrogen abstraction-recombination (b) ought to be distinguishable stereochemically. Path a is expected to be stereospecific leading to over-all retention of configuration, whereas path b should generate the products in a stereochemically random fashion under some conditions. In order to distinguish between these two mechanisms, we examined the stereochemical course of the insertion reaction. We employed the stereoisomeric 1,2-dimethylcyclohexanes as paraffinic substrates because of their ready availability in high purity and because the key products, 1-amino- and 1-methylamino-1,2-dimethylcyclohexane, are known in both stereoisomeric (but unassigned) forms. The results of these experiments are depicted in Scheme VI and tabulated in Table II.

Scheme VI



(22) C. Walling, "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 421.

(23) R. Kotani, *J. Org. Chem.*, **30**, 350 (1965).

(24) Authentic materials were synthesized according to R. Jacquier and H. Christol, *Bull. Soc. Chim. France*, 596 (1957).

(25) The selectivity values shown in Table I suggest that ca. 6% of the product should arise from attack on primary C-H which, in the event that a carbonium ion is an intermediate, should mostly afford **11** ($Y = \text{NHCH}_3$). The amount of **11** expected is well above the detection limits of our glpc analysis.

Table II. Stereochemistry of the Insertion Reaction of Cyanonitrene into the Tertiary C-H Bonds of *cis*- and *trans*-1,2-Dimethylcyclohexane

Hydrocarbon	Temp, °C	Products, %	
		<i>trans</i> -RNHCN (12)	<i>cis</i> -RNHCN (13)
<i>trans</i>	46.1	>98	<2
<i>cis</i>	46.1	<2	>98

It is seen that the reaction is highly stereospecific, each isomeric substrate producing a single (>98%) stereoisomeric cyanamide which was identified in each case by analysis of the configurationally homogeneous mixture of 1-amino- and 1-methylamino-1,2-dimethylcyclohexane (**14a,b** and **15a,b**). These products were assigned the indicated stereochemistry on mechanistic grounds, since the absolute stereochemistry of the known isomers has not yet been determined. It should be noted that a reversal of these assignments would imply that stereospecific insertion occurs with net inversion of configuration, which we consider unlikely. The assignments are also consistent with the glpc data which show that the more sterically hindered *cis* isomers have higher retention times. Irrespective of the specific assignments, the observed stereospecificity is consistent with a one-step insertion process and militates against any two-step processes such as those depicted in (b) and (c), which could lead to stereospecific product formation only in the unlikely event that recombination of the intermediate ion or radical pair occurs prior to inversion of the asymmetric center.

To obtain some information concerning this latter point, we have examined the stereochemical fate of the tertiary 1,2-dimethylcyclohexane radical generated in the liquid-phase, free-radical nitration²⁶ of *cis*-1,2-dimethylcyclohexane with 50% nitric acid. The amine mixture obtained by reduction of the originally produced nitro compounds consisted of 28% of a 1:1 *cis-trans* mixture of 1-amino-1,2-dimethylcyclohexane. This is in keeping with the anticipated configurational instability of the hydrocarbon radical.

Product Analysis. In the intramolecular competition experiments, cyanogen azide was thermolyzed in the various hydrocarbon substrates to yield mixtures of cyanamides. The constitutions of the *crude* mixtures were determined from the nmr spectra (neat). Under these conditions the N-H proton appears at $\tau \sim 4.2$ and is quite sharp, exhibiting splitting consistent with the number of hydrogen atoms at the α -carbon.²⁷ The protons bound to the α -carbon appear at $\tau \sim 7$. Both these signals are well separated from the remaining absorptions which appear in the usual aliphatic region. All attempts to separate the various isomeric products in mixtures by gas-liquid partition chromatography were unsuccessful because of their extremely low volatility. Satisfactory product identification rests on correct elemental analyses of the high-vacuum distillation product mixtures and nmr and infrared spectra. The absence of any significant amount of impurity in the crude mixtures is indicated by the iden-

(26) H. Shechter and D. K. Brain, *J. Am. Chem. Soc.*, **85**, 1806 (1963).

(27) For example, the N-H proton of *neat* cyclohexylcyanamide appears as a doublet ($J \sim 5$ cps) at $\tau 4.3$ and that of *neat* *t*-butylcyanamide as a sharp singlet at $\tau 4.2$.

of their spectral characteristics (nmr, infrared) compared with those of the analytically pure mixtures. In the intermolecular competition runs, N_2CN was polymerized in the appropriate hydrocarbon pair, the composition of which was determined previously by

The mixtures of cyanamides produced were converted to the corresponding amino and methylamino derivatives by treatment with excess lithium aluminum hydride in boiling tetrahydrofuran; the relative amounts of amines were then determined by glpc. The secondary amines were characterized by direct comparison of their retention times and mass spectrometric cracking patterns with those of authentic samples. Similarly, the reaction of NCN with the 1,2-dimethylcyclohexanes, the mixture of amines after reduction was analyzed by glpc, and the key isomers were characterized by direct comparison of glpc retention times and mass spectrometric cracking patterns with those of authentic samples.²⁸ Similar methods of conversion to amines for analysis were employed in the reaction of 1,1-dimethylcyclohexane with NCN and *cis*-1,2-dimethylcyclohexane with nitric acid.

Conclusions

Thermolysis of cyanogen azide at 40–50° affords free cyanonitrene which, in the absence of an inert diluent, inserts with tertiary C–H bonds stereospecifically. Information about the insertion process into the less reactive secondary and primary C–H bonds is not as easily obtainable experimentally. Here the mechanism may depend on the relative rates for direct insertion (path of intersystem crossing of singlet NCN to its triplet ground state ($^1NCN \rightarrow ^3NCN$); i.e., if direct insertion is more rapid than intersystem crossing, singlet NCN will insert in a one-step process, whereas if the latter is true, the reaction will occur by a hydrogen abstraction–recombination process by triplet NCN. Evidence will be presented in a subsequent paper that at least in the case of tertiary C–H bonds the direct insertion mechanism prevails. A hydrogen abstraction–recombination process by singlet NCN does not at all probability occur with either type of C–H

Experimental Section²⁹

Extreme caution should be exercised in handling cyanogen azide. It detonates with great violence and it should be prepared and used only in solvents. Solutions of cyanogen azide in paraffinic hydrocarbons can be handled safely, but should nevertheless be treated as potentially explosive because of its poor solubility in non-solvents. The concentration of such solutions should not exceed 10%.

K. E. Hamlin and M. Freifelder, *J. Am. Chem. Soc.*, **75**, 369 (1953).

All melting points and boiling points are uncorrected. Nmr spectra were measured with a Varian A-60 spectrometer and infrared spectra with a Perkin-Elmer 21 spectrometer. The glpc results were obtained under the following conditions: A, 2 m \times 0.24 in. stainless steel column packed with 20% tetrakis(hydroxyethyl)ethylenediamine (TD) on 60–80 mesh Chromosorb W (not acid washed) at 101° with helium at 155°; helium was used as the carrier gas at a flow rate of 1 ml/min; B, same as in A except column and vaporizer temperatures 102 and 165°, respectively; C, 2 m \times 0.25 in. stainless steel column packed with 20% TCEG on 60–80 mesh Gas Chrom R at 52° with the vaporizer at 120°; D, 2 m \times 0.25 in. stainless steel column of 20% THEED on Chromosorb W (not acid washed) at 110°, and a helium flow rate of 810 cc/min.

Materials. Activated sodium azide³⁰ was used throughout. Of the hydrocarbons, 2,3-dimethylbutane, 2,2-dimethylbutane, and *cis*- and *trans*-1,2-dimethylcyclohexane were "Phillips Research Grade" and were used without further purification. Cyclohexane, cycloheptane, cyclooctane, 3-methylpentane, 1,1-dimethylcyclohexane, and *n*-hexane were treated with concentrated sulfuric acid and carefully fractionated before use. The materials thus obtained were >99.6% pure by glpc (conditions D). Labeled potassium azide (ca. 95 atoms % ^{14}N at positions 1 and 3) was purchased from Merck Sharp and Dohme of Canada.

Thermolysis of Cyanogen Azide in *n*-Hexane. Cyanogen chloride (50 ml) was allowed to evaporate into a stirred suspension of sodium azide (6.0 g) in *n*-hexane (30 ml) maintained under nitrogen and contained in a three-necked flask fitted with thermometer, inlet tube, and condenser held at -5 to 0° by a circulation coolant. The addition was made over a 2.5-hr period, while the temperature of the mixture was maintained at -4 to 0° . The suspension was then stirred at room temperature overnight, *n*-hexane (70 ml) was added, and the excess cyanogen chloride was removed at room temperature³¹ at 100–200-mm pressure. The suspension was subsequently filtered under nitrogen pressure into a graduated cylinder. To the clear filtrate was then added more *n*-hexane to a total volume of 295 ml. A 2-ml sample of this solution gave 7 ml of gas when treated with trimethyl phosphite in an azotometer at 0 – 2° (46% yield).

The solution was subsequently transferred into a 500-ml, three-necked, round-bottomed flask fitted with thermometer and condenser. A water test meter was connected through a Dry Ice trap to the top of the condenser. When the solution was heated at 48 – 52° with stirring for 18 hr, 900 ml ($\sim 90\%$) of gas was evolved. The yellow hexane solution was subsequently filtered free of any residue, and the volatile constituents of the filtrate were evaporated at 40° under water-aspirator pressure to yield a residual orange oil. This was distilled in a molecular still at $\sim 0.05 \mu$ and a maximum bath temperature of 90° . The colorless distillate amounted to 2.76 g (53% yield based on N_2CN) and the residual resin to 0.5 g. The infrared spectrum of the distillate exhibits characteristic strong bands at 3180 (N–H) and 2200 ($C\equiv N$) cm^{-1} . The nmr spectrum is equally consistent with signals at τ 4.2 (doublet), 7.0 (multiplet), and 8.3–9.2 (multiplet).

Anal. Calcd for $C_7H_{14}N_2$: C, 66.62; H, 11.18; N, 22.20. Found: C, 66.48; H, 11.12; N, 22.87.

Thermolysis of Cyanogen Azide in 2,3-Dimethylbutane, 3-Methylpentane, and 2,2-Dimethylbutane. A procedure similar to that described for *n*-hexane was employed. The results are given in Table III.

Intramolecular Competition Runs. The following general procedure was employed. Cyanogen azide was prepared by stirring overnight under reflux ($\sim 15^\circ$)³² a mixture of 2.0 g of sodium azide and ca. 40 ml of cyanogen chloride under nitrogen. The appropriate hydrocarbon was then added, and the excess cyanogen chloride removed at room temperature³¹ (100–200 mm). The suspension was subsequently filtered under nitrogen pressure and the clear filtrate made up to ca. 200 ml by further addition of hydrocarbon. The solution was transferred into a one-necked, round-bottomed flask fitted with a condenser, and the flask was placed in a constant-temperature water bath maintained at $46.1 \pm 0.1^\circ$. The solution was held at this temperature for ca. 21 hr; the theoretical amount of nitrogen had then been evolved. The mixture was then filtered free from any traces of precipitate that might be present, and the filtrate was concentrated to a tan oil under water-aspirator pressure and below 40° . A 250-cps nmr spectrum of the residual oil was determined immediately, and the areas of interest were carefully cut and weighed. The results of duplicate runs are shown in Table IV. In each case the nmr and infrared spectra of these mixtures were the same as those of their analytically pure counterparts described above.

The figures in Table IV were corrected for statistical factors and translated into the relative rates shown in Table I (A) by the following relations: a, for products derived from 2,3-dimethylbutane, tertiary product/primary product = $(A_1 - A_2/2)/(A_2/2)$; b, for products derived from *n*-hexane and 2,2-dimethylbutane, secondary product/primary product = $[A_1 - (A_2 - A_1)]/(A_2 - A_1)$.

(30) P. A. S. Smith, *Org. Reactions*, **3**, 382 (1946).

(31) It is essential that the temperature be kept above $+10^\circ$ to avoid separation of a highly explosive layer of neat cyanogen azide.

(32) It is essential to keep the temperature of the condenser at ca. -5 to 0° to contain the cyanogen chloride (bp 12°). In the course of one run, failure of the cooling system led to a violent explosion.

Table III. Thermolyses of Cyanogen Azide in C₆H₁₄ Hydrocarbons

Hydrocarbon	Yield of N ₂ CN, %	Yield of cyanamide, % ^a	Infrared (neat), cm ⁻¹		Spectral data			Elemental composition, %
			N-H	C≡N	N-H	Nmr (neat), τ α(C-H)	Other	
2,3-Dimethylbutane	85	40	3205	2217	4.3	7.0	8.1-9.1	C, 66.82 H, 11.13 N, 22.46
2,2-Dimethylbutane	58	42	3210	2200	4.3	7.2	8.8-9.3	C, 66.57 H, 10.94 N, 22.19
3-Methylpentane	88	41	3200	2210	4.2	6.9	8.2-9.3	C, 66.42 H, 11.05 N, 22.05

^a Based on N₂CN. ^b Found.

Table IV. Nmr Data of Intermolecular Competition Experiments

Hydrocarbon	Area A ₁		Area A ₂	
	Wt, g	Chem shift, τ	Wt, g	Chem shift, τ
n-Hexane	0.1750	4.2	0.1890	7.0
	0.2459		0.2640	
2,3-Dimethylbutane	0.0912	4.3	0.0152	7.0
	0.0868		0.0145	
2,2-Dimethylbutane	0.2080	4.2	0.2701	7.2
	0.2095		0.2695	

mass spectrometric cracking patterns with those of authentic samples. The structural assignments of 2- and 3-methylaminohexane derive from the mass spectrometric cracking patterns which are fully consistent with these structures. The relevant data employed in the identification of the amines are compiled in Table VI.

Preparation of 1-Amino- and 1-Methylamino-1-methylcycloheptane. 1-Amino-1-methylcycloheptane was prepared as described in the literature.²⁴ To a solution of this material (1.75 g) in chloroform (15 ml) was added with stirring freshly distilled chloral (2.6 g) at such a rate as to maintain the temperature at 0-2°. The mixture was then stirred at room temperature overnight. Removal of the volatile constituents at water aspirator pressure gave an

Table V. Quantitative Data from Intermolecular Competition Runs

Hydrocarbon mixture	Composition ^a	Reaction	Composition of amine mixtures ^d									
			A	B	C	D	E	F	G	H	I	J
Cyclohexane	37.0	1 ^b	8.5	24.3	9.2	21.1	9.4	14.2
n-Hexane	63.0											
Cyclohexane	67.6	2 ^{c,e}	16.2	39.2	11.3	30.9
Cycloheptane	32.4											
Cyclohexane	75.6	3 ^{c,e}	20.0	43.1	7.5	25.1
Cyclooctane	24.4											

^a Mole %, determined by glpc under conditions D. ^b Average of four glpc determinations under conditions A. ^c Average of three glpc determinations under conditions C. ^d Weight %, A = cyclohexylamine, B = N-methylcyclohexylamine, C = 2-aminohexane, D = 2-methylaminohexane, E = 3-aminohexane, F = 3-methylaminohexane, G = cycloheptylamine, H = N-methylcycloheptylamine, I = cyclooctylamine, and J = N-methylcyclooctylamine. ^e In these runs, known mixtures of the amines were used for quantitative glpc calibrations.

Intermolecular Competition Runs. The procedure was essentially the same as that described for the intramolecular competition runs. The appropriate hydrocarbon mixture was added, the cyanogen chloride removed, the suspension filtered, and the filtrate made up to 200-ml volume. The exact composition of the mixture was determined by glpc. The reaction mixture was then heated at 46.1 ± 0.1° in a constant-temperature water bath for 20 hr. The crude cyanamides were isolated in the usual way and were treated with lithium aluminum hydride according to the following procedure.

A solution of the crude cyanamide mixture (3.0 g) in tetrahydrofuran (50 ml) was added with stirring to a boiling suspension of lithium aluminum hydride (5.0 g) in tetrahydrofuran (150 ml) over a period of 1.5 hr. The mixture was stirred under reflux for an additional 15 hr. It was cooled in an ice bath and treated carefully with a saturated aqueous solution of sodium sulfate until the slurry turned white. The mixture was filtered and the filter cake washed with tetrahydrofuran. The filtrate was made strongly acid with 25 ml of concentrated hydrochloric acid and evaporated to dryness to afford a hygroscopic, crystalline, tan solid. This product was dissolved in 15 ml of distilled water, and the resulting solution transferred into a 50-ml separatory funnel. The funnel was placed in an ice bath, and the solution was made strongly basic by the addition of sodium hydroxide pellets. The mixture was shaken vigorously; the layers were allowed to separate, and the dark upper layer was collected and dried over sodium hydroxide pellets under nitrogen and analyzed by glpc. The results are shown in Table V. All amines except 2- and 3-methylaminohexane were identified by direct comparison of their glpc retention times and

Table VI. Identifying Features of the Amines

Compd ^a	Retention time, min	Molecular ion, m/e	100% ion, m/e
A	5.6 ^b	99	56
A	32.8 ^c	99	56
B	4.1 ^b	113	70
B	24.2 ^c	113	70
C	10.6 ^c	101	44
D	8.0 ^c	115	58
E	8.8 ^c	101	58
F	5.8 ^c	115	72
G	11.4 ^b	113	56
H	7.7 ^b	127	70
I	21.4 ^b	127	56
J	14.1 ^b	141	70

^a See Table V. ^b Retention times under glpc conditions C. ^c Retention times under glpc conditions A.

oil, bp 85-86° (1 mm). The colorless distillate amounted to 2.4 g, n_D²⁰ 1.4991. A solution of this material (2.4 g) in ether (8 ml) was added with stirring to a suspension of lithium aluminum hydride (2.1 g) in ether (30 ml) maintained at ice-bath temperature. The resulting mixture was stirred under reflux for 2 hr. The mixture was cooled in an ice-salt bath and treated with 10% aqueous sodium hydroxide until the solid turned completely white. The suspension

Table VII

Temp, °C (mm)	Amount, g	n_D^{20}	Composition ^a
100–106 (38)	0.4	1.4639	11a, 35.7%; 11b, 17.0%
108–113 (39–42)	0.78	1.4654	11a, 8.0%; 11b, 14.8%

^a Amounts were determined by glpc under conditions C. Structural assignments were made on the basis of mass spectrometric cracking patterns. Compound 11a: molecular ion at m/e 127, 100% ion at m/e 70; compound 11b: molecular ion at m/e 141, 100% ion at m/e 84.

was filtered; the filter cake was washed with ether, and the combined extracts were dried over sodium hydroxide pellets. The ether was then removed and the residual liquid distilled (see Table VII).

Thermolysis of Cyanogen Azide in 1,1-Dimethylcyclohexane. Cyanogen azide, prepared from 2.0 g of sodium azide and 40 ml of cyanogen chloride, was thermolyzed at $46.25 \pm 0.05^\circ$ in 110 ml of 1,1-dimethylcyclohexane. The cyanamide mixture (2.5 g) was isolated as described previously. This product was subsequently reduced with lithium aluminum hydride in tetrahydrofuran in the usual manner. The amine mixture amounted to 2.0 g. Glpc analysis of the mixture under conditions C indicated the absence of 11a and 11b.

Preparation of 1-Amino-1,2-dimethylcyclohexane. This compound was prepared as described in the literature.²⁸ Nitration (aluminum nitrate nonahydrate) of a 2:1 mixture of *cis*- and *trans*-1,2-dimethylcyclohexane and subsequent catalytic hydrogenation (Raney nickel) of the resulting nitro compounds gave a stereoisomeric mixture of *cis*- and *trans*-1,2-dimethylcyclohexane. The component with the higher retention time (30.9 min, conditions A) constituted 51% of the mixture and the one with the lower retention time (20.3 min, conditions A), 42.4% of the mixture. The components with the higher and lower retention times are assigned the *cis* and the *trans* configurations, respectively. The two isomers were separated by preparative glpc under conditions E. Stereoisomers 14a and 15a exhibit identical mass spectrometric cracking patterns (100% ion at m/e 70; molecular ion at m/e 127). Their infrared spectra are identical except for minor differences in the fingerprint region.

1-Methylamino-*trans*-1,2-dimethylcyclohexane and 1-Methylamino-*cis*-1,2-dimethylcyclohexane. Stereopure 14a and 15a were converted to the monomethyl derivatives by the procedure described for the conversion of 11a to 11b.

1. *cis* Isomer 15b. A 2.5-g sample of the *cis*-amino compound 15a gave 0.77 g of colorless amine, bp $81\text{--}82^\circ$ (33 mm). Glpc analysis under conditions A showed 54.8% 15a (RT (retention time) = 30.9 min) and 32.7% 15b (RT = 23.6 min). The mass spectrum of 15b shows 100% ion at m/e 84 and molecular ion at m/e 141.

2. *trans* Isomer 14b. A 2.5-g sample of 14a gave 0.57 g of amine. Glpc analysis under conditions A indicated 66.9% 14a (RT = 20.3 min) and 29.0% 14b (RT = 13.0 min). The mass spectrum of 14b shows 100% ion at m/e 84 and molecular ion at m/e 141 and is qualitatively identical with the spectrum of its stereoisomer 15b.

Thermolysis of Cyanogen Azide in *cis*-1,2-Dimethylcyclohexane. Cyanogen azide, prepared from 2 g of sodium azide and 40 ml of cyanogen chloride, was heated at $46.05 \pm 0.05^\circ$ in 200 ml of *cis*-1,2-dimethylcyclohexane. The resulting mixture of cyanamides was isolated and converted to the corresponding amines (2.2 g) in the usual way (lithium aluminum hydride in tetrahydrofuran). The mixture was analyzed by glpc (conditions A) and consisted of 0.5% 14b (RT = 12.8 min), <0.3% 14a, 28.9% 15b (RT = 23.7 min), and 15.4% 15a (RT = 30.4 min). Compounds 14b, 15b, and 15a were identified mass spectrometrically.

Thermolysis of Cyanogen Azide in *trans*-1,2-Dimethylcyclohexane. The mixture of amines (2.0 g) was obtained by a procedure analogous to that described for the *cis* hydrocarbon. Glpc analysis under conditions A gave 25.3% 14b (RT = 12.8 min), 14.7% 14a (RT = 19.7 min), and <0.3% 15a. Compounds 14b and 14a were identified by their mass spectrometric cracking patterns.

Nitration of *cis*-1,2-Dimethylcyclohexane. A mixture of *cis*-1,2-dimethylcyclohexane (50 g) and 50% nitric acid (350 g) was stirred at the boiling temperature (oil bath at 140°) for 3 hr. The mixture was allowed to cool to room temperature; the layers were separated, and the aqueous layer was cooled in ice and extracted with two 50-ml portions of ether. The ether extracts were combined with the organic layer and washed first with four 50-ml portions of 20% aqueous sodium hydroxide, then with water, and fi-

nally dried over Drierite. Removal of the ether and the excess hydrocarbon at 50° (10 mm) and distillation of the residue gave a pale yellow liquid (3.23 g, 4.6%), bp $82\text{--}87^\circ$ (3–5 mm); n_D^{20} 1.4667. This product was treated with lithium aluminum hydride in the usual way and glpc analysis of the crude amine mixture under conditions A indicated the presence of 14.2% 14a (RT = 19.5 min) and 14.6% 15a (RT = 30.0 min). The two materials exhibit essentially identical mass spectrometric cracking patterns with a molecular ion at m/e 127 and a 100% ion at m/e 70.

Thermolysis of ¹⁵N-Labeled Cyanogen Azide in Cyclohexane. Cyanogen azide in cyclohexane (290 ml) was prepared from isotopically labeled potassium azide (2.1 g) according to the procedure already described. This solution was heated at $49\text{--}50^\circ$ overnight, and the crude cyclohexylcyanamide (2.27 g, 57%) was isolated in the usual way and distilled at ca. 0.003μ to afford 1.54 g of pure 1. The purified cyanamide was suspended in 10 ml of distilled water, 20 drops of concentrated sulfuric acid was added, and the mixture was stirred under reflux for 0.5 hr. The precipitated white solid was isolated by filtration, washed with water, and dried in a drying pistol, yielding 1.1 g (63%) of cyclohexylurea, mp $186\text{--}186.7^\circ$. A suspension of this material (1.1 g) in tetrahydrofuran (30 ml) was added with stirring to a boiling mixture of lithium aluminum hydride (2.0 g) in tetrahydrofuran (130 ml) under nitrogen. The addition was made over 1 hr, and the mixture was stirred under reflux for an additional 24 hr. The usual work-up afforded a yellow liquid which was dried over sodium hydroxide pellets and distilled ($10\text{--}20$ mm). The colorless distillate (2 + 3) amounted to 0.25 g. The corresponding unenriched materials were prepared analogously.

Analysis. Starting potassium azide was burned to nitrogen and the isotopic enrichment of this species determined mass spectrometrically: atom % of ¹⁵N in nitrogen = 3.26, total ¹⁵N in potassium azide = $3.26 \times 3 = 9.78\%$, atom % of ¹⁵N in the terminal position of azide less the ¹⁵N natural abundance (net enrichment): $[(9.78 - 0.36)/2] - 0.36 = 4.35$.

The amount of ¹⁵N in 1 and 2 was determined mass spectrometrically employing the ratio of intensities of molecular ion + 1 to molecular ion. The results are shown in Table VIII.

Table VIII. Ratio of Intensities of Molecular Ion + 1 to Molecular Ion at 70 ev

	1 (¹⁵ N), %	1 (¹⁵ N), %	2 (¹⁵ N), %	2 (¹⁵ N), %
	8.92	13.29	8.17	10.66
	8.86	13.31	8.18	10.71
	8.89	13.31	8.16	10.74
	8.87	13.22	8.12	10.56
	8.85	13.20	8.00	10.72
			8.12	10.74
			8.17	10.64
			8.20	10.74
Av	8.86	13.26	8.14	10.69
Total ¹⁵ N enrichment in 1 = 4.40%				
Total ¹⁵ N enrichment in 2 = 2.55%				

Compound 2 was burned to nitrogen and the isotopic enrichment was determined mass spectrometrically (in duplicate); total enrichment in 2 = 2.35%, 2.55%.

Reaction of Norbornene with ¹⁵N-Labeled Cyanogen Azide. Enriched cyanogen azide was prepared from 2 g of isotopically labeled potassium azide and 35 ml of cyanogen chloride. To the cyanogen chloride suspension was added 55 ml of water-free acetonitrile; the excess cyanogen chloride was removed at $100\text{--}200$ mm, and the residual suspension was pressure filtered under nitrogen. The clear acetonitrile solution amounted to 55 ml and liberated 7.5 cc of gas (N_2) per 1 ml of sample when treated with trimethyl phosphite. The solution was subsequently maintained at 49° for 2.5 hr. At the conclusion a 1-ml sample of the solution liberated 6.5 cc of gas. The mixture was cooled in an ice bath, and a solution of freshly distilled norbornene (6 g) in acetonitrile (30 ml) was added over 1.5 hr, while the temperature was maintained at -2 to 4° . After the addition was complete (theoretical amount of gas had been evolved), the reaction mixture was held at room temperature for an additional 16 hr. Removal of the volatile constituents under water-aspirator pressure and at 55° gave 2.4 g of an orange oil. This product was dissolved in benzene (10 ml) and passed through a chromatographic column containing 100 g of grade IV

"Woelm" neutral alumina. Evaporation of the eluents (400 ml) afforded a slightly tan oil, which exhibited a strong infrared band at 2200 ($\text{C}\equiv\text{N}$) and 1730 ($\text{C}=\text{O}$) cm^{-1} . Distillation of this material through a micro-Vigreux column gave pure cyanoaziridine as a colorless liquid (1.53 g, 41%), bp 97° (0.35 mm), the infrared spectrum of which showed a strong band at 2200 cm^{-1} and no absorption at 1730 cm^{-1} .

Removal of the nitrile group from 6 was accomplished as follows. A solution of the cyanoaziridine (1.53 g) in ether (15 ml) was added to a stirred suspension of lithium aluminum hydride (0.24 g) in ether (25 ml) over 20 min. The temperature of the mixture was maintained below 25° throughout the addition by an ice bath. The suspension was then stirred at reflux for 3 hr. The suspension was subsequently cooled with an ice-salt bath and treated with a saturated aqueous solution of sodium sulfate. The white suspension was filtered; the colorless filtrate was dried over anhydrous sodium sulfate and the ether removed. Distillation of the residual

oil through a short path head at 0.2–0.5 mm with a bath temperature of 150° afforded a colorless semisolid (0.80 g, 67%) which solidified immediately when placed on a porous plate. The infrared spectrum of this material was identical in all respects with that of an authentic sample.¹¹

Analysis. Starting potassium azide was burned to nitrogen and the isotopic enrichment of this species determined mass spectrometrically: atom % of ^{15}N in nitrogen = 3.25, total ^{15}N in potassium azide = $3.25 \times 3 = 9.75\%$, atom % of ^{15}N in terminal position of azide less the ^{15}N natural abundance (net enrichment): $[(9.75 - 0.36)/2] - 0.36 = 4.33$.

Compounds 5 and 6 were converted to nitrogen, and the isotopic enrichment was determined mass spectrometrically (in duplicate): total enrichment in 5 = 4.18%, 4.38%; total enrichment in 6 = 3.90%, 4.19%.

(33) F. D. Marsh, M. E. Hermes, and H. E. Simmons, to be published.

The Electronic Multiplicity of Thermally Generated Cyanonitrene¹

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Contribution No. 1258 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898. Received February 4, 1967

Abstract: The stereochemistry of the insertion of cyanonitrene, generated thermally from cyanogen azide, into the tertiary C–H bonds of *cis*- and *trans*-1,2-dimethylcyclohexane was studied in a variety of solvents. The stereospecificity observed when the reaction was conducted in the absence of a solvent was completely preserved in acetonitrile and fully destroyed in methylene bromide. In methylene chloride and ethyl acetate, the reaction is stereoselective. Triplet cyanonitrene displays a slightly more pronounced discrimination in selecting between secondary and tertiary C–H bonds than does singlet cyanonitrene. Mechanisms are discussed.

Recent years have witnessed a number of elegant and fruitful investigations concerning the electronic states of neutral electron-deficient fragments (carbenes,³ nitrenes, etc.). In most cases, information about ground electronic states is readily available through a variety of spectroscopic methods such as electron paramagnetic resonance (epr) and flash photolysis. In contrast, information concerning electronic configurations of such species during the course of chemical reactions is not easily accessible and can only be adduced by an interplay of intuitive reasoning and experiment, the former being very often controversial. In chemical reactions, three situations arise: (1) the reacting species is in the ground electronic state, (2) the reacting species is in the first excited electronic state (usually of different multiplicity than the ground state), and (3) the reacting species is a composite of both ground electronic state and first excited electronic state. The great majority of reactions involving neutral electron-deficient intermediates is complicated by situation 3. The most widely employed criterion for arriving at the electronic multiplicity of a reacting carbene was advanced 11 years ago by Skell and Wood-

worth⁴ and concerns the stereochemistry of addition of such a fragment to olefinic bonds. It states that singlet carbenes should add in one step to yield cyclopropanes in a stereospecific fashion, whereas the triplet counterparts ought to react by means of a diradical intermediate which, being essentially a free rotator, leads to stereorandom ring closure. Skell's postulate has received ample experimental support over the years and constitutes a reliable working hypothesis. Care must be exercised in its use, however, since, as has been repeatedly pointed out, it cannot be justified theoretically.^{1,5} Three recent reports lend particularly strong support to the postulate. These deal with the effect of dilution by a nonolefinic substrate on the stereochemistry of addition of fluorenylidene⁶ and dicyanocarbene,⁷ both of which have triplet ground states,^{8,9} to the isomeric 2-butenes and of carbethoxynitrene¹⁰ to *cis*- and *trans*-4-methyl-2-pentene. In each case, the stereoselectivity

(4) P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **78**, 4496 (1956).

(5) Hoffmann has recently advanced the notion that symmetry rather than multiplicity of an electronic state is the deciding factor in the stereochemical course of addition: R. Hoffmann, Abstracts of Papers, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, p 109K.

(6) M. Jones, Jr., and K. R. Rettig, *J. Am. Chem. Soc.*, **87**, 4013 (1965).

(7) E. Ciganek, *ibid.*, **88**, 1979 (1966).

(8) A. M. Trozzolo, R. W. Murray, and E. Wasserman, *ibid.*, **84**, 4990 (1962).

(9) E. Wasserman, L. Barash, and W. A. Yager, *ibid.*, **87**, 2075 (1965).

(10) W. Lwowski and J. S. McConaghy, Jr., *ibid.*, **87**, 5490 (1965).

(1) Communicated in preliminary form: A. G. Anastassiou, *J. Am. Chem. Soc.*, **88**, 2322 (1966).

(2) Department of Chemistry, Syracuse University, Syracuse, N. Y. 13210.

(3) For a critical and thorough account see: P. P. Gaspar and G. S. Hammond in "Carbene Chemistry," W. Kirmse, Ed., Academic Press Inc., New York, N. Y., 1964, Chapter 12.

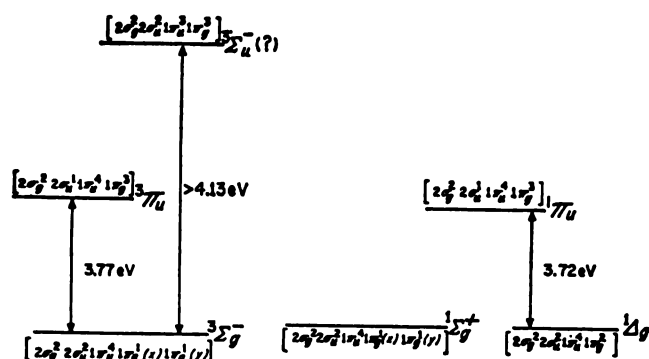


Figure 1. Observed spectroscopic states of cyanonitrene.

of the addition decreases drastically with increasing amount of diluent, a condition which favors situation 1 indicated above. Furthermore, in the case of dicyanocarbene⁷ at high dilution, the same relative amounts of stereoisomeric cyclopropanes are formed starting from either olefinic isomer, in full agreement with Skell's free rotator model of the intermediate diradical.

Results and Discussion

In the present paper, we present a full account of our work dealing with the electronic multiplicity of reacting cyanonitrene (NCN) generated thermally from cyanogen azide (N_3CN). We chose not to study the stereochemical course of the addition of NCN to olefins because of a major experimental difficulty. Cyanogen azide itself reacts readily with olefinic functions¹¹ at room temperature, with over-all loss of molecular nitrogen, to yield products which, in the absence of appropriate isotopic labeling, are indistinguishable from those expected to form from NCN. Hence, we employed the stereochemistry of the insertion reaction into the C-H bonds of paraffinic hydrocarbons as a criterion of electronic multiplicity.

Electronic Structure of NCN. In the preceding paper¹² we mentioned that NCN has been studied by a variety of spectroscopic methods and the configuration of the ground electronic state and a few excited states determined. The information derived from these studies is compiled in Figure 1. It is interesting to consider the various configurations in connection with their ability to undergo stereospecific reactions with C-H bonds and olefinic functions. In so doing, we will not discuss the triplet states since here the stereochemistry of the reaction is independent of symmetry and configuration and depends only on factors succeeding the homolytic bond-breaking step, such as the magnitude of the rate of radical recombination *vs.* that of loss of configurational integrity, both of which are sensitive functions of environment.

The *donor* molecular orbitals (highest occupied MO's) of C-H and C=C bonds are of symmetry¹³ σ_g and π_u , respectively. In the transition state, these could interact in either a bonding or antibonding fashion depending on the symmetry of the *acceptor* MO (lowest unoccupied) of the electron-deficient species. In the present case, since the transition state almost certainly involves interaction of a single nitrogen atom

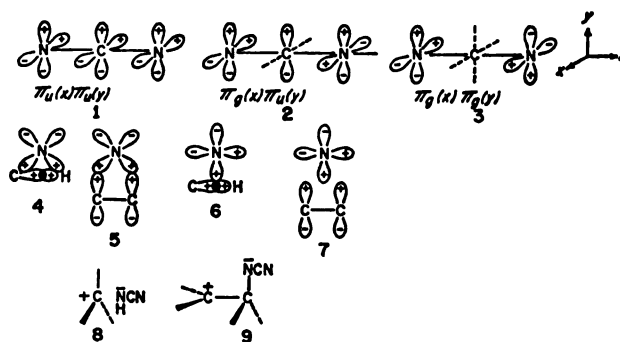


Figure 2. Symmetry requirements of cyanonitrene in addition and insertion reactions.

of NCN with the C-H or the C=C bond, the symmetry of the *acceptor* MO as a whole is of no consequence and what is important is the local symmetry of that MO on the interacting nitrogen atom. This, coupled with the cylindrical symmetry of linear NCN, suggests that the nature of the interaction ought to be independent of the π symmetry of NCN, *i.e.*, both the π_g and π_u MO's of NCN can interact with C-H and C=C bonds in a bonding fashion. This is shown diagrammatically (molecular axis of NCN (z) perpendicular to the plane of the paper) in 4 and 5 of Figure 2. In Figure 2 are also shown the various π -orbital combinations of linear NCN. The two low-lying singlets of NCN, $^1\Sigma_g^+$ and $^1\Delta_g$, are similar with respect to symmetry of the *acceptor* MO(s), which in both cases is π_g , but differ in the way this degenerate MO is occupied. In $^1\Sigma_g^+$, each π_g is occupied singly whereas in $^1\Delta_g$, one is filled and the other empty (Figure 1). This difference in the occupancy of the π_g MO will in all probability determine the nature of overlap in the transition state. Thus the $^1\Sigma_g^+$ state having evenly occupied *acceptor* MO's will probably overlap with the *donor* MO's of C-H and C=C in the fashion shown in 4 and 5, whereas electron repulsion considerations would suggest that the $^1\Delta_g$ state ought to interact as shown in 6 and 7, with maximum overlap occurring between the *donor* MO and the empty π_g MO of the acceptor. Translating this crude picture into stereochemistry, we conclude that of the two low-lying singlet states, $^1\Sigma_g^+$ should react stereospecifically in a one-step, three-center process whereas the $^1\Delta_g$ state could probably react by way of the dipolar intermediates shown in 8 and 9 for C-H insertion and C=C addition, respectively. This latter process could lead to nonstereospecific results.

The higher energy singlet $^1\Pi_u$ poses an interesting problem in connection with insertion and addition reactions. Here, one π_g and one σ_u MO are singly occupied, and we have a situation where two paired electrons differ widely in energy. This energy difference will weaken the pairing between the two electrons, and it is not inconceivable, especially since the two electrons are in MO's of different spatial symmetry, that enough weakening could occur so as to allow the two electrons to behave independently. If this occurs, it would be possible for the $^1\Pi_u$ state to react with C-H and C=C bonds by a radical process commonly reserved for triplet species. It should be noted, however, that reaction of NCN in its $^1\Pi_u$ state is very unlikely irrespective of the substrate employed since its deactiva-

(11) F. D. Marsh and M. E. Hermes, *J. Am. Chem. Soc.*, **86**, 4506 (1964).

(12) A. G. Anastassiou and H. E. Simmons, *ibid.*, **89**, 3177 (1967).

(13) This is strictly the symmetry of the bare bond.

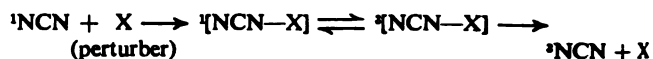
tion to either the $^1\Sigma_g^+$ or $^1\Delta_g$ state ought to occur very rapidly compared to chemical reaction.

Controlled Generation and Reaction of Singlet and Triplet NCN. In previous work,¹² we studied the stereochemical course of the insertion reaction of thermally generated NCN into the tertiary C-H bonds of the two stereoisomeric 1,2-dimethylcyclohexanes and found it to occur with virtually complete stereospecificity. This result is best rationalized by assuming that the reaction occurs in one step by way of singlet NCN. The singlet nature of the reacting NCN is also suggested from considerations of spin conservation in the thermal fragmentation of N_2CN as well as the experimental conditions employed. Thus the low decomposition temperature strongly suggests that singlet N_2CN fragments to singlet molecular nitrogen¹⁴ and, by the principle of conservation of spin, to singlet NCN which in the absence of a solvent would probably undergo reaction prior to collisional deactivation to the lower energy $^3\Sigma_g^-$ state. Nevertheless, the stereochemical results can also be accommodated by a hydrogen abstraction by triplet NCN followed by spin inversion and recombination of the resulting radical pair, provided these latter processes are rapid compared to configurational inversion of the hydrocarbon radical.¹⁵ To obtain definitive information concerning the nature of reacting NCN, it was therefore necessary to design experiments which would unambiguously distinguish between the two mechanisms. One simple way of achieving this is by inducing NCN to insert nonstereospecifically under conditions strongly favoring the presence of triplet NCN. We have examined this possibility by conducting the insertion reaction in the presence of various inert diluents. Under these conditions, collisional deactivation of the originally formed NCN to its $^3\Sigma_g^-$ ground state should compete favorably with reaction. In the course of these experiments, we have also uncovered a thermochemical heavy atom effect. Since this effect provided most of the rationale in designing our experiments, it appears appropriate at this point to briefly summarize its mechanism.

The ability of heavy atoms to promote spin-forbidden electronic transitions is a well-recognized phenomenon and has been the subject of extensive spectroscopic and theoretical studies.¹⁶ Both intramolecular (heavy atom incorporated in the substrate) and intermolecular (heavy atom incorporated in the solvent) "heavy-atom" effects have been observed spectroscopically. For example, the ultraviolet spectrum of 9,10-dibromoanthracene in a light solvent exhibits a fairly intense singlet to triplet ($S_0 \rightarrow T_1$) absorption, whereas that of the parent hydrocarbon, determined under the same conditions, does not. Also the spectrum of neat 1-chloronaphthalene does not possess an $S_0 \rightarrow T_1$ band, whereas the

spectrum of the same molecule determined in ethyl iodide does possess one. There exists a formal similarity between the deactivating processes available to the photoexcited states of a stable molecule and those open to carbenes and nitrenes. In both cases, conservation of spin requires the originally produced state to be a singlet which given an appropriate environment and enough time could decay to a lower energy triplet. However, the similarity ends here since the $S_1 \rightarrow T_1$ intersystem crossing in the photoexcited substrate has to compete with the far more efficient spin-allowed $S_1 \rightarrow S_0$ process, whereas in the case of an electron-deficient fragment with a triplet ground state intersystem crossing $S_1 \rightarrow T_0$ is the only path available for deactivation. This lack of spin-allowed deactivation in most nitrenes and carbenes makes the use of external perturbations to the quantization of spin, such as the "heavy-atom" effect, exceedingly valuable in determining and controlling electronic multiplicity chemically. Two distinct processes are necessary for efficient collisional intersystem crossing which in the present case involves an $S_1 \rightarrow T_0$ transition: (1) vibrational deactivation of the vibronically excited molecule to low vibrational levels of the first excited electronic state, from which energy transfer to high vibrational levels of the ground state can occur; and (2) removal of spin forbiddenness through coupling of spin and orbital angular momenta. The first process is strictly collisional and should depend on the number of degrees of freedom available to the perturbing molecule, as well as the number of perturbing molecules,¹⁷ whereas the second is a function of the amount of spin-orbit coupling introduced by the perturber molecule which in turn depends on the spin-orbit coupling constant (ζ) of the atom responsible for the perturbation. Some relevant ζ values are:¹⁸ C, 28; N, 70; O, 152; Cl, 587; Br, 2460; and I, 5060 cm^{-1} . For the case of NCN, the over-all mechanism for collisional deactivation is depicted in Scheme I.

Scheme I



It is clear, therefore, from these considerations that an inert solvent containing one or more heavy atoms or other perturbing functionalities should fulfill the various requirements for efficient relaxation to the ground electronic state. With this in mind and because in the absence of a solvent insertion of NCN into the C-H bonds of *cis*- and *trans*-1,2-dimethylcyclohexane occurs stereospecifically, we studied this reaction employing CH_2Cl_2 , CH_2Br_2 , CH_3CN , and $\text{CH}_3\text{COOC}_2\text{H}_5$ as solvents. The results are compiled in Table I.

It is amply clear from the data in Table I that the insertion reaction can be induced to occur nonstereospecifically by the use of appropriate solvents. The results obtained with the methylene halide solvents (reactions 4-12) are especially interesting. Both CH_2Cl_2 and CH_2Br_2 contain the same number and type of atoms and hence should be equally effective in deacti-

(14) The alternate process, *i.e.*, $N_2CN \xrightarrow{\Delta} ^3N_2 + ^3NCN$, is undoubtedly unfavorable energetically since the $^1N_2 \rightarrow ^3N_2$ energy separation is in all probability much larger than the $^3NCN \rightarrow ^1NCN$ energy gap.

(15) Inversion of the asymmetric center with respect to NHCN can occur either by rotation of the hydrocarbon radical by 180° prior to recombination with the counter radical or by migration of NHCN to a site at which recombination would invert the configuration of the original hydrocarbon.

(16) Heavy atoms are known to enhance the probability of spin-forbidden transitions through coupling of spin and orbital angular momenta. See, for example, C. D. Dijkgraaf and G. J. Hoijtink, "Quantum Chemistry Symposium," *Tetrahedron Suppl.*, 2, 179 (1963); and J. N. Murrell, "The Theory of the Electronic Spectra of Organic Molecules," John Wiley and Sons, Inc., New York, N. Y., 1963, pp 294-300.

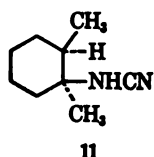
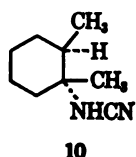
(17) For a striking example of the effect of the number of degrees of freedom available to an inert diluent on the rate of intersystem crossing of methylene, see R. F. Bader and J. I. Generosa, *Can. J. Chem.*, 43, 1631 (1965).

(18) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 29.

Table I. Stereochemistry of the Insertion of Cyanonitrene into the Tertiary C-H bonds of *cis*- and *trans*-1,2-Dimethylcyclohexane as a Function of Solvent

Reaction	Solvent	Concn. ^a %	Hydrocarbon	Temp. ^b °C	% <i>cis</i> - RNHCH (10) ^d	% <i>trans</i> - RNHCN (11) ^d	Over-all yield, ^c %
1	None	100	<i>cis</i>	43.5	>98	<2	44
2	None	100	<i>trans</i>	43.5	<2	>98	46
3	None	100	74% <i>cis</i> 26% <i>trans</i>	43.5	83	17	45
4	CH ₂ Cl ₂	10	<i>cis</i>	41.0	75	25	26
5	CH ₂ Cl ₂	10	<i>trans</i>	41.0	36	64	32
6	CH ₂ Cl ₂	10	74% <i>cis</i> 26% <i>trans</i>	41.0	70	30	27
7	CH ₂ Cl ₂	2	<i>cis</i>	41.0	62	38	34
8	CH ₂ Cl ₂	2	<i>trans</i>	41.0	39	61	23
9	CH ₂ Br ₂	10	<i>cis</i>	43.5	52	48	28
10	CH ₂ Br ₂	10	<i>trans</i>	43.5	52	48	26
11	CH ₂ Br ₂	10	74% <i>cis</i> 26% <i>trans</i>	43.5	54	46	20
12	CH ₂ Br ₂	10	<i>trans</i>	53.0	50	50	24
13	CH ₃ CN	10	<i>cis</i>	53.0	>98	<2	19
14	CH ₃ CN	10	<i>trans</i>	53.0	<2	>98	19
15	CH ₃ COOC ₂ H ₅	10	<i>cis</i>	53.0	53	47	21
16	CH ₃ COOC ₂ H ₅	10	<i>trans</i>	53.0	44	56	23
17	CH ₃ COOC ₂ H ₅	2	<i>cis</i>	53.0	52	48	11
18	CH ₃ COOC ₂ H ₅	2	<i>trans</i>	53.0	50	50	13

^a Volume per cent of hydrocarbon in solvent. ^b Maintained to within ± 0.1 . ^c Yield of a 1:1 mixture of amino- and methylamino-1,2-methylcyclohexanes, based on sodium azide. ^d Compounds 10 and 11 are



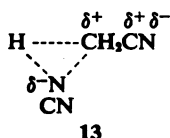
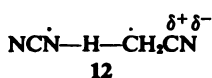
ing NCN by a strictly collisional process. In actual fact, however, the heavier of the two solvents appears to be more efficient in the over-all deactivation of NCN. This is most readily seen from the results of reactions 5, 9, and 10. In CH₂Cl₂ the reaction loses its stereospecificity in part but still exhibits considerable stereochemical bias toward retention of the original configuration,¹⁹ whereas in CH₂Br₂ the reaction is stereochemically random, yielding the same mixture of stereoisomers irrespective of the stereochemical identity of the pure hydrocarbon substrate (reactions 9 and 10) or the hydrocarbon mixture (reaction 11). The greater efficacy of CH₂Br₂ in destroying the stereospecificity of the reaction is indicated even more strikingly from the results of reactions 7 and 8. Here it is seen that in CH₂Cl₂ the insertion is still strongly stereoselective even when the ratio of solvent to hydrocarbon is increased by a factor of 5 over that of reactions 4, 5, 9, and 10. We interpret these results to mean that NCN reacts partly as a triplet in CH₂Cl₂ and exclusively as a triplet in CH₂Br₂, and we conclude that the hydrogen-abstraction-combination process by which in all certainty this species reacts with C-H bonds occurs in a completely nonstereospecific fashion. This is in full agreement with the notion that triplet NCN is produced from decay of singlet NCN since CH₂Br₂, possessing a heavier halogen, is required by theory to be the more effective of the two solvents in bringing about singlet-triplet interconversions. The widely different effectiveness of the two halocarbon solvents in destroying the stereospecificity of the reaction clearly eliminates the possibility that we are witnessing deactivation of an origi-

nally produced stereospecifically inserting singlet, say $^1\Sigma_g^+$, to a lower energy, nonstereospecifically inserting singlet, say $^1\Delta_g$. Deactivation within such a spin-allowed process should be strictly collisional and should be independent of the nature of the halogen in the inert diluent. In this context, it should be noted that the results of reactions 4-12 can be rationalized without invoking a difference in the effectiveness between CH₂Cl₂ and CH₂Br₂ in deactivating NCN. For example, it could be argued that the same relative amounts of singlet and triplet NCN are produced in both solvents but that in CH₂Cl₂, unlike CH₂Br₂, the hydrocarbon fragment has a good memory of its origin, and recombination leads to product in a stereoselective fashion. In view of the similarity of the two halocarbons, we consider such a process to be a very poor alternative to the operation of a "heavy-atom" effect. Alternatively it could be rationalized that the different results in the two halocarbons are due to partial reaction of NCN with solvent. At first glance, this explanation is especially appealing because of the lower yields observed in the halocarbons. However, to explain the results on this basis, one has to assume that CH₂Br₂ scavenges singlet NCN exclusively whereas CH₂Cl₂ reacts with both spin variants of NCN. Again the structural similarity of the two solvents makes this situation very unlikely. In connection with the poorer yields observed when the reaction was carried out in the halocarbons, it should be noted that these do not detract in any way from the significance of the stereochemical results. For example, even on the extreme assumption that the difference in yields between the reactions carried out in CH₂Cl₂ and CH₂Br₂ (20-34%) and those conducted in the absence of a solvent (44-46%) is due exclusively to

(19) The configurational assignment rests on rational assumptions rather than experimental fact (see ref 12).

reaction of singlet NCN with solvent, one can readily estimate a minimum stereochemical crossover of 17% in CH_2Cl_2 and 22% in CH_2Br_2 , as compared to <2% in the neat hydrocarbon.

Acetonitrile presents an interesting case. It is seen from the results of reactions 13 and 14 that this solvent is completely effective in preserving the stereospecificity of the reaction. Two possible explanations come to mind: (1) acetonitrile is totally ineffective in promoting singlet to triplet interconversions, and (2) triplet NCN is produced but is trapped effectively by CH_3CN . The low over-all yields of reactions 13 and 14 point strongly to the latter explanation as the correct one. In fact, it is reasonable to assume that an electron-deficient molecule such as CH_3CN would react preferentially with the less electrophilic triplet NCN. For example, for reaction of NCN with the C-H bonds of acetonitrile, there should be, for obvious reasons, a distinct preference for hydrogen abstraction by triplet NCN over direct insertion by singlet NCN. These two processes are depicted by 12 and 13, respectively. In great con-



trast to acetonitrile, ethyl acetate is almost as ineffective as CH_2Br_2 in preserving stereospecificity, as is seen from the results of reactions 15 to 18. We can conceive of a number of reasons as to why this should be so. (1) Ethyl acetate, containing a greater number of atoms than the other inert diluents studied here, ought to be the most effective in the purely collisional part of the deactivation process. In addition, the carbonyl functionality in all probability introduces some triplet character to the ground state²⁰ of ethyl acetate, a property that should make this solvent effective in promoting intersystem crossing in NCN by the mechanism in Scheme I. (2) Triplet NCN could form from singlet NCN by a process involving spin exchange with the solvent, *i.e.*, $^1\text{NCN} + [\text{CH}_3\text{COOC}_2\text{H}_5] \rightarrow ^3\text{NCN} + [\text{CH}_3\text{COOC}_2\text{H}_5]$. (3) The loss of stereospecificity may be due to reaction of singlet NCN by a hydride-abstraction-recombination process ($\text{RH} + ^1\text{NCN} \rightarrow \text{R}+\text{N}-\text{HCN} \rightarrow \text{RNHCN}$) which ought to be more favorable in ethyl acetate than in the less polar halocarbon solvents. (4) The presence of relatively large amounts of triplet NCN could be a consequence of preferential scavenging of singlet NCN by solvent. Of these four, possibilities 2 and 3 can be eliminated fairly readily. In (2), the occurrence of a spin-transfer process between NCN and solvent requires that the $S_0 \rightarrow T_1$ energy separation in ethyl acetate be smaller than or equal to the $T_0 \rightarrow S_1$ energy gap in NCN. This is not the case; T_1 in ethyl acetate is probably in the vicinity of 130 kcal/mole above the ground state²¹ whereas, as one can readily see from Figure 1, the maximum possible $T_0 \rightarrow S_1$ separation in the NCN system has to be less than 3.72 eV or 87 kcal/mole.²² Pos-

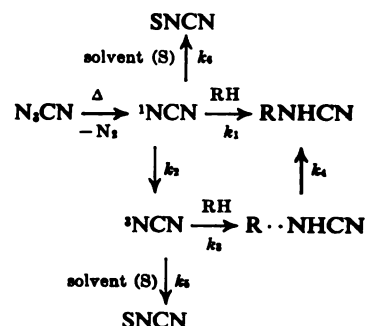
(20) This is a consequence of the small singlet to triplet energy gap which characterizes $n-\pi^*$ states.

(21) This value represents the energy of the first excited $n-\pi^*$ singlet in ethyl acetate (J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley and Sons, Inc., New York, N. Y., 1966, p 429). Experience suggests that the energy of the first excited triplet should be close to this value.

sibility 3 can be reasonably dismissed on the argument that if hydride abstraction occurs in ethyl acetate, it should occur in acetonitrile as well, since both solvents ought to provide equally favorable polar environments. The complete stereospecificity of the reaction in acetonitrile attests to the absence of such a two-step process. The two remaining possibilities (1 and 4) are both attractive, but a distinction between them is not possible on the available information. It is quite possible that ethyl acetate derives its efficacy for destroying the stereospecificity of the reaction from both processes.

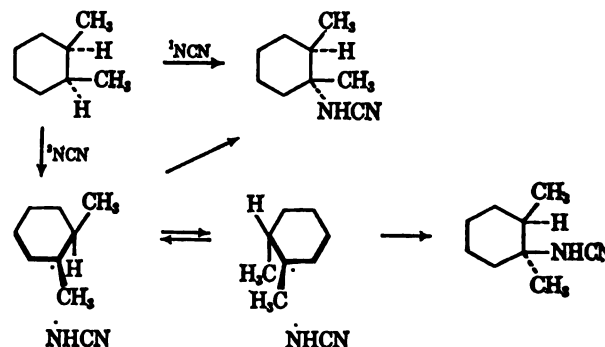
The results collected in Table I are best rationalized by the set of reactions shown in Scheme II. Within

Scheme II



this mechanism, k_1 is much larger than k_2 in the absence of a solvent, comparable to k_2 in CH_2Cl_2 and much smaller than k_2 in CH_2Br_2 and possibly $\text{CH}_2\text{COOC}_2\text{H}_5$. In CH_3CN , k_5 is probably large compared to k_2 , leading to results identical with those obtained in the case where $k_1 \gg k_2$. In $\text{CH}_3\text{COOC}_2\text{H}_5$, a large k_6 may be partly responsible for the similarity of the results to those obtained when $k_2 \gg k_1$. It should be noted that any radical processes involving attack by substrate or solvent radicals on N_2CN can be reasonably dismissed since under these conditions stereoisomerization of the hydrocarbon by way of its radical should set in. In all cases, the recovered hydrocarbon was uncontaminated with its isomer. The stereochemical details of the reaction (employing the *cis* hydrocarbon as reference) are depicted in Scheme III. Here equilibration between the stereoisomeric radicals should be a rapid process compared with over-all recombination.

Scheme III



The ready and efficient environmental control of the electronic multiplicity of NCN described here provides a convenient means for studying reactions of the two spin variants separately. In order to determine the elec-

(22) The assumption here is that the usual energy alternation of singlets and triplets holds for the low-energy states of NCN, *i.e.*, $E(^1\Pi_u) < E(^3\Pi_u)$.

multiplicity of NCN in a certain reaction, one must know the rate of that reaction relative to the rate of insertion into the tertiary C-H bonds of 1,2-dimethylcyclohexane. Reactions that involve a lower energy path than insertion into the tertiary C-H bonds do not occur by way of singlet NCN when conducted in the absence of a solvent. Conversely under the same conditions, NCN could enter reactions that are faster than the reference reactions as either a singlet or triplet. Furthermore, these latter reactions should occur exclusively through triplet NCN when conducted in I_2Br_2 . The complexity of the 1,2-dimethylcyclohexanes poses a serious problem in their use as reference compounds since they produce a large number of isomeric cyanamides, some of which may interfere in the isolation and structural elucidation of the product(s) of interest. Hence, we examined the structurally simpler cyclohexane and cyclopentane, as additional reference materials. The results are shown in Table II. It is clear from the data that the difference in reactivity between the tertiary C-H bonds of the 1,2-dimethylcyclohexanes and the methylene functions of cycloalkanes toward singlet NCN is quite small, indicating that the two cycloalkanes could conceivably be used as reference materials. These results also indicate a small difference between the reactivities of the tertiary C-H bonds of *cis*- and *trans*-1,2-dimethylcyclohexane. One can estimate a factor of 1.7 in favor of the *trans* isomer. Interestingly, the same factor can be determined from the results of reaction 3 and those of 4 and 5 in conjunction with those of 9 and 10) shown in Table I. This small but reproducible difference in reactivity may be due to steric reasons since the tertiary hydrogens of the *trans* compound, being *cis* to the methyl groups, should be less accessible sterically. However, the difference is fairly small and could be the result of a small experimental error as well. Another interesting feature of the results of Table II is that triplet NCN discriminates slightly better (2.1 times) than singlet NCN between tertiary and secondary C-H bonds. This is consistent with the lower energy content of triplet NCN.

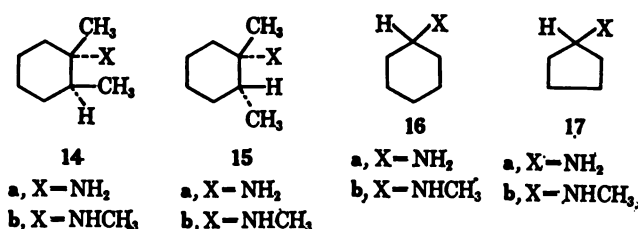
I. Relative Affinity of NCN for the Tertiary C-H Bonds of *cis*- and *trans*-1,2-Dimethylcyclohexane and the C-H Bonds of Cyclopentane and Cyclohexane at $43.5 \pm 0.1^\circ$

Reaction	Solvent	Hydrocarbon ^a	C-H bond	Affinity ^{b,c}
19	None	A	3	4.2
		C	2	1.0
20	None	B	3	2.4
		C	2	1.0
21	None	B	3	3.5
		D	2	1.0
22	CH_2Br_2	B	3	5.0
		C	2	1.0

^a A, *cis*-1,2-dimethylcyclohexane; B, *trans*-1,2-dimethylcyclohexane; C, cyclopentane; and D, cyclohexane. ^b In each reaction, the relative rates of insertion into tertiary and secondary C-H bonds are assigned the arbitrary value of 1.0. ^c Values are corrected for statistical factors.

Product Analysis. The information collected in Tables I and II was obtained as follows. Dilute solutions of N_3CN in the appropriate hydrocarbon(s) and these were thermolyzed at the temperatures indicated. Higher temperatures were necessary to effect thermolysis

at reasonable rates in the more polar solvents CH_3CN and $CH_3COOC_2H_5$ in view of the greater stability of N_3CN in such media. A control experiment in CH_2Br_2 at the higher temperature (reaction 12) indicated that the results are not temperature dependent within the narrow temperature range employed here. The crude mixtures of cyanamides were converted to the corresponding amino and methylamino compounds by treatment with a large excess of lithium aluminum hydride in boiling tetrahydrofuran. The mixtures of amines were analyzed by gas-liquid partition chromatography (glpc), and the amines of interest, 14 to 17, identified by direct comparison of their retention times and mass spectrometric cracking patterns with those of authentic materials.²³ The yields indicated are those of crude 1:1 mixtures of amino and methylamino compounds and are based on the amount of sodium azide employed in the preparation of cyanogen azide. The yields of all reactions conducted in the absence of a solvent were calculated from the weight of the crude amine mixture. The yields of the reactions which were carried out in a solvent were those calculated from the weight of the crude amines multiplied by a factor which was obtained by dividing the total glpc area of the amine mixture from that reaction by the total glpc area of the amine mixture obtained from the same hydrocarbon in the absence of a solvent. This method of calculation rests on the assumption that all volatile components in the product mixture of the reaction conducted in a solvent are amines derived from the hydrocarbon substrate(s). That this is a valid assumption is indicated from the virtual identity of the glpc patterns of mixtures from reactions in different solvents containing comparable amounts of the various stereoisomers. For example, the glpc patterns from reactions 13, 14, 15, and 16 are the same as those from 1, 2, 9, and 10, respectively. Only in one case (reaction 21) did the retention times of two amines of interest coincide. The amines were N-methylcyclohexylamine (16b) and 1-amino-*trans*-1,2-dimethylcyclohexane (15a). The relative amounts of these two components were estimated from the relatively constant ratio in which 15a and 15b are present in the various amine mixtures.



Conclusion

The results reported in this paper indicate that the thermolysis of cyanogen azide in the temperature range of $41-53^\circ$ proceeds with conservation of spin to yield singlet NCN which inserts stereospecifically into tertiary C-H bonds. This species can be readily deactivated through collisions with a suitable inert diluent to triplet NCN which reacts with tertiary C-H bonds by a totally stereorandom hydrogen-abstraction-recombination process. Triplet NCN is slightly more selec-

(23) Authentic amines 14a, 14b, 15a, and 15b were prepared according to K. E. Hamlin and M. Freifelder, *J. Am. Chem. Soc.*, **75**, 369 (1953). See also ref 12.

Table III. Identifying Features of the Amines

Compd	Retention time, min	Molecular ion, m/e	100% Ion, m/e
14a	33.0	127	70
b	24.8	141	84
15a	21.2	127	70
b	13.5	141	84
16a	30.6	99	56
b	21.3	113	70
17a	16.0	85	56
b	12.4	99	70

were better than 99.7% pure by glpc and were used without further purification. Of the solvents, ethyl acetate was "Fisher Reagent Grade," and acetonitrile (anhydrous) and dichloromethane were Eastman (White Label) and were used without further purification. Methylene bromide was purified by careful distillation immediately before use (better than 99.5% pure).

General Procedure of the Reaction. In the absence of a solvent, the reaction was carried out in the manner described in the preceding paper.¹² When a solvent was employed, the general procedure was as follows. Cyanogen azide was prepared in the usual manner¹³ from sodium azide (2 g) and cyanogen chloride (ca. 50 ml). The appropriate solvent (ca. 100 ml) was added and the excess cyanogen chloride removed at 200–300 mm, through the condenser maintained at 5–10°, until the temperature of the sus-

Table IV. Quantitative Data of Reactions of the 1,2-Dimethylcyclohexanes with NCN in Various Solvents

Reaction ^a	Sodium azide, g	Cyanamide mixture, g	Amine mixture, g	Compn of amine mixtures, ^b %				Total glpc area, %	Over-all yield, %
				14a	14b	15a	15b		
1	2	2.6	1.8	20.0	30.5	...	~0.5	100	44
2	2	2.5	1.9	10.7	25.0	100	46
3	2	2.3	2.0	23.8	28.5	3.5	7.0	90	45
4	2	2.6	1.2	13.0	20.4	3.8	8.4	90	26
5	2	2.2	1.4	5.7	8.4	7.3	18.6	93	32
6	2	2.2	1.5	11.0	20.3	2.8	10.7	73	27
7	2	2.4	1.6	10.5	19.2	6.3	12.5	87	34
8	2	2.6	1.4	6.1	13.6	11.6	19.2	69	23
9	2	2.6	1.6	10.6	22.7	7.6	23.0	73	28
10	2	2.6	1.3	12.3	21.8	8.7	22.9	84	26
11	2	3.0	1.4	18.0	20.1	13.5	18.3	59	20
12	2	3.1	1.6	10.2	20.4	8.3	22.3	63	24
13	2	2.5	1.0	13.1	32.0	...	~0.5	77	19
14	2	2.1	1.0	8.9	24.6	78	19
15	2	2.5	1.4	9.7	18.1	9.0	14.7	61	21
16	2	2.6	1.3	7.9	12.9	9.0	18.5	72	23
17	2	1.5	0.8	13.0	20.6	11.5	19.1	55	11
18	2	1.3	0.6	7.8	15.7	7.8	16.4	90	13

^a As per Table I. ^b By weight.

Table V. Quantitative Data of Reactions of NCN with the 1,2-Dimethylcyclohexanes, Cyclopentane, and Cyclohexane

Reaction ^a	Solvent	Hydrocarbon ^{b,c}	Amine mixture, g	Compn ^d of amine mixtures, %								Total glpc area, %	Over-all yield, %
				14a	14b	15a	15b	16a	16b	17a	17b		
19	None	A = 46.4 C = 53.6	1.4	13.2	17.1	6.8	22.7	96	38
20	None	B = 37.0 C = 63.0	1.3	4.9	13.8	11.0	35.9	100	37
21	None	B = 39.6 D = 60.4	1.9	5.0	12.9	15.6	37.0	99	43
22	CH ₂ Br ₂	B = 46.0 C = 54.0	1.5	9.5	11.6	6.1	14.8	8.4	26.7	79	27

^a As per Table II. ^b A, *cis*-1,2-dimethylcyclohexane; B, *trans*-1,2-dimethylcyclohexane; C, cyclopentane; D, cyclohexane. ^c Mole per cent. ^d By weight. ^e Calculated on the assumption that the mixture consists of an equal amount of the components shown in columns 5–12.

tive in its reaction between tertiary and secondary C–H bonds than is singlet NCN, as is expected from its lower energy content. Overlap considerations suggest that, in the absence of perturbation in the transition state, the ¹Σ_g⁺ state is more likely to react stereospecifically with C–H and C=C bonds than is the ¹Δ_g state.

Experimental Section²⁴

Materials. Of the hydrocarbons employed, the 1,2-dimethylcyclohexane and cyclopentane were "Phillips Research Grade," and the cyclohexane was "Eastman Spectrograde." They all

(24) Infrared spectra were obtained with a Perkin-Elmer 21 spectrometer, and mass spectra were determined with a Bendix time-of-flight mass spectrometer. The glpc results were obtained under the following conditions: A, 2 × 2 m × 0.25 in., stainless steel column packed with

pension was 20–25°. The amount of time required for this operation varies with the solvent; polar media such as acetonitrile and ethyl acetate require longer periods. The suspension was filtered under nitrogen pressure and the filtrate made up to a total of 300 ml with solvent. To this was added the appropriate hydrocarbon or hydrocarbon mixture²⁵ (30 ml) and the well-mixed solution transferred into a one-necked, 500-ml flask fitted with a condenser and connected (through the top of the condenser) to a wet test meter by way of a trap maintained at Dry Ice-acetone temperatures.

20% tetrakis(hydroxyethyl)ethylenediamine (THEED) on 60–80 mesh Chromosorb W (not acid washed) at 101° with the vaporizer at 165°; helium was used as the carrier gas at a flow rate of 74 cc/min; B, 2 m × 0.25 in., copper column packed with 20% 1,2,3-tris(2-cyanoethoxy)propane (TCEGE) on 60–80 mesh Gas Chromosorb R at 52° with the vaporizer at 120°; helium was used as the carrier gas at a flow rate of 67 cc/min.

(25) The composition of this mixture was determined by glpc under conditions B.

The flask was immersed in a constant-temperature water bath and maintained to within 0.1° of the required temperature overnight, after which period the theoretical amount of nitrogen had evolved. The mixture was then filtered free of any traces of precipitate that might be present and a glpc sample (ca. 1 ml) taken from the filtrate and analyzed for type of hydrocarbon present, under conditions B. The remainder of the filtrate was then concentrated first under water-aspirator pressure at ca. $30-40^\circ$ and then at 3–5 mm and room temperature to yield a light orange viscous oil (ca. 2 g), which exhibited strong characteristic -NHCN infrared absorption at 3200 (N-H) and 2200 cm^{-1} ($\text{C}\equiv\text{N}$). The cyanamide mixture was then converted to an amine mixture by treatment with a great excess of lithium aluminum hydride in boiling tetrahydrofuran as described in the preceding paper.¹³ The mixture of amines was analyzed by gas-liquid partition chromatography

under conditions A, and the amines of interest were identified by direct comparison of their glpc retention times and mass spectrometric cracking patterns with those of authentic samples. The relevant data employed in the identification are shown in Table III. The quantitative results are compiled in Tables IV and V. The yields tabulated were calculated from the weights of the crude amine mixtures in conjunction with the total glpc area observed in each case. For example, the yield of reaction 7 based on weight of amine mixture (assuming a 1:1 mixture of amino and methyl-amino compounds) is 39% which, after correction for total amount of volatile material, becomes $39 \times 87/100 = 34\%$. The various reaction numbers correspond to those shown in Tables I and II.

Acknowledgment. The author is indebted to Miss Patricia Canfield for the glpc determinations.

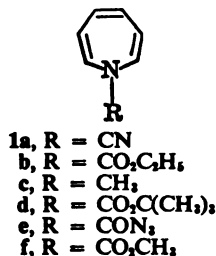
The Preparation and Properties of 13,14-Diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene and Its Derivatives

Alexander L. Johnson and Howard E. Simmons

Contribution No. 1287 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898. Received February 10, 1967

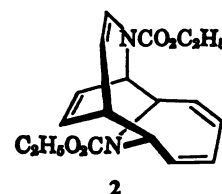
Abstract: The thermodynamically more stable dimers of 1-cyano-, 1-ethoxycarbonyl-, 1-*t*-butoxycarbonyl-, and 1-methylazepine are all representatives of the new 13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene ring system. These compounds are formed from kinetically produced isomers which rearrange on further thermal treatment to the doubly bridged piperazine system. The chemistry of this system and the fully reduced 13,14-diazatricyclo[6.4.1.1^{2,7}]tetradecane system is discussed in detail.

Recently, brief descriptions have appeared¹ of the dimers of 1-cyanoazepine (1a),^{1a,b} 1-ethoxycarbonylazepine (1b),^{1c} and 1-methylazepine (1c).^{1d} Our more recent observation of the dimerization of 1-*t*-butoxycarbonylazepine (1d) suggests that this is a general property of the azepine nucleus. This paper is

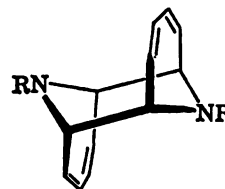


concerned with the thermally more stable dimers which belong to the new 13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene ring system (3).

At relatively low temperatures, the parent azepines dimerize readily to kinetically controlled products which lack an element of symmetry. In particular, 1a dimerizes at $25-60^\circ$ to a white crystalline product, mp $220-221^\circ$ dec,^{1a,b} 1b dimerizes at 130° to a white solid, mp 78° ,^{1c} and 1c forms a colorless solid, mp 66° .^{1d} The structure of the dimer of 1a is different from that postulated for the dimers of 1b (2)^{1c} and 1c² and it will



be discussed elsewhere.² At higher temperatures, thermally more stable isomers are obtained which are 13,14-disubstituted 13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraenes (3). Specifically, the dimer



- | | |
|--|--|
| 3a, R = CN | l, R = CH_2CO |
| b, R = $\text{CO}_2\text{C}_2\text{H}_5$ | m, R = <i>cis</i> - $\text{COCH=CHCO}_2\text{H}$ |
| c, R = CH_3 | n, R = $\text{C}_6\text{H}_5\text{CO}$ |
| d, R = $\text{CO}_2\text{C}(\text{CH}_3)_3$ | o, R = <i>p</i> - $\text{BrC}_6\text{H}_4\text{CO}$ |
| e, R = CONH_2 | p, R = $\text{C}_6\text{H}_5\text{NHCO}$ |
| f, R = H | q, R = $\text{C}_6\text{H}_5\text{NHCS}$ |
| g, R = NO | r, R = $\text{CO}_2\text{C}_6\text{H}_5$ |
| h, R = C_6H_5 | s, R = COCH_2Cl |
| i, R = $\text{CH}_2\text{CH=CH}_2$ | t, R = $\text{COCH}_2\text{N}(\text{C}_2\text{H}_5)_2$ |
| j, R = $\text{CH}_2\text{CH}_2\text{CH=CH}_2$ | u, R = $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$ |
| k, R = <i>trans</i> - $\text{CH}_2\text{CH=CHC}_6\text{H}_5$ | |

(1) (a) F. D. Marsh and H. E. Simmons, *J. Am. Chem. Soc.*, **87**, 3529 (1965); (b) A. L. Johnson and H. E. Simmons, *ibid.*, **88**, 2591 (1966); (c) L. A. Paquette and J. H. Barrett, *ibid.*, **88**, 2590 (1966); (d) K. Hafner and J. Mondt, *Angew. Chem.*, **78**, 822 (1966).

(2) K. Hafner, private communication.

(3) F. D. Marsh, A. L. Johnson, and H. E. Simmons, in preparation.

of 1a is converted smoothly to 3a at 210°,^{1b} either 1b or 2 is converted to 3b at 200°,^{1c} 1c to 3c above 0°,^{1d} and 1d to 3d at 156°. The presence of dimeric products in the solid fraction of the reaction product from which 1-azidocarbonylazepine (1e) was obtained⁴ also seems likely. The generality of the formation of ring system 3 is clearly demonstrated by its preparation from four different azepines.

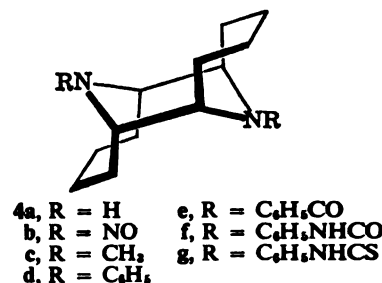
The stability of system 3 is illustrated by the high melting points of its derivatives and by its resistance to strong mineral acid. Hydrolysis of 13,14-dicyano-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3a) with 50% sulfuric acid at 100–120° proceeds in two stages through the biscarbamoyl derivative 3e to the parent diamine 3f. The latter is produced immediately when the bis-*t*-butoxycarbonyl derivative 3d is treated with hydrogen bromide in glacial acetic acid.⁸ The common difunctional derivatives 3g–u of 13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3f) were prepared by conventional methods, and their analytical and spectral properties clearly indicate their relationship to 3f.

The concerted formation of the (6 + 6) addition products 3a–d from the monocycles 1a–d is a thermally forbidden process according to the Woodward–Hoffmann rules.⁶ The proposed (2 + 6) addition of tetracyanoethylene to 1-ethoxycarbonylazepine, 1b,⁷ has since been shown to be the normal thermally allowed (2 + 4) Diels–Alder addition.⁸ The same results were obtained for a series of substituted 1-methoxycarbonylazepines, 1f, with tetracyanoethylene.⁹ It therefore seems reasonable that the thermal formation of structures 3 from 1 must involve an allowed intermediate (2 + 4) *endo* Diels–Alder product or a (4 + 6) *exo* product (e.g., 2)^{1c} which rearranges to the symmetrical isomer at higher temperatures. In our case (1a → 3a) the symmetrical compound arises solely by rearrangement of the dimer of 1a.

The proof of structure 3a is based upon these observations. (1) Zinc dust distillation of 3a at 350° produces aniline in low yield as the only volatile product.

(2) The parent diamine 3f readily absorbs 4 molar equiv of hydrogen on hydrogenation in dilute hydrochloric acid over platinum oxide. The relationship of the octahydro derivative, 13,14-diazatricyclo[6.4.1.1^{2,7}]tetradecane (4a), to 3f and to the simple difunctional derivatives (4b–g) is apparent from their analytical and spectral properties.

(3) In contrast to their precursor, the dimer of 1a, compounds 3 show only weak carbon–carbon double bond absorption in the 1600-cm⁻¹ region of the infrared spectrum. This fact, coupled with polarization studies¹⁰ on the intense Raman band at 1615 cm⁻¹



observed in compounds 3c and f (CHCl₃ solution), can be accounted for by the symmetrical diene vibration of the proposed centrosymmetric C_{2h} structure.

(4) The constancy of position and intensity of the ultraviolet maxima of compounds 3 in the 230–240-mμ region (ε 9500–21,000) (Table I) is consistent with the presence of two independent cisoid diene chromophores¹¹ rather than azepine, enamine, or enamide functions.¹² This absorption remains constant even in the dihydrochloride of 3f and the monomethiodide of 3c, indicating that the nitrogen atoms are isolated from the diene chromophores.^{12b,e,i} In most cases, two maxima separated by 5–8 mμ and of approximately the same intensity can be resolved (Table I). In two examples (3g, 3k) the extra chromophores are attributed to independent absorption by the nitrogen substituent. As expected, the saturated compounds 4 do not show diene absorption in the ultraviolet.

(5) The simple nmr spectra of these compounds enable the protons to be assigned readily. In compounds 3 the eight-proton vinyl signal usually appears as a broad singlet in the τ 3.5–4.0 region, while the four tertiary bridgehead protons adjacent to nitrogen are observed in the τ 5.2–5.8 region. In compounds 4 the vinyl proton signals of 3 are replaced by a broad 16-proton methylene multiplet near τ 8.3, and the bridgehead protons are now shifted upfield by 1.0–1.5 ppm. These generalizations are illustrated for the parent compounds 3f and 4a in Figures 1 and 2. The rigidity of system 3 provides an ideal case in which to study the effects of nitrogen substituents on nearby proton signals.¹³ The four equatorial bridgehead

(11) Cf.: (a) 1,3-cycloheptadiene, λ_{max} 248 mμ (ε 7500), E. Pesch and S. L. Friess, *J. Am. Chem. Soc.*, **72**, 5756 (1950); (b) 9-cyano-9-azabicyclo[4.2.1]nona-2,4,7-triene, λ_{max}^{CH₃CN} 255 mμ (ε 4500), A. G. Anastassiou, *ibid.*, **87**, 5512 (1965).

(12) These data are rather scattered in the literature; some typical values of λ_{max} (ε) are: (a) enamines C=CNR₂, 223–238 mμ (5100–9600), N. J. Leonard and D. M. Locke, *ibid.*, **77**, 437 (1955); (b) dienamines C=C–C=CNR₂, 250–305 mμ (7050–34,200), L. A. Paquette, *ibid.*, **86**, 4092 (1964); L. A. Paquette, *Tetrahedron Letters*, 2027 (1963); G. Opitz and W. Merz, *Ann.*, **652**, 139 (1962); (c) bisenamines C=C–NH–C=C, 226–233.5 mμ (16,350–17,200), 315–350 mμ (7650–15,500), M. Anderson and A. W. Johnson, *J. Chem. Soc., Org.*, 1075 (1966); (d) enamides C=CNHCOR, 240 mμ (6600), G. Rosencranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956); (e) dienamides C=C–C=CNHCOR', 252–255 mμ (4900–6300), L. A. Paquette, *J. Am. Chem. Soc.*, **84**, 4987 (1962); L. A. Paquette, *ibid.*, **85**, 3288 (1963); L. A. Paquette, *ibid.*, **86**, 500 (1964); E. Vogel and R. Erb, *Angew. Chem.*, **74**, 76 (1962); L. A. Paquette and J. K. Reed, *J. Med. Chem.*, **6**, 771 (1963); (f) α,β-unsaturated urethans C=CNRCOR', 229–255 mμ (4200–9000);^{10,8,9} (g) N-cyanoenamides C=CNCN, 249–251 mμ (2800–4900), A. G. Anastassiou, *J. Org. Chem.*, **31**, 1131 (1966); (h) α,β-unsaturated amides C=CCONR₂, 218 mμ (11,800), R. H. Marx, *ibid.*, **26**, 1289 (1961); (i) azepines, 293–332 mμ (338–1440), 202–219.5 mμ (9750–36,300),¹⁰ K. Hafner and C. König, *Angew. Chem.*, **75**, 89 (1963); K. Hafner, D. Zinser, and K.-L. Moritz, *Tetrahedron Letters*, 1733 (1964); W. Lwowski, T. J. Maricich, and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **85**, 1200 (1963); W. Lwowski and T. J. Maricich, *ibid.*, **87**, 3630 (1965); R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964).

(13) E.g., cf. the cases of (a) the more flexible 2,3,5,6-tetramethylpiperazines, R. K. Harris and N. Sheppard, *J. Chem. Soc., Phys. Org.*

(4) L. E. Chapman and R. F. Robbins, *Chem. Ind. (London)*, 1266 (1966).

(5) This hydrolysis procedure is described by G. W. Anderson and A. C. McGregor, *J. Am. Chem. Soc.*, **79**, 6180 (1957).

(6) (a) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965); (b) R. Hoffmann and R. B. Woodward, *ibid.*, **87**, 2046 (1965); (c) R. Hoffmann and R. B. Woodward, *ibid.*, **87**, 4388 (1965); (d) H. C. Longuet-Higgins and E. W. Abrahamson, *ibid.*, **87**, 2045 (1965).

(7) K. Hafner, *Angew. Chem. Intern. Ed. Engl.*, **3**, 165 (1964).

(8) (a) J. H. van den Hende and A. S. Kende, *Chem. Commun.*, 384 (1965); (b) A. S. Kende, P. T. Izzo, and J. E. Lancaster, *J. Am. Chem. Soc.*, **87**, 5044 (1965).

(9) (a) J. E. Baldwin and R. A. Smith, *ibid.*, **87**, 4819 (1965); (b) I. C. Paul, J. E. Baldwin, and R. A. Smith, *ibid.*, **88**, 3653 (1966).

(10) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., Inc., Princeton, N. J., 1945, p 360.

Table I. Ultraviolet Maxima of 13,14-Diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraenes (3)^a

Compd	R	Solvent	λ_{\max} m μ (ϵ_{\max})
3a	CN	CH ₃ CN	237 (16,300), 230 (15,150)
b	CO ₂ C ₆ H ₅	CH ₃ CN	237 (14,200), 232 (13,750)
c	CH ₃	CH ₃ OH	237 (14,100), 230 (13,900)
d	CO ₂ C(CH ₃) ₃	C ₆ H ₅ OH	238 (14,350), 233 (13,700)
e	CONH ₂	50% H ₂ SO ₄	234 (9,450)
f	H	CH ₃ CN	240 (15,800), 234 (16,400)
f·2HCl	H ₃ ⁺ Cl ⁻	H ₂ O	235 (16,400) 230 (16,600)
g	NO	CH ₃ CN	375 (132), 365 (142)
			235 (19,000)
10	N ₆ CH ₃ , N ₆ (CH ₃) ₃ ⁺ I ⁻	CH ₃ OH	240 (17,500), 232 (21,100)
			224 (22,400)
3h	C ₆ H ₅	CH ₃ OH	239 (14,300), 232 (14,100)
i	CH ₂ CH=CH ₂	CH ₃ OH	238 (13,800), 232 (13,700)
j	CH ₂ CH ₂ CH=CH ₂	CH ₃ OH	240 (15,700), 232 (14,700)
k	<i>trans</i> -CH ₂ CH=CHC ₆ H ₅	CH ₃ CN	292 (3,500), 282 (sh 5,350)
			250 (22,100)
l	CH ₃ CO	CH ₃ OH	238 (14,500), 230 (14,100)
m	<i>cis</i> -COCH=CHCO ₂ H	C ₆ H ₅ OH	234 (19,400)
s	COCH ₂ Cl	CH ₃ CN	231.5 (16,200)
t	COCH ₂ N(C ₆ H ₅) ₂	CH ₃ OH	234.5 (14,350)
u	CH ₂ CO ₂ C ₆ H ₅	C ₆ H ₅ OH	239 (14,300), 232 (14,400)

^a Determined in 1-cm solution cells on a Cary Model 14 spectrophotometer.**Table II.** Proton Nmr Data on 13,14-Diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraenes (3)^a

Compd	Substituent	Solvent	Proton assignments		
			Vinyl	Tertiary bridgehead	Other
3f	H	CDCl ₃	361	214	NH 101
f·2HCl	H ₃ ⁺ Cl ⁻	D ₂ O	398–361 ^b	240	HOD 246
g	NO	(CD ₃) ₂ SO	349	342	
e	CONH ₂	4FK·D ₂ O ^c	362	280	HOD 280
a	CN	4FK·D ₂ O ^c	375	255, 249	HOD 295
c	CH ₃	CDCl ₃	371–334 (m)	201, 196	CH ₃ 133
c·2HCl	CH ₃ ·HCl	D ₂ O	400–350 ^b	285, 280	HOD 285, NCH ₂ 175
h	C ₆ H ₅	CDCl ₃	353	206, 202	CH ₂ 142 (q, <i>J</i> = 7 cps)
					CH ₂ 54 (t, <i>J</i> = 7 cps)
i	CH ₂ CH=CH ₂	CDCl ₃	370–292 ^d	205, 200	NCH ₂ 177 (d, <i>J</i> = 5 cps)
j	CH ₂ CH ₂ CH=CH ₂	CDCl ₃	370–285 ^d	204, 200	NCH ₂ CH ₂ 153–120 (m)
k	<i>trans</i> -CH ₂ CH=CHC ₆ H ₅	CDCl ₃	385–334 ^d	208, 203	C ₆ H ₅ 434, NCH ₂ 187 (d, <i>J</i> = 6 cps)
u	CH ₂ CO ₂ C ₆ H ₅	CDCl ₃	358	215, 210	OCH ₂ 246 (q, <i>J</i> = 7 cps)
					CH ₂ 71 (t, <i>J</i> = 7 cps)
b	CO ₂ C ₆ H ₅	CDCl ₃	353	296, 287	OCH ₂ 246 (q, <i>J</i> = 7 cps)
					CH ₂ 71 (t, <i>J</i> = 7 cps)
d	CO ₂ C(CH ₃) ₃	CDCl ₃	353	294, 284	C(CH ₃) ₃ 83
r	CO ₂ C ₁₀ H ₁₅ ^e	CDCl ₃	352	291, 283	C ₁₀ H ₁₅ 123–96 (m)
m	<i>cis</i> -COCH=CHCO ₂ H	(CD ₃) ₂ SO	350	311, 271	CH=CH 387, 356 (2 doublets, <i>J</i> = 12 cps)
l	CH ₃ CO	CF ₃ CO ₂ H ^c	339	313, 270	CH ₃ 118
n	C ₆ H ₅ CO	CF ₃ CO ₂ H ^c	342	314, 250	C ₆ H ₅ 418
o	<i>p</i> -BrC ₆ H ₄ CO	4FK·D ₂ O ^c	357	330, 269	<i>p</i> -BrC ₆ H ₄ CO 459, 430
					(2 doublets, <i>J</i> = 8 cps)
s	COCH ₂ Cl	CF ₃ CO ₂ H ^c	334	303, 264	COCH ₂ Cl 225
t	COCH ₂ N(C ₆ H ₅) ₂	CDCl ₃	354	322	NCOCH ₂ 191 (d, <i>J</i> = 3 cps)
					NCH ₂ 149 (q, <i>J</i> = 7 cps)
					CH ₂ 59 (t, <i>J</i> = 7 cps)
10	N ₆ CH ₃ , N ₆ (CH ₃) ₃ ⁺ I ⁻	(CD ₃) ₂ SO	378–355 ^b	277, 272/ 225 ^f	Axial NCH ₂ 201
					Equatorial NCH ₂ 191
					Tertiary NCH ₂ 127

^a Recorded at 60 Mc/sec on a Varian Associates A-60 spectrometer. Signals are recorded in cycles per second downfield from internal tetramethylsilane as singlets unless otherwise noted: d, doublet; t, triplet; q, quartet; m, multiplet. ^b Charged nitrogen produces a complex multiplet for the diene proton signals. ^c External tetramethylsilane calibration 4FK = CF₃ClCOCF₃Cl. ^d Diene protons appear as a broad singlet superimposed upon the —CH=CH₂ system multiplet. ^e C₁₀H₁₅ = 1-adamantyl. ^f Two distinct sets of bridgehead protons are seen because of the chemical nonequivalence of the two nitrogen atoms.

protons are quite sensitive to substituents on nitrogen and show the expected dependence of chemical shift upon substituent electronegativity. With simple linear

200 (1966); (b) the rigid boat-ring piperazines in the 2,5-diazabicyclo-[2.2.1]heptane system, P. S. Portoghese and A. A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966).

substituents (e.g., H, NO) a single, broad, unresolved signal is observed. With a cyano or alkyl substituent the bridgehead proton signal is a doublet (*J* = 4–6 cps). The origin of this splitting is the adjacent vinyl proton since the more intense member of the doublet lies on the downfield side and in some cases the vinyl region

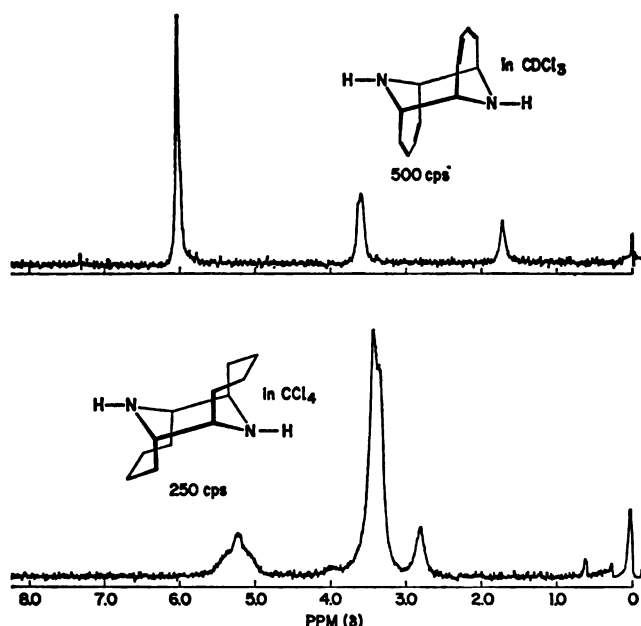
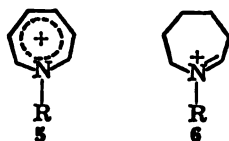


Figure 1 (top). Proton spectrum (60 Mc/sec) of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3f) (500-cps sweep width).

Figure 2 (bottom). Proton spectrum (60 Mc/sec) of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane (4a) (250-cps sweep width).

becomes resolved into a complex multiplet. Alkoxy-carbonyl and acyl substituents cause the bridgehead protons to exhibit two broad signals equal in area and separated by 8–60 cps. This is clearly a case of amide isomerism in which two of the bridgehead protons have a different chemical shift from the other two.¹⁴ Collapse of these two signals to a single broad signal was observed at temperatures of 60–100° in the case of the alkoxy-carbonyl derivatives 3b and 3d, but not in the acyl derivative 3m. Protonation or quaternization of one or both nitrogen atoms of system 3 resolves the usual broad vinyl signal into a complex multiplet. Obviously, the proximity of a further substituent increases the nonequivalence of the central and terminal protons of the diene system. These observations are summarized in Table II.

(6) The mass spectra of the unsaturated compounds 3 confirm the expected molecular weights and consistently exhibit half-parent ions as the base peak unless the nitrogen substituent is more readily fragmented. The lower mass values fall into a pattern characteristic of the azepine. Clearly, structure 3 undergoes ready fragmentation into azepinium ions¹⁵ C₆H₈NR⁺ (5).



The mass spectra of compounds 4 also confirm their molecular weights and usually exhibit base peaks corresponding to protonated half-parent ions C₆H₁₁NR⁺

(14) In the case of the ethoxycarbonyl derivative 3b, Paquette¹⁶ has incorrectly described the bridgehead signals as a doublet ($J = 8.5$ cps). At 100 Mc/sec, the separation of the bridgehead signals increases to 16.5 cps in 3b, and to 17.0 cps in 3d, but is unaffected in 3c.

(15) Cf. F. W. McLafferty, "Mass Spectrometry of Organic Ions," Academic Press Inc., New York, N. Y., 1963, p 506.

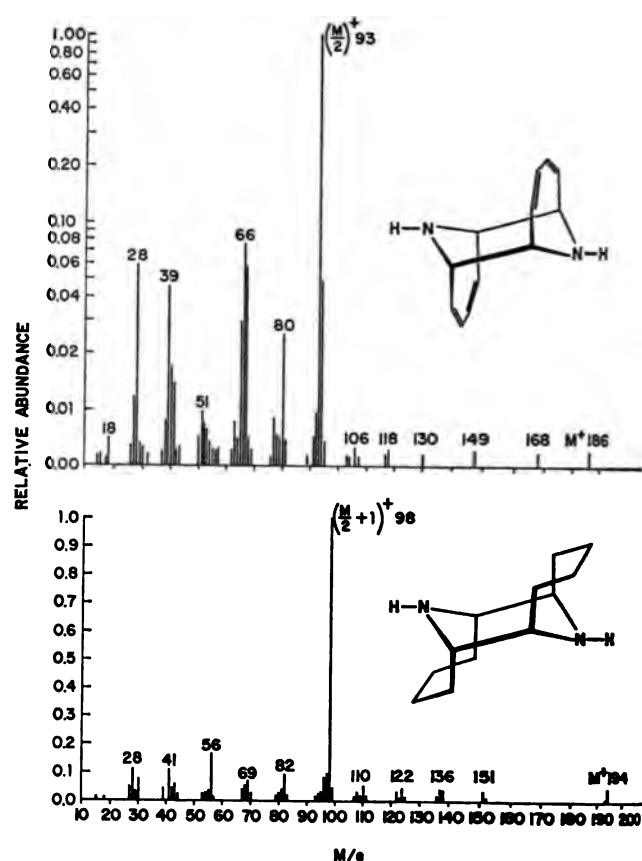
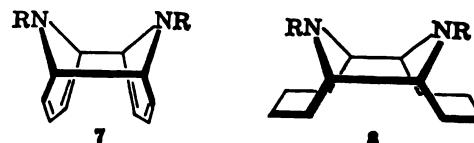


Figure 3 (top). Mass spectrum of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3f).

Figure 4 (bottom). Mass spectrum of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane (4a).

(6). Their features are illustrated in Figures 3 and 4 for the parent compounds 3f and 4a.

(7) Examination of Dreiding models of 3f and 4a indicates that they are very rigid structures. The *trans* arrangement of the two four-carbon bridges is almost certainly favored over the *cis* arrangements 7 and 8 from the viewpoint of nonbonded interactions and the



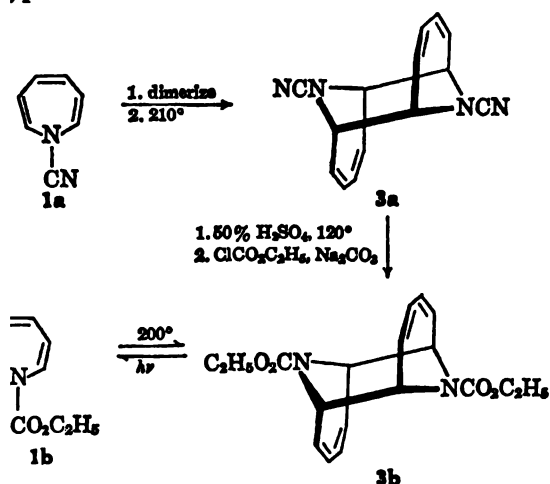
unusual thermal stability of the compounds in the two series. The low dipole moment (0.57 D. in carbon tetrachloride) of 3c lends support to this structural assignment. "Angstrom ruler" calculations of the nonbonded H–H repulsion energies¹⁶ place structure 8 (R = H) 63 kcal/mole above structure 4a in energy. Similar arguments have been advanced for the structure and stereochemistry of the parent carbocyclic system, tricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene-13,14-dione.¹⁷

(8) The conversion of 1-cyanoazepine (1a) to 1-ethoxycarbonylazepine (1b) was observed according to Scheme I. Paquette's compound 3b^{1c} was prepared independently by the reaction of ethyl chloroformate with the parent diamine 3f. Direct photolysis of 3b

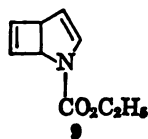
(16) H. E. Simmons and J. K. Williams, *J. Am. Chem. Soc.*, **86**, 3222 (1964).

(17) T. Mukai, T. Tezuka, and Y. Akasaki, *ibid.*, **88**, 5025 (1966).

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monitrile solution using a 2537-A source gave the mer 1b, isolated in 12% yield by distillation. Generality of the photodecomposition of structure 3 examined for a number of derivatives. Under same conditions, the bis-*t*-butoxycarbonyl derivative 3b reverted to the monomer 1b in 13% yield. In cases (3a, c, f, n, and r) recognizable products were obtained. The vibrations induced in the diene nophore on irradiation must be sufficient to break relatively weak central bonds linking the monounits (*cf.* the mass spectrometry observations). Azepine can only be isolated if it is reasonably stable to further degradation. The amount of time required to cause the further cyclization of 1b to 9 observed by Paquette¹⁸ provides further evidence of the lability of this particular azepine. Under our irradiation conditions detectable amounts of bicyclic products like 9 were not observed as products from



Structure 3.

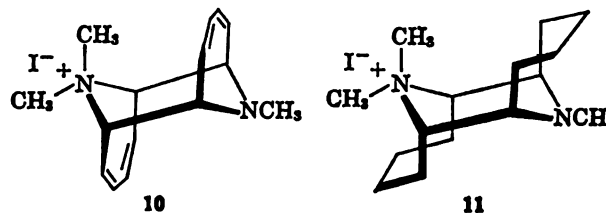
Further consequence of the geometry of ring systems 1 and 4 is seen in the formation of metallic complexes.

Both parent diamines 3f and 4a have their six-membered piperazine ring frozen into the chair conformation, bonding of both nitrogen atoms to the same cobalt atom is impossible. The cobalt(II) halides only form 1:1 complexes $C_{12}H_{14}N_2CoX_2$ ($X = Cl, Br$) with 3f in ethanol solution. With larger anions cobalt(II) forms complexes such as $[C_{12}H_{14}N_2]_2Co(SCN)_4$ and $[C_{12}H_{14}N_2]_2Co(ClO_4)_2 \cdot 4H_2O$ are produced. Analytical, spectroscopic, and magnetic evidence suggests that the halides thiocyanate contain tetrahedral cobalt(II).¹⁹ Attempts to produce cobalt(II) complexes of the more rigid compound 4a were unsuccessful. Reaction of cobalt(II) chloride hexahydrate with 4a produced the monohydrochloride of 4a.

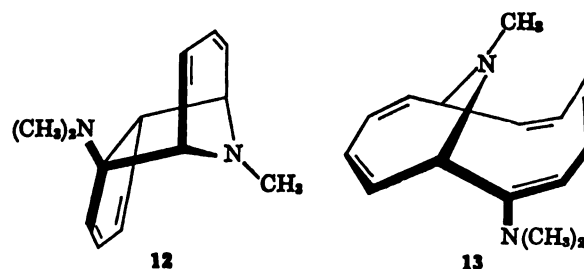
L. A. Paquette and J. H. Barrett, *J. Am. Chem. Soc.*, **88**, 1718

(a) A. F. Wells, "Structural Inorganic Chemistry," 3rd ed, Oxford University Press, London, 1962, p 913; (b) D. H. Busch in "Coordination Chemistry, Metallurgy and Uses," R. S. Young, Ed., Reinhold Publishing Corp., New York, N. Y., 1960, p 120, and references cited therein; (c) F. A. Cotton, D. M. L. Goodgame, and M. Goodgame, *J. Chem. Soc.*, **83**, 4690 (1961); (d) M. Goodgame, *J. Chem. Soc.*, **63** (1966); (e) A. B. P. Lever and S. M. Nelson, *ibid.*, 859 (1966).

Quaternization of the dimethyl derivatives 3c and 4c in both systems proceeds under moderately vigorous conditions to form the monomethiodides 10 and 11.^{1b,d} The formation of only monoquaternary derivatives is



not unusual and has been observed with other bridged piperazines.²⁰ The Hofmann elimination on 10 proceeds in up to 92% yield and produces an unstable solid diamine, $C_{12}H_{20}N_2$, whose properties appear to be consistent with a product of further cyclization, such as 12, rather than the cyclododecapentaene derivative 13 postulated by Hafner.^{1d} The stable crystalline bis-methiodide of this product eliminates trimethylamine on further Hofmann reaction, indicating that a dimethylamino group is produced in the first elimination. The other products of this second Hofmann reaction are produced in low yield and have not yet been characterized.



Experimental Section²¹

13,14-Dicyano-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3a). Crude 1-cyanoazepine dimer was purified by dissolving 200-g lots in boiling dichloromethane, filtering, and passing the filtrate down a 4-in. layer of Florisil packed into a chromatography column 3 ft in length and 4 in. in diameter. Each batch required a total of 10 l. of dichloromethane to elute the purified material, which was isolated by evaporation. A 5-l., four-necked Morton flask equipped with mechanical stirrer, thermometer, two hot water reflux condensers, and a heating mantle was charged with practical grade naphthalene (1000 g) and flushed with nitrogen. After the naphthalene had melted, the stirrer was started, and at a liquid temperature of 140°, powdered 1-cyanoazepine dimer (200 g) was added rapidly down one condenser. The dimer dissolved in the hot naphthalene, and when the temperature of the mixture reached 190°, a mildly exothermic reaction began in which the product precipitated and the temperature rose spontaneously to 210° where it was maintained for 30 min. After the mixture had cooled to 100°, it was diluted with 2500 ml of benzene and filtered. The brown finely crystalline residue of 13,14-dicyano-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene was washed with a further 1250 ml of benzene and air dried. The yield of almost pure product was 137.0–145.6 g (69–73%). Analytically pure material was obtained by continuous chromatography using an extractor 3 ft in height and 4 in. in diameter with dichloromethane as the eluent. The column was packed successively with 3 in. of 4-mm glass beads, 0.5 in. of fine silica sand, 3 in. of Florisil, and 14.5 g of colored product. Elution for 96 hr produced 5.38 g of pure

(20) M. V. Rubtsov and E. S. Nikitskaya, *Usp. Khim.*, **34**, 1040 (1965).

(21) Melting points are uncorrected and were determined in a Mel-Temp capillary apparatus. Infrared spectra in potassium bromide, Nujol, or solution media were determined on Perkin-Elmer 21 and 221 instruments. Raman spectra were determined on a Cary Model 83 spectrophotometer. Dipole moments were measured in solution on a WTW Dipolimeter Type DMO1. Molecular weights and mass spectra were determined by direct injection into a CEC 21-103 instrument.

white, finely crystalline dicyano compound **3a**, mp $>400^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 3040 (CH=CH), 2210 (C≡N), 1660, and 1625 cm^{-1} (C=C); m/e 236 (parent), 208, 195, 194, 193, 181, 169, 168, 167, 153, 144, 131, 119, 118 (base peak), 105, 91, 69, 57, and 55.

Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.03, 71.36; H, 5.14, 5.13; N, 23.77, 23.74.

An intimate mixture of 13,14-dicyano-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (1.0 g) and zinc dust (10 g) was heated in a pyrolysis tube at 350° for 30 min. The distillate (0.1 ml) was identified as aniline by infrared spectrum, azo dye formation, and gas chromatography.

13,14-Biscarbamoyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3e). A mixture of 13,14-dicyano-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (5.6 g) and 50% sulfuric acid (50 ml) was stirred under nitrogen at $100\text{--}120^{\circ}$ for 6 hr. The mixture was cooled, neutralized with sodium bicarbonate, and filtered to leave a residue of the crude biscarbamoyl compound (5.25 g, 81%). Two recrystallizations from 20-ml portions of 1:2 dichlorotetrafluoroacetone-water with Darco G-60 treatment produced 2.4 g of fine white crystalline 13,14-biscarbamoyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene, mp $>300^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 3420, 3300, 3160, 1650, and 1585 cm^{-1} (NCONH₂); m/e 272 (parent), 229, 228, 212, 211, 186, 185, 183, 170, 169, 168, 167, 154, 149, 144, 143, 136 (base peak), 123, 118, 106, 97, 93, 87, 85, 83, 81, 69, 57, 56, 55, 43, 42, 41, 31, 29, 28, 27, and 18.

Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 62.08, 62.02; H, 6.17, 5.98; N, 20.01.

A 2:1 mixture of *p*-toluenesulfonic acid monohydrate and water was equally effective in promoting this hydrolysis.

13,14-Diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3f). A 5-l., four-necked Morton flask equipped with heating mantle, mechanical stirrer, two long reflux condensers, nitrogen inlet, and thermometer was charged with a cold mixture of sulfuric acid (500 ml), water (1000 ml), and 13,14-dicyano-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (140 g). The apparatus was flushed with nitrogen, and the temperature of the mixture was gradually raised to $110\text{--}120^{\circ}$ where it was maintained for 24 hr. The dark brown mixture was cooled to 50° , poured onto 600 g of ice, mixed with Celite, and filtered. The residue was discarded, and the filtrate was stirred and cooled in a 4-l. erlenmeyer flask while it was cautiously basified with sodium hydroxide (~ 750 g). The precipitate was filtered at room temperature, air dried, and extracted with chloroform in a Soxhlet apparatus. Evaporation of the dried chloroform extracts yielded 49–63 g (45–58%) of yellow powdery diamine **3f**, mp $141\text{--}145^{\circ}$ dec, which was sufficiently pure for most purposes. Analytically pure material was obtained by repeated crystallization from water with Darco G-60 treatment (50% recovery) or by sublimation at 110° (0.1 mm) (87% recovery). Pure 13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene forms fine white crystals, mp $147\text{--}148^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 3420, 3290 (NH), 3030 (CH=CH), and 1655 cm^{-1} (C=C).

Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.33; H, 7.72; N, 15.10, 14.84.

Derivatives of this diamine were prepared as follows.

13,14-Diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene Dihydrochloride (3f·2HCl). A suspension of the diamine **3f** (2.25 g) in acetone (20 ml) was treated with concentrated hydrochloric acid (3.2 ml). The precipitate was recrystallized from 1% hydrochloric acid (20 ml) and acetone (350 ml). The white crystals of the dihydrochloride (1.38 g) had mp $>300^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 2940–2680 (NH_3^+), 1630 (C=C), and 1550 cm^{-1} (NH_3^+).

Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{Cl}_2$: C, 55.60; H, 6.22; N, 10.81. Found: C, 55.88; H, 6.38; N, 11.16.

13,14-Dinitroso-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3g). A mixture of the diamine **3f** (1.86 g, 0.01 mole), water (10 ml), and concentrated hydrochloric acid (3.3 ml, 0.03 mole) was stirred at 0° and treated with a solution of sodium nitrite (1.52 g, 0.022 mole) in water (5 ml) for 1.5 hr. Two recrystallizations of 0.30 g of the crude product from 60–80 ml of ethanol produced 0.12 g of pure dinitroso compound as golden needles, mp $>250^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 3030 (CH=CH), 1625 (C=C), 1450, 1370, and 1055 cm^{-1} (N=N=O); m/e 184 (parent – 2NO), 105, 93, 92 (base peak, half parent – NO), 80, 79, 78, 66, 65, 63, 52, 51, 39, 38, 30 (NO), and 27.

Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.07, 59.02; H, 5.03, 5.14; N, 22.72.

13,14-Dimethyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3c). Methyl iodide (80 ml) at 0° in a polymer tube was treated gradually with diamine **3f** (8.0 g). The tube was sealed and heated overnight at 100° . The contents of the tube were evap-

orated to dryness, stirred with 30 ml of water, and basified with 25% sodium hydroxide. The dried precipitate was sublimed at 125° (0.1 mm) to provide colorless crystals of the dimethyl compound (6.70 g, 73%), mp $165\text{--}166^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 3080, 3030 (CH=CH), and 1450 cm^{-1} (NCH₃); m/e 214 (parent), 108, 107 (base peak), 106, 95, 94, 93, 92, 91, 82, 81, 80, 79, 78, 77, 67, 66, 65, 64, 63, 55, 54, 53, 52, 51, 50, 44, 43, 42, 41, 40, 39, 38, 28, 26, 18, and 15.

Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.60; H, 8.56; N, 13.09.

13,14-Diethyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3h). A mixture of diamine **3f** (1.86 g, 0.01 mole), ethanol (30 ml), ethyl bromide (10 ml), and anhydrous sodium carbonate (1.20 g, 0.011 mole) was heated overnight under reflux. After evaporation and addition of water (20 ml) to the residue, the insoluble material was distilled at $100\text{--}120^{\circ}$ (0.1 mm) to produce 1.71 g (71%) of white crystalline diethyl derivative, mp $93\text{--}94.5^{\circ}$; $\nu_{\text{max}}^{\text{KBr}}$ 3060 (CH=CH) and $3000\text{--}2850\text{ cm}^{-1}$ (CH, NC_2H_5).

Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.59; H, 9.30; N, 11.50.

13,14-Diallyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3i). The procedure for preparing the diethyl derivative **3h** was repeated using allyl bromide in place of ethyl bromide and a reflux time of 2 hr. The crude product was sublimed at 95° (0.1 mm), yield 2.22 g (84%) of colorless crystalline diallyl derivative, mp $103\text{--}104^{\circ}$; $\nu_{\text{max}}^{\text{KBr}}$ 3080, 3070, 3020, 3010 (CH=CH, CH=CH₂), 1640, and 1620 cm^{-1} (C=C). This compound and the dibutenyl derivative **3j** rapidly darken on standing and should be sealed under nitrogen and stored at 0° in a dark place.

Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2$: C, 81.16; H, 8.33; N, 10.52. Found: C, 81.53; H, 8.35; N, 10.93.

13,14-Bis-4-butenyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3j). The above procedure was repeated using 4-bromo-1-butene (5 ml) in place of ethyl bromide. The crude product was distilled at 110° (0.1 mm), yield 2.26 g (77%) of colorless plates of the bis-4-butenyl derivative, mp $53\text{--}55^{\circ}$; $\nu_{\text{max}}^{\text{KBr}}$ 3070, 3060, 3010 (CH=CH, CH=CH₂), 1630, and 1610 cm^{-1} (C=C).

Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2$: N, 9.52. Found: N, 9.63.

13,14-Dicinnamyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3k). A mixture of diamine **3f** (1.86 g, 0.01 mole), benzene (30 ml), triethylamine (2.50 g, 0.025 mole), and *trans*-3-chloropropenylbenzene (3.20 g, 0.021 mole) was heated under reflux overnight. The crude product was isolated as above. The pure dicinnamyl derivative was obtained as pale yellow needles (1.48 g), mp $156\text{--}157^{\circ}$, by recrystallization from a mixture of chloroform (20 ml) and *n*-hexane (200 ml). It had $\nu_{\text{max}}^{\text{KBr}}$ 3085, 3010 (CH=CH, C_6H_5), and 1600 cm^{-1} (C=C).

Anal. Calcd for $\text{C}_{30}\text{H}_{30}\text{N}_2$: C, 86.08; H, 7.22. Found: C, 86.04, 85.95; H, 7.59, 7.59.

13,14-Diacetyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3l). A suspension of diamine **3f** (2.0 g) in methanol (100 ml) was treated with acetic anhydride (10 ml).²² After standing overnight at 25° , the fine white crystalline precipitate of the diacetyl derivative was filtered (2.43–2.51 g, 84–87%) and purified by Soxhlet extraction with methanol, mp $317\text{--}319^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 3060 (CH=CH) and 1650 cm^{-1} (NCOCH₃).

Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.19, 71.11; H, 7.08, 7.20; N, 10.24, 10.29.

13,14-Diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene-13,14-bis(cis-4-oxo-2-butenic acid) (3m). A mixture of diamine **3f** (1.0 g), benzene (25 ml), and maleic anhydride (1.05 g) was heated under reflux for 6 hr. The precipitated maleamic acid derivative (1.84 g, 90%) was recrystallized twice from ethanol as a white powder, mp $>350^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 3030 (CH=CH), 1710 (CO_2H), and 1625 cm^{-1} (NCOR).

Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.52; H, 4.77; N, 7.26.

13,14-Dibenzoyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene (3n). To a suspension of diamine **3f** (3.72 g, 0.02 mole) in 5% aqueous sodium hydroxide (40 ml) was added slowly a solution of benzoyl chloride (6.50 g, 0.046 mole) in chloroform (50 ml). One gram of the precipitate of crude dibenzoyl derivative (7.70 g, 97%) was recrystallized from a mixture of trifluoroacetic acid (7 ml) and water (200 ml) as a white powder, mp $312\text{--}313^{\circ}$ dec; $\nu_{\text{max}}^{\text{KBr}}$ 3030 (C_6H_5 , CH=CH) and 1645 cm^{-1} (NCO C_6H_5).

Anal. Calcd for $\text{C}_{28}\text{H}_{22}\text{N}_2\text{O}_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.76; H, 5.57; N, 7.36.

(22) Cf. A. L. Johnson, R. H. Gourlay, D. S. Tarbell, and R. L. Aurey, *J. Org. Chem.*, **28**, 300 (1963).

13,14-Bis-*p*-bromobenzoyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3o). The above method was used with *p*-obenzoyl chloride to obtain the crude bis-*p*-bromobenzoyl derivative in 60% yield. This derivative was recrystallized from a mixture of dichlorotetrafluoroacetone hydrate (2 ml) and water) as colorless crystals, mp 322–323° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3040 (C_6H_4 , CH), 1675, and 1630 cm^{-1} ($\text{NCOCH}_2\text{H}_2\text{Br}$); m/e 554, 552, 550 (ts), 278, 277, 276, 275 (half-parents), 264, 262, 186, 185, 183 (peak), 168, 157, 155, 104, 92, 76, 65, 50, and 39.
al. Calcd for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_4\text{Br}_2$: C, 56.65; H, 3.65. Found: 76; H, 3.42.

13,14-Bisphenylthiocarbamoyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3p). To a stirred solution of diamine 3f (0.01 mole) in carbon tetrachloride (20 ml) was added dropwise a solution of phenyl isocyanate (2.50 ml, 0.023 mole) in carbon chloride (20 ml). The mixture was heated under reflux for 1 hr, cooled, and filtered. The residue of bisphenylthiocarbamoyl derivative was recrystallized in 1-g lots from a mixture of dimethyl-imide (55 ml) and water (1000 ml) as a white powder, mp 205–206° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3320 (NH), 3130, 3060, 3030 (C_6H_5 , $\text{CH}=\text{CH}$), 1600, 1530, and 1500 cm^{-1} ($\text{NCONHC}_6\text{H}_5$).
al. Calcd for $\text{C}_{28}\text{H}_{24}\text{N}_4\text{O}_2$: N, 13.20; mol wt, 424. Found: 97; mol wt, 424.

13,14-Bisphenylthiocarbamoyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3q). A solution of diamine 3f (0.26 g) in ethanol (1 ml) was treated with 50% ethanolic phenyl isothiourea (2.8 ml). After brief warming, the white crystalline bis-thiourea was filtered (0.39 g, 63%) and purified by Soxhlet extraction with ethanol, mp 211–212° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3040 (C_6H_5 , CH), 1600, 1345, and 1230 cm^{-1} ($\text{NCSNHC}_6\text{H}_5$).
al. Calcd for $\text{C}_{28}\text{H}_{24}\text{N}_4\text{S}_2$: C, 68.39; H, 5.30; N, 12.27; S, 14.14. Found: C, 68.23; H, 5.36; N, 12.05; S, 14.14.

13,14-Bisadamantylloxycarbonyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3r). Adamantyl chloroformate was dissolved in benzene solution.²² A slurry of diamine 3f (1.86 g, 0.01 mole), sodium carbonate (1.06 g, 0.01 mole), and ether (20 ml) was treated slowly with 34 ml of the benzene solution of adamantyl chloroformate (4.3 g, 0.02 mole). After being stirred overnight, the mixture was evaporated to dryness, stirred with 25 ml of water, filtered. The crude residue of bisadamantylloxycarbonyl derivative was recrystallized from a mixture of chloroform (25 ml) and ethanol (50 ml), yield 2.94 g (56%) of colorless crystals, mp 114° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3020 ($\text{CH}=\text{CH}$) and 1690 cm^{-1} (NCO_2R).
al. Calcd for $\text{C}_{34}\text{H}_{42}\text{N}_2\text{O}_4$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.22, 75.22; H, 7.34, 7.18; N, 5.49.

13,14-Bisethoxycarbonyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3b) and Its Photolysis to 1-Ethoxycarbonylazepine (1b). A suspension of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3f) (7.44 g) and anhydrous sodium carbonate (4.14 g) in ether (70 ml) was stirred at room temperature and treated dropwise with a solution of ethyl chloroformate (8.50 g) in ether (100 ml). After standing overnight, the solvent was evaporated, and the residue was stirred with water and filtered. Two recrystallizations of the crude damp yellow product from ethanol (20 ml) yielded 7.72 g (59%) of fine white crystalline bisethoxycarbonyl derivative,²⁴ mp 196.5–197.5° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3070, 3030 ($\text{CH}=\text{CH}$), ($\text{NCO}_2\text{C}_2\text{H}_5$), and 1650 cm^{-1} ($\text{C}=\text{C}$); m/e 330 (parent), 166, 165 (base peak), 152, 137, 130, 128, 118, 117, 115, 108, 106, 104, 103, 80, 66, 65, and 29.

al. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.39, 65.66; H, 6.52, 6.54; N, 8.65, 8.76. A mixture of the bisethoxycarbonyl derivative 3b (4.1 g) and nitrile (400 ml) was agitated with a nitrogen bubbler in a water-d (12°) quartz apparatus and photolyzed with a low-pressure 2537-A source. The progress of the reaction was followed by gas chromatography at 140° on a 6-ft, 20% silicone 200-80 AWFB column and by ultraviolet spectroscopy in acetone solution. The reaction was complete after 24-hr irradiation. After evaporation of the solvent, the dark red residue was distilled (0.1 mm) to give 1-ethoxycarbonylazepine (1b) as an orange oil (1.5 g, 12%) identified by gas chromatography retention time (min) and infrared and nmr spectra. This material was identical to that prepared by reaction of benzene with ethoxycarbonyl azepine.^{12i,25} Similar irradiation of compounds 3a, c, f, and n

produced tars from which the corresponding azepines (1) were not obtained.

13,14-Bis-*t*-butoxycarbonyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3d) and Its Photolysis to 1-*t*-Butoxycarbonylazepine (1d). 1-*t*-Butoxycarbonylazepine (1d) was prepared according to Hafner¹²ⁱ and Cotter and Beach¹²ⁱ from a solution of *t*-butyl azidoformate (50 g, Aldrich) in benzene (4 l.) at 125° for 2 hr. In addition to the azepine (12.80 g) (63% yield based on azidoformate not converted to oxazolidone), bp 40–60° (0.1 mm), there was isolated 22.4 g of hexane-insoluble 5,5-dimethyl-2-oxazolidone, mp 80–81°, produced by intramolecular insertion of the nitrene.²⁷ A 7.2-g charge of the azepine was degassed, sealed *in vacuo*, and heated at 156° for 2 hr. The contents of the tube were rinsed out with hexane and filtered. The insoluble residue (2.75 g, 38%) of bis-*t*-butoxycarbonyl derivative 3d was recrystallized twice from 50 ml of 1:1 ethanol-water with Darco G-60 treatment to give colorless needles of the pure compound, mp 205–206° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3030, 3010 ($\text{CH}=\text{CH}$), and 1680 cm^{-1} ($\text{NCO}_2\text{C}(\text{CH}_3)_3$); m/e 386 (parent), 274, 230, 193 (half-parent), 186, 185, 168, 138, 137, 130, 124, 120, 118, 107, 106, 94, 93, (base peak), 92, 81, 80, 79, 69, 67, 66, 65, 58, 57, 56, 55, 53, 51, 44, 43, 42, 41, 40, 39, 38, 29, 27, and 15.

Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.35; H, 7.58; N, 7.36, 7.38.

Chemical proof of the structure of 3d was obtained by conversion to 3f with hydrogen bromide in glacial acetic acid.⁸ When 0.5 g of the bis-*t*-butoxycarbonyl compound was added to 5 ml of 30% $\text{HBr}-\text{CH}_2\text{CO}_2\text{H}$ (Eastman) there was an immediate evolution of gas (C_4H_8 and CO_2). The mixture was poured onto ice, basified with sodium hydroxide, and extracted with chloroform. The chloroform extracts yielded the parent diamine 3f, identified by mixture melting point and infrared and nmr spectra.

The bis-*t*-butoxycarbonyl derivative (2.0 g) was dissolved in 250 ml of acetonitrile and photolyzed in the same way as the bisethoxycarbonyl derivative. Recovered starting material weighed 0.80 g, and after distillation 0.16 g (13%) of 1-*t*-butoxycarbonylazepine (1d) was obtained, identified by comparison of infrared and nmr spectra with those of authentic material.

13,14-Bischloroacetyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3e). A solution of diamine 3f (1.86 g) and triethylamine (2.50 g) in benzene (30 ml) was treated with a solution of chloroacetyl chloride (2.50 g) in benzene (10 ml). The product was isolated by evaporation and recrystallized from a mixture of trifluoroacetic acid (35 ml) and water (200 ml), yield 2.54 g (75%) of the bischloroacetyl derivative, mp >215° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3030 ($\text{CH}=\text{CH}$) and 1660 cm^{-1} (NCOCH_2Cl).

Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2\text{Cl}_2$: N, 8.26. Found: N, 8.17, 8.41.

13,14-Bisdiethylaminoacetyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3t). A mixture of the bischloroacetyl derivative 3e (0.90 g), ethanol (40 ml), and diethylamine (10 ml) was heated under reflux overnight. The product was isolated by evaporation and recrystallization from 50% methanol (10 ml), yield 0.69 g (63%) of colorless crystals, mp 165–166°, $\nu_{\text{max}}^{\text{KBr}}$ 3030 ($\text{CH}=\text{CH}$) and 1640 cm^{-1} ($\text{NCOCH}_2\text{N}(\text{C}_2\text{H}_5)_2$).

Anal. Calcd for $\text{C}_{24}\text{H}_{34}\text{N}_4\text{O}_2$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.99, 69.95; H, 9.06, 9.11; N, 13.61, 13.64.

13,14-Bisethoxycarbonylmethyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3u). A solution of ethyl bromoacetate (3.34 g) in benzene (15 ml) was added dropwise to diamine 3f (3.72 g) in ethanol (15 ml).²⁸ After being stirred overnight, the precipitate of 3f·2HBr (3.27 g, 94%) was filtered, and the filtrate was evaporated to leave 3.27 g (91%) of crude bisethoxycarbonylmethyl derivative. Recrystallization of the derivative from 50% ethanol (55 ml) produced 1.67 g of colorless needles, mp 99–100°; $\nu_{\text{max}}^{\text{KBr}}$ 3030 ($\text{CH}=\text{CH}$) and 1750 cm^{-1} ($\text{CO}_2\text{C}_2\text{H}_5$).

Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.00; H, 7.52; N, 8.10.

13,14-Diazatricyclo[6.4.1.1^{3,7}]tetradecane (4a). A mixture of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3f) (20.0 g), water (150 ml), concentrated hydrochloric acid (25 ml), and platinum oxide (2.0 g) was hydrogenated overnight in a Parr shaker.

(25) Dr. M. E. Hermes, Plastics Department, E. I. du Pont de Nemours and Co., personal communication.

(26) W. J. Close, *J. Am. Chem. Soc.*, **73**, 95 (1951).

(27) (a) R. Kreher and G. H. Bockhorn, *Angew. Chem.*, **76**, 681 (1964); (b) R. Puttner and K. Hafner, *Tetrahedron Letters*, 3119 (1964); (c) R. Kreher and D. Kühling, *Angew. Chem.*, **77**, 42 (1965).

(28) Cf. G. Fodor, J. Tóth, and I. Vincze, *J. Chem. Soc.*, 3504 (1955).

) W. L. Haas, E. V. Krumkalns, and K. Gerzon, *J. Am. Chem. Soc.*, **88**, 1988 (1966).

) This product gave no mixture melting point depression and was identical in its spectral properties with Paquette's thermally prepared compound.¹²

The mixture was filtered; the residue was rinsed with water, and the combined filtrate and washings were concentrated to 40 ml and basified with 30% sodium hydroxide. After cooling to 0°, the precipitate of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane was filtered, air dried, and sublimed at 70° (0.1 mm). The pure saturated base was a colorless crystalline solid (15.3 g, 73%), mp 61–62°; $\nu_{\text{max}}^{\text{KBr}}$ 3290 and 1450 cm^{-1} (NH); nmr (CCl_4) τ 7.29 (multiplet, four tertiary protons), 8.29 (multiplet, 16 CH_2 protons), and 8.50 (singlet, two exchangeable NH protons).

Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{N}_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.06, 74.08; H, 11.13, 11.33; N, 14.36, 14.43.

In an analytical scale experiment using an atmospheric pressure hydrogenator, 4 molar equiv of hydrogen was absorbed at 25° (760 mm) over 5.5 hr.

The dihydrochloride and dihydrobromide of 4a were prepared by the same procedure as the dihydrochloride of 3f. 13,14-Diazatricyclo[6.4.1.1^{3,7}]tetradecane dihydrochloride forms white crystals, mp >320° dec; $\nu_{\text{max}}^{\text{Nujol}}$ 2740, 2700, 2630, and 1575 cm^{-1} (NH_2^+); nmr (D_2O) τ 5.30 (singlet, four NH_2^+ protons), 6.00 (multiplet, four tertiary protons), and 8.10 (multiplet, 16 CH_2 protons).

Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{N}_2\text{Cl}_2$: C, 53.94; H, 9.06. Found: C, 53.88; H, 8.99.

13,14-Diazatricyclo[6.4.1.1^{3,7}]tetradecane dihydrobromide is a white powder, mp >320° dec; $\nu_{\text{max}}^{\text{KBr}}$ 2820–2600 and 1570 cm^{-1} (NH_2^+); nmr (D_2O) τ 5.34 (singlet, four NH_2^+ protons), 6.02 (multiplet, four tertiary protons), and 8.18 (multiplet, 16 CH_2 protons); m/e 356, 355, 354 (parents), 194, 138, 137, 124, 123, 122, 111, 110, 109, 108, 107, 106, 99, 98 (base peak), 97, 96, 95, 94, 93, 91, 84, 83, 82, 81, 80, 79, 68, 67, 57, 56, 55, 54, 53, 44, 43, 42, 41, 39, 30, 29, 28, 27, and 18.

Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{N}_2\text{Br}_2$: C, 40.47; H, 6.79; N, 7.78. Found: C, 40.71; H, 6.79; N, 7.98.

13,14-Diazatricyclo[6.4.1.1^{3,7}]tetradecane monohydrochloride, described below as a reaction product from diamine 4a and cobalt(II) chloride, was prepared independently by (a) neutralization of 4a with 1 equiv of hydrochloric acid and (b) mixing equimolar amounts of 4a and its dihydrochloride in chloroform.

13,14-Dinitroso-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane (4b). The crude nitroso compound, prepared in the same way as 3g, was obtained in 92% yield after two recrystallizations from aqueous ethanol as pale yellow crystals, mp 180–182.5° dec; $\lambda_{\text{max}}^{\text{CH}_2\text{OH}}$ 363 μm (ϵ 153), 355 μm (ϵ 146), and 248 μm (ϵ 12,300); $\nu_{\text{max}}^{\text{KBr}}$ 1460, 1450, 1430, 1370, and 1355 cm^{-1} (N=N=O); nmr (CDCl_3) τ 4.89 (multiplet, four tertiary protons) and 8.60 (multiplet, 16 CH_2 protons).

Anal. Calcd for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2$: C, 57.11; H, 7.99; N, 22.21. Found: C, 57.32, 57.17; H, 7.79, 7.68; N, 22.24, 22.12.

13,14-Dimethyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane (4c). A mixture of diamine 4a (6.0 g), methanol (100 ml), anhydrous sodium carbonate (3.50 g), and methyl iodide (20 ml) was heated under reflux for 20 hr. The mixture was evaporated to dryness; the residue was stirred with water (35 ml), cooled to 0°, and filtered. The crude dimethyl compound was purified by sublimation at 100–110° (0.1 mm). The colorless waxy product (6.66 g, 97%) had mp 125–130°; $\nu_{\text{max}}^{\text{KBr}}$ 2780 and 1440 cm^{-1} (NCH_3); nmr (CCl_4) τ 7.35 (singlet, four tertiary protons), 7.45 (singlet, six NCH_3 protons), and 7.90–8.50 (broad multiplet, 16 CH_2 protons); m/e 222 (parent), 208, 207 (parent – CH_3), 192, 180, 179, 166, 165, 151, 138, 124, 123, 122, 113, 112 (base peak, half-parent + H), 111, 110, 109, 108, 98, 97, 96, 95, 94, 84, 83, 82, 81, 70, 68, 67, 58, 57, 55, 42, 41, 39, 30, 29, 28, 27, and 15.

Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2$: C, 75.61; H, 11.79; N, 12.60. Found: C, 75.78; H, 11.69; N, 12.75.

13,14-Diethyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane (4d). The above procedure was employed substituting ethanol for methanol and ethyl iodide for methyl iodide. The yield of pure diethyl derivative, bp 95° (0.1 mm), was 2.15 g (86%) of colorless crystals, mp 35–37°; $\nu_{\text{max}}^{\text{KBr}}$ 2960–2850, 1465, and 1440 cm^{-1} (NCH_2CH_3); nmr (CCl_4) τ 7.12 (quartet, $J = 7$ cps, + broad multiplet, four NCH_2 + four tertiary protons), 8.0–8.60 (broad multiplet, 16 CH_2 protons), and 8.96 (triplet, $J = 7$ cps, six CH_3 protons).

Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.90; H, 11.79; N, 11.43.

(29) Our freshly sublimed and analytically pure material contracted near 95° and melted at 125–130°. Paquette^{10,24} observed mp 128–145° for sublimed product and mp 148–150° for sublimed product recrystallized from Skellysolve B at 0 to –5°. On the basis of direct comparison of analytical and spectral data of these differently prepared samples we have concluded that they are identical.

13,14-Dibenzoyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane (4e). A mixture of diamine 4a (1.94 g, 0.01 mole) and 10% sodium hydroxide (40 ml) was shaken with benzoyl chloride (5 ml). The crude product was recrystallized twice from a mixture of ethanol and chloroform, mp 319.5–320.5° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3070 (C_6H_5), 1635, and 1595 cm^{-1} ($\text{C}_6\text{H}_5\text{CO}$); nmr (CDCl_3) τ 2.65 (doublet, $J = 6$ cps, ten aromatic protons), 5.04 (multiplet, two tertiary protons), 6.36 (multiplet, two tertiary protons), and 8.33 (multiplet, 16 CH_2 protons). Temperature probe nmr experiments between –60 and +126° did not cause any coalescence of the tertiary proton signals. The mass spectrum showed m/e 402 (parent), 298, 297, 296, 295 (base peak), 294, 293, 292, 291, 289, 277, 276, 275, 202, 201, 200, 199, 198, 197, 105, 85, 81, 71, 69, 57, and 55.

Anal. Calcd for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_2$: N, 6.96. Found: N, 6.72.

13,14-Bisphenylcarbamoyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane (4f). The crude bisphenylcarbamoyl derivative, obtained in 94% yield by a procedure analogous to that used to prepare 3p, was purified by Soxhlet extraction with ethanol as a white powder, mp 374–375° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3320 (NH), 3060 (C_6H_5), 1640, 1595, 1530, and 1505 cm^{-1} ($\text{NCONHC}_6\text{H}_5$).

Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{N}_4\text{O}_2$: C, 72.19; H, 7.46; N, 12.95; mol wt, 432. Found: C, 72.12, 72.06; H, 7.48, 7.55; N, 13.08, 13.20; mol wt, 432.

13,14-Bisphenylthiocarbamoyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane (4g). The white crystalline bisphenylthiocarbamoyl derivative obtained analogously to 3q in 84% yield was purified by Soxhlet extraction with ethanol. The pure material had mp 289–289.5° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3070 (C_6H_5), 1605, 1505, 1450, 1375, and 1340 cm^{-1} ($\text{NCSNHC}_6\text{H}_5$).

Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{N}_4\text{S}_2$: C, 67.20; H, 6.94; N, 12.06; S, 13.80; mol wt, 464. Found: C, 67.35, 67.30; H, 7.04, 7.02; N, 11.83, 11.84; S, 14.02, 14.22; mol wt, 464.

Cobalt(II) Complexes of 13,14-Diazatricyclo[6.4.1.1^{3,7}]tetradecane-3,5,9,11-tetraene (3f). The general procedure was to heat under reflux for 30 min a mixture of the cobalt(II) salt (5–10 mmoles), ethanol (50 ml), and diamine 3f (1.86 g, 10 mmoles). After cooling to 25°, the precipitated complex was filtered, rinsed with chloroform, and dried at 25–100° (0.1 mm). The insolubility of these complexes in common organic solvents precluded the measurement of solution ultraviolet or nuclear magnetic resonance spectra. In the donor solvents water, dimethylformamide, and dimethyl sulfoxide, these complexes dissolved with decomposition.

(a) Cobalt(II) chloride hexahydrate formed a blue powder in 90% yield, mp >300° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3450, 3200 (NH), 3030, and 1625 cm^{-1} ($\text{CH}=\text{CH}$); $\mu = 4.54$ BM.³⁰

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{CoCl}_2$: C, 45.59; H, 4.46; N, 8.86; Co, 18.65; Cl, 22.43. Found: C, 45.28, 45.28; H, 4.57, 4.68; N, 8.73, 8.70; Co, 18.51; Cl, 21.50, 21.50.

(b) Cobalt(II) bromide formed a blue powder in 90% yield, mp >280° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3190 (NH), 3030, and 1620 cm^{-1} ($\text{CH}=\text{CH}$), $\mu = 4.53$ BM.

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{CoBr}_2$: C, 35.68; H, 3.49; N, 6.93; Co, 14.59. Found: C, 35.32, 35.46; H, 3.85, 3.96; N, 6.99, 7.07; Co, 14.40, 14.41.

(c) Cobalt(II) iodide formed a green powder in 75% yield, mp >380° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3190 (NH), 3040, and 1600 cm^{-1} ($\text{CH}=\text{CH}$); $\mu = 4.69$ BM.

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{CoI}_2$: C, 28.89; H, 2.83; N, 5.61; Co, 11.81. Found: C, 28.24, 28.34; H, 3.14, 3.14; N, 5.31, 5.40; Co, 11.98, 12.09.

(d) Cobalt(II) nitrate hexahydrate formed a gray powder which was a mixture of products.

(e) Cobalt(II) acetate tetrahydrate did not form a complex under these conditions.

(f) Cobalt(II) thiocyanate formed a violet powder in 46% yield, mp >200° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3340, 3220 (NH), 3030, 1605 ($\text{CH}=\text{CH}$), 2170 cm^{-1} (SCN); $\mu = 4.83$ BM.

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{S}_2\text{Co}$: Co, 10.76; N, 15.35; S, 11.71. Found: Co, 11.11; N, 15.07; S, 12.08.

(g) Cobalt(II) perchlorate hexahydrate formed a pale green powder in 30% yield, mp 270° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3600, 3300, 3130 (OH, NH), 1610 ($\text{C}=\text{C}$), and 1080 cm^{-1} (ClO_4).

Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{Cl}_2\text{O}_7\text{Co}$: C, 41.04; H, 5.17; Co, 8.39; Cl, 10.10. Found: C, 40.87; H, 5.34; Co, 8.68; Cl, 9.74.

(30) The magnetic susceptibility of the four compounds at 297°K was independent of field from 18 to kgauss. Diamagnetic contributions were calculated from Pascal's constants.

Reaction of 13,14-Diazatricyclo[6.4.1.1^{3,7}]tetradecane (4a) with Cobalt(II) Chloride. A mixture of cobalt(II) chloride hexahydrate (1.0 g), ethanol (50 ml), and diamine 4a (1.60 g) was heated under reflux for 24 hr, cooled, and filtered free of cobalt(II) chloride (0.40 g). Evaporation of the filtrate left a solid (1.71 g) from which 0.40 g of unreacted diamine was sublimed at 70° (0.1 mm). The residue (1.30 g) was recrystallized twice from a mixture of ethanol (10 ml) and acetone (20 ml) to produce colorless needles of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane monohydrochloride (0.55 g), mp 270–280° dec; no $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 208–400 m μ ; $\nu_{\text{max}}^{\text{KBr}}$ 1590 cm⁻¹ (NH₂⁺); nmr (CDCl₃) τ 6.79 (4 protons) and 8.07 (16 protons).

Anal. Calcd for C₁₂H₂₂N₂Cl: C, 62.44; H, 10.05; N, 12.14; Cl, 15.37. Found: C, 62.63; H, 9.71; N, 11.86; Cl, 15.75.

13,14-Dimethyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene Monomethiodide (10) Method a. A mixture of 13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3f) (18.6 g, 0.10 mole), methanol (200 ml), anhydrous sodium carbonate (15.9 g, 0.15 mole), and methyl iodide (31 ml, 0.50 mole) was heated under reflux for 24 hr. After evaporation to dryness, the residue was stirred with ice-water (50 ml) and filtered. The residue was recrystallized from acetonitrile (500 ml), yield 27.77 g (78%) of monomethiodide.

Method b. A mixture of 13,14-dimethyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (3c) (3.0 g), acetonitrile (15 ml), and methyl iodide (15 ml) was heated overnight in a sealed tube at 100°. Evaporation of the mixture produced 4.44 g (89%) of the monoquaternary iodide. The analytical sample was recrystallized twice from acetonitrile as white crystals, mp 300–302° dec; $\nu_{\text{max}}^{\text{KBr}}$ 3110, 3085, 3020 (CH=CH), 2970, 2935, 2890, 2870, 2830, and 2790 cm⁻¹ (CH, NCH₃).

Anal. Calcd for C₁₄H₂₄N₂I: C, 50.58; H, 5.94; N, 7.87. Found: C, 50.62, 50.41; H, 5.80, 5.63; N, 8.01, 7.84.

13,14-Dimethyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradecane Monomethiodide (11). Application of method a above with 4a produced only the dimethyl compound 4c. Method b above with 4c produced an 84% yield of the desired monomethiodide after recrystallization from ethanol. Two further recrystallizations from ethanol produced long colorless needles of 11, mp 246–248° dec; $\nu_{\text{max}}^{\text{KBr}}$ 2960–2790 and 1470 cm⁻¹ (CH, NCH₃); nmr (CDCl₃) τ 6.37 (multiplet, two tertiary protons), 6.57 (singlet, three axial NCH₃ protons), 6.65 (singlet, three equatorial NCH₃ protons), 6.80 (multiplet, two tertiary protons), 7.15 (singlet, three tertiary NCH₃ protons), and 7.50–8.33 (broad multiplet, 16 CH₂ protons), and 7.50–8.33 (broad multiplet, 16 CH₂ protons).

Anal. Calcd for C₁₆H₂₆N₂I: N, 7.52; I, 34.83. Found: N, 7.60, 7.61; I, 35.64.

Hofmann Elimination on 13,14-Dimethyl-13,14-diazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene Monomethiodide (10). 1. A mixture of the monomethiodide 10 (7.29 g), water (50 ml), methanol (275 ml), and freshly prepared silver oxide (from 10 g of silver nitrate) was stirred at room temperature overnight. The silver salts were filtered, washed with methanol, and air dried (yield 9.55 g, theory). Evaporation of the filtrate left a brown viscous residue which was heated at 120° (0.1 mm) for 30 min, then distilled in a short-path still at 120° (0.1 mm). Redistillation produced the Hofmann product 12 as a pale yellow oil (4.29 g, 92%) from which the color was removed completely after one further distillation. The

unstable distillate crystallized on cooling to -78°. The crystalline dimethylamino-N-methylazatricyclo[6.4.1.1^{3,7}]tetradeca-3,5,9,11-tetraene (12) had mp 43–44°; $\lambda_{\text{max}}^{\text{CH}_2\text{OH}}$ 250 m μ (ϵ 9700); $\nu_{\text{max}}^{\text{CDCl}_3}$ 3040, 3020 (CH=CH), and 1470 cm⁻¹ (NCH₃); nmr (CDCl₃) τ 4.14–4.32 (complex multiplet, eight vinyl protons), 6.53 (multiplet, one tertiary proton), 7.12 (doublet, J = 4 cps, two tertiary protons), 7.62 (singlet, six N(CH₃)₂ protons), and 7.75 (singlet, three NCH₃ protons).

Anal. Calcd for C₁₆H₂₆N₂: C, 78.90; H, 8.83; N, 12.27; mol wt, 228. Found: C, 78.39; 78.31; H, 8.75, 8.92; N, 12.01; mol wt, 228.

2. A solution of the Hofmann product 12 (8.38 g) in acetonitrile (150 ml) was treated dropwise with methyl iodide (30 ml) and stirred overnight at 25°. The crude crystalline bismethiodide (5.01 g, 26%) was filtered. Two recrystallizations of 1.45 g of this product from water (25 ml) and acetone (300 ml) with Darco G-60 treatment produced 0.92 g of the white crystalline bismethiodide of 12, mp 160–165° dec; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 260 m μ (sh, ϵ 8000), 227 m μ (ϵ 28,800); $\nu_{\text{max}}^{\text{KBr}}$ 3080, 3050, 3025, 3010 (CH=CH), 1485, 1460, 1440, and 1410 cm⁻¹ (NCH₃); nmr (CF₃CO₂H) τ 3.45–4.28 (complex multiplet, eight vinyl protons), 4.64 (triplet, J = 7 cps, two tertiary protons), 5.73 (multiplet, one tertiary proton), 6.55 (singlet, 12 NCH₃ protons), and 6.82 (singlet, three NCH₃ protons).

Anal. Calcd for C₁₇H₂₈N₂I₂: C, 39.86; H, 5.12; N, 5.47. Found: C, 40.15; H, 4.99; N, 5.54.

Evaporation of the mother liquors from this reaction left a dark intractable gum.

3. A further Hofmann degradation on 2.45 g of the bismethiodide of 12 with the silver oxide from 3 g of silver nitrate in water (20 ml) and methanol (30 ml) produced 3.23 g of silver salts (theory 3.19 g) and a gummy residue which formed a brown oily distillate at 180° (0.1 mm). Redistillation produced 0.06 g of a yellow unstable oil which appeared to consist of several products. Addition of 10% hydrochloric acid to the pump trap followed by evaporation produced 0.42 g (1 molar ratio) of trimethylamine hydrochloride, identified by conversion to trimethylammonium picrate, mp 215–217° dec (lit.²¹ mp 216°).

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Mechanisms of Photochemical Reactions in Solution. XLIII.¹ Addition of Maleic Anhydride to Benzene

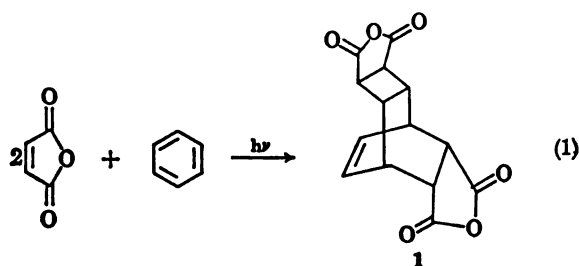
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Abstract: The photoaddition of maleic anhydride to benzene by both direct and sensitized excitation has been studied. Use of suitable quenchers and sensitizers and variation of the concentration of the reactants indicate that a triplet mechanism obtains. Key steps in the mechanism are: (1) excitation of the maleic anhydride-benzene complex to its triplet state, (2) collapse of the excited complex to a monoadduct, and (3) reaction of the first adduct with maleic anhydride in a thermal reaction. Study of quenching reactivities indicates that the triplet excitation energy of the maleic anhydride-benzene complex is at least 2 kcal/mole less than the excitation energy of maleic anhydride.

The photochemical addition of maleic anhydride to benzene was discovered almost simultaneously by three groups of workers.²⁻⁴



Schenck and Steinmetz² showed that the reaction could be conveniently carried out using benzophenone as a sensitizer and Bryce-Smith and Lodge³ made a preliminary comparison of the sensitized and unsensitized reactions. Both groups suggested that the mechanisms of the direct and indirect reactions are distinctly different. Furthermore, the English workers reported some very unusual characteristics of the reactions³ although one very important observation has since been reported by the same group⁴ to have been in error. We should point out that quantitative studies of the reaction, including our own, have depended upon isolation of 1 which crystallizes from the reaction mixtures. Crystallization is slow and any isolated, negative result may be attributed to supersaturation.

Because of the complexity of the reaction and the provocative nature of the first suggestions concerning mechanism, we felt that the process deserved detailed study. A preliminary report of part of our results has already been published.⁷

Results and Discussion

Samples were irradiated in ampoules made from thin-walled Pyrex culture tubes in a merry-go-round ap-

paratus⁸ so that a number of samples, including actinometric samples, could be irradiated simultaneously. The light source was a 450-w, medium-pressure mercury lamp. The 3130-, 3660-, and 4045-A lines from the source are transmitted to the extent of 78, 87, and 90% by the Pyrex tubes. In most experiments with sensitizers a uranium glass filter was used, eliminating essentially all source lines of wavelength shorter than 3300 Å. Some measurements of quantum yields were made using a collimated beam from a high-pressure arc (Westinghouse SAH 800-C)⁹ with glass filters chosen to isolate the 3660-A line. The reaction was monitored by isolating and weighing the insoluble product, 1.

Sensitizers and Inhibitors. A survey of potential sensitizers was carried out, giving the results shown in Table I. The yields, given in milligrams, were determined at relatively low conversions (10 mg \cong 2%) using 1.0 M maleic anhydride in benzene. The yields are not necessarily proportional to quantum yields since no corrections have been made for variation in either intersystem crossing efficiencies or variation in the absorption spectra of the additives. Although the experiments with compounds listed as "inhibitors" were not pursued exhaustively, there seems to be a clear-cut difference between these compounds and the effective sensitizers. None of the addition compound was formed even when the uranium glass filter was removed. Obviously the "inhibitors" not only fail to sensitize the reaction but also interfere with the unsensitized reaction. No attempt has been made to quantitatively dissect the effects into quenching and internal light filtering. Concentrations of the additives were adjusted so as to absorb essentially all incident light at 3660 Å, where the benzene-maleic anhydride complex does not absorb. In the experiments with the uranium glass filter, 1-20% of the total incident light was estimated to be absorbed by the complex.

Separation of the sensitizers and inhibitors on the basis of triplet excitation energies is almost, but not quite, perfect. There seems to be a cutoff point with

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Table I. Yields of Addition Product Obtained by Irradiation of Solutions of Maleic Anhydride in Benzene in the Presence of Various Additives

Additive	Concn of additive, M	Yield of product, ^a mg	Triplet energy ^b
Sensitizers^c			
Propiophenone	0.80	26	74.7
Xanthone	0.01	14	74.2
Acetophenone	0.80	41	73.6
Benzaldehyde	0.30	36	71.9
Benzophenone	0.050	46	68.5
4,4'-Dichlorobenzophenone	0.050	59	68.0
<i>p</i> -Diacetylbenzene	0.30	35	67.7
<i>p</i> -Cyanobenzophenone	0.050	40	66.4
Inhibitors^d			
Triphenylene	0.10	0	66.6
Thioxanthone	0.05	0	65.5
Anthraquinone	0.010	0	62.4
2-Acetylfluorene	0.10	0	62.6
Naphthalene	0.10	0	60.9
2-Acetonaphthone	0.20	0	59.3
Chrysene	0.01	0	56.6
Benzil	0.050	0	53.7
Fluorenone	0.10	0	53.0

^a 1.0 M maleic anhydride in benzene, irradiation for 50 hr in a merry-go-round apparatus (outside ring). ^b W. G. Herkstroeter, A. Lamola, and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 4537 (1964). ^c All reported results with uranium glass filter. ^d Results reported were obtained without uranium glass filter.

sensitizers having about 66-kcal/mole excitation energy; those having higher excitation energies sensitize the reaction and those having less available energy do not. When energy transfer becomes insignificant, the rate of the process must fall below the first-order rate of decay of the sensitizer triplets. From our estimates of the concentrations of the complex (*vide infra*), the lifetimes of the various triplets in solution, and data from flash kinetic studies of triplet quenching,¹⁰⁻¹³ we infer that energy transfer must be several kilocalories per mole endothermic at the cutoff point. The apparent anomalies with *p*-cyanobenzophenone and triphenylene may not be significant. Measurement of triplet excitation energies is not highly precise and we have observed other apparently deviant behavior with triphenylene.¹³

Triplet Excitation Energy of Maleic Anhydride. The emission spectra from MCIP (5:1 methylcyclohexane-isopentane) glasses containing approximately 10⁻³ M maleic anhydride were measured at 77°K. A very weak, long-lived emission was observed. After subtraction of the background emission from the solvent the spectrum shown in Figure 1 was obtained. The spectrum was not very reproducible and that shown is the strongest obtained. Although other details varied, the first maximum (at 3980 Å) was reproducible.¹⁴ This indicates that the phosphorescent state has

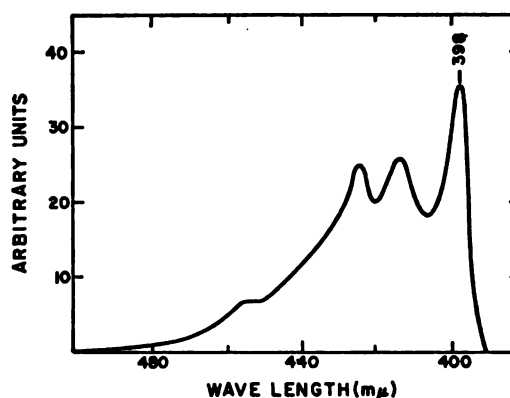


Figure 1. Emission spectrum of maleic anhydride in MCIP glass at 77°K. Weak emission from the glass has been subtracted.

an excitation energy of about 72 kcal/mole. Addition of benzene in amounts slightly greater than molar equivalence to the maleic anhydride led to complete disappearance of the phosphorescence. Apparently formation of the complex provides faster modes of decay for maleic anhydride triplets than are available to the uncomplexed molecule. The extent to which this is associated with the chemical reaction is not entirely clear.

The absorption spectrum of a 0.067 M solution of maleic anhydride in ethyl iodide was measured in a 1-cm cell. The long wavelength spectrum shown in Figure 2 was obtained. The spectrum is probably due to a singlet-triplet transition induced by the external heavy-atom effect.¹⁵ Although the spectrum is ab-

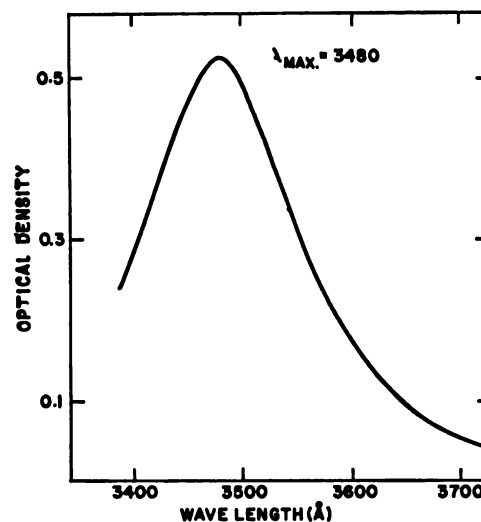


Figure 2. Long wavelength absorption spectrum of maleic anhydride in ethyl iodide solution.

solutely featureless, it is entirely possible that the long wavelength limit occurs close to 3900 Å, the apparent position of the 0-0 band in the phosphorescence spectrum. If anything the absorption spectrum indicates a slightly higher value of the $S_0 \rightarrow T_1$ excitation energy.

Quenching of Triplets by Maleic Anhydride. The reaction of benzophenone with benzhydrol was used to

(15) M. Kasha, *J. Chem. Phys.*, **20**, 74 (1952).

(10) K. Sandros and H. L. J. Backström, *Acta Chem. Scand.*, **16**, 8 (1962).

(11) G. Porter and F. Wilkinson, *Proc. Roy. Soc. (London)*, **A264**, 1 (1961).

(12) W. G. Herkstroeter and G. S. Hammond, *J. Am. Chem. Soc.*, in press.

(13) L. M. Coyne, unpublished observations.

(14) Factors known to effect the quality of a recorded spectrum are: (1) the purity of the constituents of the solvent, (2) variation in the amount of cracking in the glass, and (3) the phototube. The spectrum shown was the only one recorded with our best phototube.

measure the relative efficiency of maleic anhydride as a quencher for benzophenone triplets.^{9,16} The spectroscopic studies reported above indicate that the excitation energy of maleic anhydride is too high to allow it to be a good quencher for benzophenone. However, an earlier measurement,¹⁶ made in the course of a general survey, indicated that maleic anhydride is a good quencher in benzene solution. The study has been repeated in benzene and in nonaromatic solvents. The measurements in benzene are complicated by virtue of the fact that the addition reaction decreases the concentration of the quencher during the course of the runs. Correction for the change in concentration was made using data for the quantum yields of the addition reaction (*vide infra*). The results are shown in Table II.

Table II. Quenching of the Reaction of Benzophenone with Benzhydryl by Maleic Anhydride in Benzene^a

Run	[Benzhydryl] ₀ , M	[MA] ₀ × 10 ³ , M	Φ ^b	k _q /k _r ^c
A	0.100	2.0	0.341	79
B	0.100	1.0	0.517	56
C	0.050	1.0	0.314	59
D	0.200	2.0	0.536	70
E	0.100	0	0.731	..
			Av	65

^a Benzophenone was initially 0.100 M in each experiment. ^b The benzophenone-benzhydryl reaction without added quencher was used as an actinometer. The parameters reported in ref 18 were used in the calculations. ^c The average concentration of maleic anhydride was approximately 5% lower than the initial concentration in each run; k_q is the rate constant for quenching of benzophenone triplets by maleic anhydride and k_r is the rate constant for reaction of benzophenone triplets with benzhydryl.

The quenching reaction was also studied in carbon tetrachloride solution and a solvent consisting of 95% cyclohexane and 5% acetone. The values of k_q/k_r¹⁷ were redetermined in each medium using Foss's method.¹⁸ The value in cyclohexane-acetone was 0.036, well within experimental error of the value (0.033) for benzene solution; consequently, we infer that hydrogen abstraction from the solvent is unimportant in the former case. In carbon tetrachloride the value was 0.0526. While we have no way of dissecting the ratio, the increase is probably to be associated with an external heavy-atom effect on the radiationless decay rate in carbon tetrachloride. Adventitious quenchers could also be responsible. The quenching constants for maleic anhydride were too small for accurate measurement in both the nonaromatic solvents. In carbon tetrachloride the apparent values ranged from 1 to 9.6 with an average value of 5 ± 5. In cyclohexane-acetone the value was 8 ± 5. In the latter medium there can be no doubt that the quenching activity is real, but of an order of magnitude smaller than the activity in benzene.

The results are neatly accommodated by the hypothesis that the effective quencher in benzene solution is

the benzene-maleic anhydride complex.^{19,20} Attempts were made to use the data of Andrews and Keefer¹⁹ for benzene-chloroform mixtures to evaluate the fraction of the anhydride that is in complexed form in neat benzene. The ultraviolet spectra of 1 × 10⁻³ and 2 × 10⁻³ M solutions indicated 42.5 and 51.0% complex, respectively, if the reported value of ε₂₇₀₀ for the complex is used. On the other hand, use of the reported equilibrium constant indicates that the anhydride should be 88% complexed. If the absorbance of the solutions at 2700 Å is taken as a measure of the amount of complex, the value of k_q/k_r for that species is about 130, a factor of 5 smaller than the largest constants that have been measured.^{9,16} If the value of k_d reported by Bell and Linschitz²¹ is used as a reference point, the value of k_q for the complex is calculated to be 4 × 10⁸ l. mole⁻¹ sec⁻¹.

As an ancillary study we measured the reactivity of maleic anhydride as a quencher for acetophenone triplets which have more available excitation energy than benzophenone triplets (73.6 vs. 68.5 kcal/mole). The photoreduction of acetophenone by isopropyl alcohol^{22,23} was used as a reference system. The reaction was carried out in cyclohexane. The quenching constant, k_q/k_r, for maleic anhydride was evaluated by standard procedures. The results scattered more than is usual but the average value was 193 ± 78. The fact that maleic anhydride in an aliphatic solvent is a good quencher for acetophenone triplets is clear from inspection of any of the experiments. This is in agreement with the assignment of the excitation energy of the uncomplexed anhydride as 72 kcal/mole.

The quenching experiments indicate that the excitation energy of the complex is close to that of benzophenone (68 kcal), about 4 kcal lower than that of the uncomplexed anhydride. This indicates that the binding energy of the complex is greater in the excited state than in the ground state. The triplet excitation is probably partly delocalized between the two partners in the complex. Chemical intuition indicates that charge transfer is probably not a principal factor in stabilization of the excited state since the complex excitation is probably much more closely related to excitation of the acceptor (maleic anhydride) than to that of the donor (benzene). Delocalization of singlet excitation in symmetrical systems has recently been discussed extensively in connection with excimer fluorescence.²⁴

Quantum Yields. Preliminary measurements showed that quantum yields in the sensitized reaction increased with increasing maleic anhydride concentration in benzene solution. A series of carefully matched runs were then carried out, giving the results shown in Table III. The results are reported in terms of milligrams of product since measurement of relative quantum yields is more accurate than measurement of absolute quantum yields. Actinometric measurements indicate that the highest quantum yields are approximately 0.1.

(19) L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **75**, 3776 (1953).

(20) W. G. Barb, *Trans. Faraday Soc.*, **49**, 143 (1953).

(21) J. A. Bell and H. Linschitz, *ibid.*, **85**, 528 (1963).

(22) S. G. Cohen, D. A. Laufer, and W. V. Sherman, *ibid.*, **86**, 3060 (1964).

(23) J. N. Pitts, *et al.*, *ibid.*, **81**, 1068 (1959).

(24) See, for example, T. Azumi, A. T. Armstrong, and S. P. McGlynn, *J. Chem. Phys.*, **41**, 3939 (1964).

(16) G. S. Hammond and P. A. Leermakers, *J. Phys. Chem.*, **66**, 1148 (1962).

(17) The constant k_r is the specific rate constant for abstraction of hydrogen from benzhydryl and k_d is the rate constant for radiationless decay by benzophenone triplets.

(18) G. S. Hammond and R. P. Foss, *J. Phys. Chem.*, **68**, 3739 (1964).

Effect of Variation of Maleic Anhydride on Quantum Yields^a

Sensitizer ^b	[MA] ₀ , M	Wt of product, mg ^c		
		Run no. 1	Run no. 2	Run no. 3
none	0.05	8.6 ± 0.2	9.6 ± 0.1	7.5 ± 0.5
	0.10	17.5 ± 1.0	19.5 ± 0.2	15.7 ± 0.5
	0.25			28.4 ± 1.5
	0.50	25.3 ± 4.0	41.6 ± 1.0	31.9 ± 1.0
	1.00	25.0 ± 4.0	47.7 ± 1.5	35.4 ± 1.0
	1.50		49.1 ± 3.0	33.8 ± 3.0
none	0.05	12.3 ± 0.8	11.5 ± 1.0	
	0.10	21.8 ± 0.5	37.0 ± 2.0	
	0.25	25.8 ± 2.0	42.1 ± 1.5	
	0.50	22.0 ± 1.5	45.6 ± 3	
	1.00	28.3 ± 0.5	45.5 ± 3	
	1.50	25.2 ± 3.0	39.5 ± 2	
:	0.05		14.0 ± 1.0	
	0.10		25.4 ± 0.5	
	0.25		31.6 ± 1.0	
	0.50		33.0 ± 1.5	
	1.00		30.0 ± 2.0	
	1.50		25.9 ± 1.0	

liliter samples irradiated using the uranium glass filter ry-go-round apparatus. ^b Concentrations chosen to lly at 3660 Å. ^c Samples having the same run number ted at the same time. Irradiation was continued until :parated from tubes containing 0.05 M anhydride to :rate weighing. The results given are averages of tripli-

ults, especially in experiments with the higher tions of maleic anhydride, are frustratingly A number of factors may contribute, including sition of the crystalline product and scattering / crystals deposited on the walls of the tubes. major source of error must arise from reasons independent of the light intensity delivered to since there were significant variations in the of product collected from duplicate samples y run. However, the general trend of the ems reproducible. The yields increase with : maleic anhydride concentration up to the out 0.25 M and then become constant within s. Absorbance by the different sensitizers ized at 3660 Å and concentrations were high o give essentially complete absorption at that h, although there is some difference in the of the weaker source lines between 3700 and sorbed by the three sensitizers. The data in show that there is only a small dependence of sensitizer concentration, indicating close to absorption of effective incident light and y transfer is not appreciably reversible.

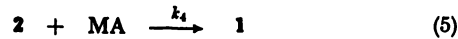
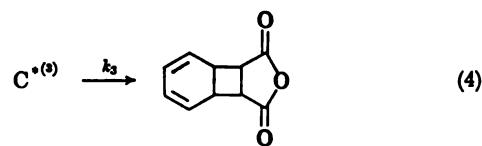
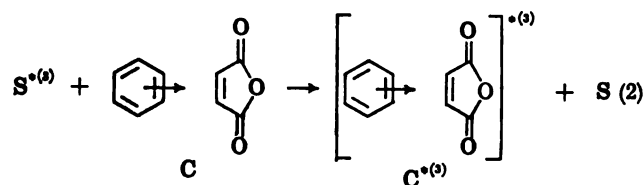
Variation in Yield as a Function of ne Concentration^a

izophenone] ₀ , M	Yield of adduct ^b
0.03	24.9 ± 1.2
0.06	24.2 ± 1.2
0.10	25.4 ± 1.2
0.15	26.1 ± 1.3
0.20	28.3 ± 1.3
0.30	29.1 ± 1.3

ial concentration of maleic anhydride was 1.00 M in all Milligrams of product formed by irradiation of 4-ml escribed in the Experimental Section for 8 hr.

Reduction of the light intensity was accomplished by placing an 80-mesh, stainless-steel screen around the lamp. This reduced the transmission to 32.5% of the unscreened value and reduced the yield to $33 \pm 3\%$ of the value in control experiments. The quantum yield is apparently independent of light intensity.

The concentrations of maleic anhydride were large enough in all experiments to assure quantitative transfer of the triplet excitation of the sensitizers (see Quenching of Triplets above). Consequently dependence of the quantum yield on the concentration of maleic anhydride must be due to competition at some step other than energy transfer. Two likely candidates come to mind: (1) capture of intermediate in a thermal reaction and (2) a two-photon process. The latter possibility is ruled out by the linear response to a change in light intensity. The first possibility is the one that would have been anticipated on the basis of all suggested mechanisms.



The dependence of quantum yields on the concentration of maleic anhydride is attributed to competition between reactions 5 and 6, two thermal processes. The above mechanism, with the assumption that energy transfer (reaction 2) is quantitative, yields the following rate law

$$\Phi = \Phi_{ic} \frac{k_2 k_4 [\text{MA}]}{(k_2 + k_3)(k_4 [\text{MA}] + k_5)} \quad (7)$$

where Φ_{ic} is the quantum yield for intersystem crossing by the sensitizer.

If the data in Table III are averaged and corrected for consumption of the reactant the numbers can be fitted surprisingly well to a function of the form of eq 7. The scatter of the numbers before averaging discourages us from a serious attempt to extract a value of the critical reactivity ratio, k_4/k_5 , from the data although it must be on the order of ten.

The mechanism suggested predicts that the yields should fall off if the concentration of complex is reduced, at constant total maleic anhydride concentration, by dilution of the benzene with a cosolvent. The decrease should become significant when the concentration of the complex becomes small enough to allow radiationless decay of sensitizer triplets to compete with energy transfer. The data for experiments using di-o-xane, chloroform, and acetonitrile as cosolvents are

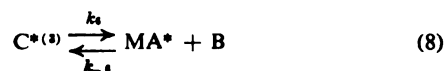
gathered in Table V. The data in the three series cannot be directly cross-compared because the light intensity was different in the three runs.

Table V. Effect of Dilution with Cosolvents^a

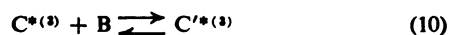
[Benzene] ₀ , M	Dioxane	Yield of product ^b Chloroform	Acetonitrile
1.1	0		
2.3		9.1 ± 0.4	15.0 ± 1.9
3.4	0		
4.5		15.3 ± 0.2	42.1 ± 1.9
5.6	23.2 ± 3		
6.8		19.0 ± 0.5	65.9 ± 1.0
7.9	65.2 ± 4		82.7 ± 3.0
9.0		27.1 ± 1.0	94.3 ± 3.0
10.7	81.8	33.5 ± 1.5	98.9 ± 1.0

^a [Benzophenone] = 0.10 M, [MA]₀ = 1.0 M. ^b Milligrams of product obtained from 3-ml samples irradiated as described in the Experimental Section for 7 hr.

The effect of variation of the concentration of benzene is surprising. If the value of Andrews and Keefer¹⁹ for the dissociation constant is even close to correct, there should be enough of the complex in all solutions to effect complete quenching of benzophenone triplets. Consequently, there must be some reversible interaction with benzene *after* the energy-transfer step. The simplest way that we can see to include such a step is as follows



The excitation energies of the complex and monomeric maleic anhydride inferred from quenching studies (*vide supra*) would indicate that reaction 8 should be endothermic. The small decrease in quantum yield with increasing temperature reported by Angus and Bryce-Smith² may be due to change in the equilibrium constant for reaction 8. Another possibility is that the excited complex is stabilized by interaction with a second molecule of benzene to form a ternary triplet complex.



Formation of such a ternary complex might well be expected to effect unusual stabilization of the excited triplet. McGlynn and his co-workers²⁶ have pointed out that the excited singlet state of a complex should lie lower than the triplet if charge transfer is dominant in the excitation process. With two acceptor molecules in the complex, the triplet should be stabilized. It is even conceivable that the complex responsible for the quenching action is a 2:1 complex in the first place. Andrews and Keefer¹⁹ found no evidence for such a species but their experiments were carried out with diluents and, as was previously mentioned, extrapolation of the spectroscopic properties of the complex as observed in chloroform solution to pure benzene is not very accurate.

(25) S. P. McGlynn and J. D. Boggus, *J. Am. Chem. Soc.*, **80**, 5096 (1958); S. P. McGlynn, J. D. Boggus, and E. Elder, *J. Chem. Phys.*, **32**, 357 (1960).

Attempts to Capture an Intermediate. The proposed intermediate, 2, should be a reactive diene so (unsuccessful) attempts were made to intercept the species with dienophiles. Irradiation of a benzene solution containing 1.0 M maleic anhydride, 2.5 M methyl acrylate, and 0.10 M benzophenone gave only the usual adduct although a viscous yellow oil, probably a polymeric material, was also formed. A toluene solution containing 0.5 M maleic anhydride and 0.05 M benzophenone was irradiated for 15 hr at -77° with the hope that 2 would accumulate. The contents of the tubes were then added quickly to concentrated solutions of tetracyanoethylene. No adducts could be isolated.

Quenching the Unsensitized Reaction. Bryce-Smith and Lodge reported that the unsensitized reaction is not quenched by oxygen.⁵ We irradiated samples sealed under oxygen at a pressure of 1 atm in parallel with degassed samples and found unmistakable evidence for quenching. The results are summarized in Table VI.

Table VI. Quenching of the Unsensitized Reaction by Oxygen

Series	[MA] ₀ ^a	Percentage of reaction quenched ^b
1	2.00	23 ± 5
2	1.50	20 ± 7
3	0.20	31 ± 7

^a Benzene solution. ^b Average results obtained from irradiation in parallel of five samples under oxygen and five degassed samples.

The effect is small but unmistakable. Other common quenchers, such as anthracene and azulene, were also tried but because of competitive absorption could not be used at concentrations greater than 5×10^{-4} M. Although some quenching was probably observed, the effect was not clearly outside the limits of experimental error. If the saturation solubility of oxygen in toluene is similar to that in benzene,²⁶ the oxygen concentration was about 5×10^{-3} M. Since quenching was observed, the rate constants for competitive reactions, including collapse to 2, must be of the order of 5×10^7 moles l.⁻¹ sec.⁻¹.

The experiment has considerable significance since it indicates that at least part of the unsensitized reaction goes by way of triplets. Since it is not feasible to do studies involving varying concentrations of a quencher, we cannot be sure that the triplet path is the only one.²⁷

Experimental Section

Materials. Acetonaphthone (Matheson Coleman and Bell, reagent grade) was recrystallized from acetic acid-water, mp 54.0°. Anthroquinone was recrystallized twice from acetic acid, mp 284–285°. Benzene (Matheson Coleman and Bell, Spectro quality) was generally used without purification. The material did not give a color on contact with sulfuric acid and less than 0.1% impurities was found by vapor chromatography. Benzaldehyde (Matheson Coleman and Bell, reagent grade) was distilled twice, the second

(26) M. Reznikovskii, Z. Tarasova, and B. Dogadkin, *Zh. Obshch. Khim.* **20**, 63 (1950); *Chem. Abstr.*, **44**, 4754 (1950).

(27) NOTE ADDED IN PROOF. We now find that maleic anhydride is an efficient quencher of the fluorescence of triphenylene and naphthalene (see ref 1 for similar observations). Consequently the significance of inhibition by those compounds (Table I) should be reevaluated. This removes the apparent anomaly presented by the cases of triphenylene and *p*-cyanobenzophenone. An attempt to reproduce the spectrum shown in Figure 1, with a less sensitive instrument, gave no resolvable emission so we cannot be entirely certain that the original result was not due to the presence of an impurity.

time through a spinning-band column, bp 65° (25 mm). Benzil (Matheson Coleman and Bell, reagent grade) was recrystallized from ethanol-water and then from ligroin, mp 96.5–96.8°. Chloroform (Matheson Coleman and Bell, Spectro quality) was used without further purification. Chrysene, recrystallized and sublimed, was supplied by Dr. J. R. Fox. *p*-Cyanobenzophenone was obtained from Dr. C.-H. Wu; it was recrystallized from ligroin-benzene, mp 115.5–116°. *p*-Diacetylbenzene (Aldrich, research grade) had been chromatographed on alumina and then recrystallized twice by Dr. A. A. Lamola. 4,4'-Dichlorobenzophenone (K and K Laboratories) was used without further purification; its phosphorescence spectrum was taken by Dr. A. A. Lamola and showed no trace of benzophenone. Fluorenone (Matheson Coleman and Bell, reagent grade) was recrystallized once from ligroin and once from ethanol, mp 83.8–84.5°. Maleic anhydride (Matheson Coleman and Bell, reagent grade) was sublimed at 45° (0.5 mm) immediately before use. Naphthalene (Matheson Coleman and Bell) was recrystallized twice from ethanol. Propiophenone (Matheson Coleman and Bell, reagent grade) was recrystallized from ligroin at –5° and then distilled at 0.5 mm through a Vigreux column; the fraction boiling at 63–64° was collected for use. Tetracyanoethylene (Aldrich, research grade) was recrystallized from ethyl acetate-chloroform. Thioxanthone was treated with carbon black and then recrystallized twice from methanol, mp 209°. Toluene (Matheson Coleman and Bell reagent grade) was shaken three times with concentrated sulfuric acid, dried over calcium chloride, and distilled from sodium. Triphenylene (Aldrich, research grade) was sublimed, mp 194–198°. Xanthone (Aldrich) was passed through an alumina column, eluted with benzene, and then recrystallized twice from methanol.

Procedures. Most irradiations were carried out in the "merry-go-round," an apparatus in which a number of tubes are rotated

about a Hanovia immersion reactor containing a 450-w, medium-pressure lamp. The entire apparatus is placed in a constant-temperature water bath. The samples were placed in Pyrex culture tubes (13 mm o.d.) which had been constricted. The tubes were washed with Orvus soap, rinsed five times with distilled water and once with methanol, and dried at 125°. Solutions were prepared in volumetric flasks and 3- or 4-ml aliquots were added to the individual tubes. The samples were then degassed using three freeze-thaw cycles, with pumping at 5×10^{-4} mm, before being sealed off. The Pyrex tubes passed very little of the 2753- and 2804-Å lines from the source and in most experiments with sensitizers a uranum-glass filter having virtually no transmission below 3300 Å was used. No filter was used in experiments involving direct irradiation.

After irradiation the tubes were opened and the product was collected by suction filtration, washed with a few milliliters of cold reaction solvent, dried for 20 min at 115°, and weighed. The solubility of the adduct in all reaction solvents is too low for convenient measurement. However, varying amounts of product may have remained in the supernatant liquid by supersaturation, since crystal growth is very slow.

Some measurements of quantum yields were made using the collimated beam provided by the apparatus previously described.⁹ Actinometry for runs with both systems was carried out by monitoring the reaction of benzophenone by benzhydrol.⁹

Acknowledgment. This work was supported in part by a grant from the National Science Foundation. W. M. H. also held summer fellowships provided by the Shell Oil Company and the National Science Foundation.

Radical Additions of Cl-CCl_3 to *cis*-Cyclooctene^{1,2}

James G. Traynham and Thomas M. Couvillon

Contribution from Coates Chemical Laboratories, Louisiana State University, Baton Rouge, Louisiana 70803. Received January 11, 1967

Abstract: Both photo- and thermally initiated additions of carbon tetrachloride to *cis*-cyclooctene give mainly stereoisomeric 1-chloro-4-(trichloromethyl)cyclooctanes, products of transannular addition. Small amounts of the stereoisomeric 1,2-addition products and several other minor products containing less chlorine per molecule are also formed. Peroxide-initiated addition of trichloromethanesulfonyl chloride (net addition of Cl-CCl_3) produces the 1,2- and 1,4-addition products in the ratio 30:70. The activation energy requirement for transannular hydrogen atom shift in this system is estimated to be approximately 18 kcal/mole. Selective dehydrochlorinations of the addition products have been achieved; potassium hydroxide in alcoholic dimethyl sulfoxide produces mostly chloro-(dichloromethylene)cyclooctanes, but alcoholic silver nitrate leads to (trichloromethyl)cyclooctenes.

Transannular hydride shifts during cationic reactions of medium-ring compounds were first reported in 1952³ and are now considered to be characteristic of those compounds.⁴ Although these rearrangements occur to small extents in unsubstituted cycloalkyl cations,

they become extensive when the initial carbonium ion center is flanked by an electron-withdrawing substituent.⁴ Examples of transannular reactions involving radical intermediates have been far fewer in number than those involving cationic intermediates. Some⁵ but not all⁶ radical additions to 1,5-cyclooctadiene yield mostly substituted bicyclo[3.3.0]octanes as products (transannular C=C participation), and thiol addition to norbornadiene gives both normal and transannular products.⁷ Recently, reports of transannular hydrogen abstraction by the intermediate alkoxy radical formed during decomposition of 1-methylcyclooctyl hypochlorite⁸ and transannular hydrogen migration to a

(1) (a) Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965; Abstracts, p 6S. (b) Based upon the Ph.D. dissertation submitted by T. M. C., Louisiana State University, Jan 1966. (c) A preliminary account of part of this research has been published: J. G. Traynham and T. M. Couvillon, *J. Am. Chem. Soc.*, **87**, 5806 (1965).

(2) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (Grant No. 1817-A.)

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(4) (a) V. Prelog and J. G. Traynham in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1963, Chapter 9; (b) A. C. Cope, M. M. Martin, and M. A. McKerver, *Quart. Rev. (London)*, **20**, 119 (1966).

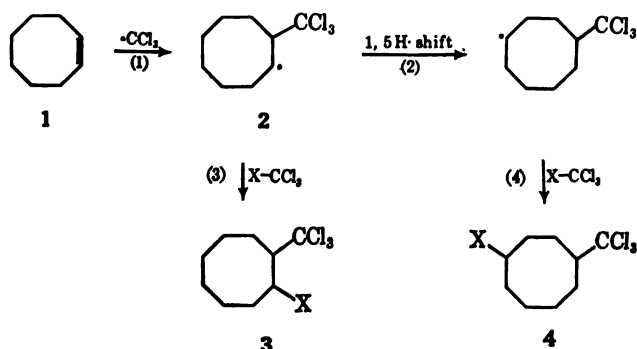
(5) R. Dowbenko, *J. Am. Chem. Soc.*, **86**, 946 (1964).

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(7) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Am. Chem. Soc.*, **80**, 635 (1958).

(8) A. C. Cope, R. S. Bly, M. M. Martin, and R. C. Petterson, *ibid* **87**, 3111 (1965).

carbon radical center during radical additions to medium-ring olefins⁹ have been reported. Only the latter rearrangement is directly comparable to the hydride shifts characteristic of medium-ring carbonium ion chemistry, and when those reports⁹ appeared, our own investigations of radical additions to the simple medium-ring olefin, *cis*-cyclooctene, were substantially complete.^{1a} We have described in detail the largely normal 1,2 addition of bromotrichloromethane to *cis*-cyclooctene.^{1c,10} This paper describes our radical additions of Cl-CCl_3 (from carbon tetrachloride and from trichloromethanesulfonyl chloride) to *cis*-cyclooctene.^{1c} These reactions are mainly transannular additions (product 4), and a rough estimate of the activation energy for transannular hydrogen atom shift in 2-(trichloromethyl)cyclooctyl radical (2) has been made.



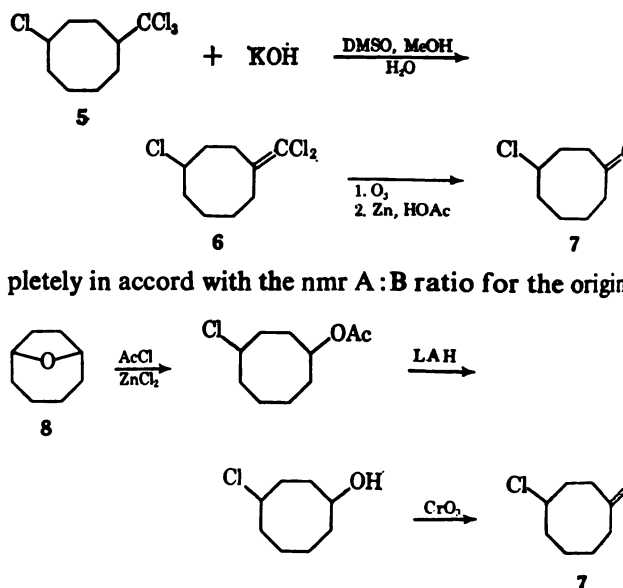
Additions of carbon tetrachloride to 1 have been carried out in different ways: photo- and thermally initiated reactions in the absence of any solvent other than excess carbon tetrachloride, and photoinitiated reaction with benzene solvent. Although the addition of benzene to the reaction mixture led to a higher conversion of cyclooctene to products and to less polymer formation, the over-all results of the three kinds of additions were substantially the same. The principal products were isomeric $\text{C}_8\text{H}_{14}\text{Cl}_4$ compounds, formed in yields of 59–71%; several minor products containing 1–3 chlorines per 8–9 carbons were obtained in combined yields of about 24–15%. Some hexachloroethane was isolated in each of the addition experiments, confirming the radical nature of the reactions.

Major Products. In contrast to a patent claim that the thermal addition of carbon tetrachloride to cyclooctene gives 1,2-addition product 3,¹¹ our product mixtures from both kinds of additions consisted primarily of *cis*- and *trans*-1-chloro-4-trichloromethylcyclooctanes (4, $\text{X} = \text{Cl}$). This identity was established on the basis of nmr spectra, selective dehydrochlorinations, and conversion to 4-chlorocyclooctanone identical with an authentic sample.

The ratio of the areas of the nmr signals centered near -2.2 ppm (A) and -1.65 ppm (B)¹² is especially valuable for structure assignments in cycloalkane derivatives. The signals near -2.2 ppm (A) are associated with CH_2CX ($\text{X} = \text{electron-withdrawing substituent}$

such as Cl or CCl_3) or with $\text{CH}_2\text{C}=\text{C}$, and those near -1.65 ppm (B) with more remote CH_2 . For a 1,2-disubstituted cyclooctane such as 3, the ratio A:B is 4:8;¹⁰ for a 1,3 isomer, the ratio is 6:6, and for 1,4 and 1,5 isomers, it is 8:4.¹³ The major fraction, $\text{C}_8\text{H}_{14}\text{Cl}_4$, from each of the CCl_4 additions gave an A:B ratio of nearly 8:4, clearly excluding normal 1,2 addition. That fraction, separated from lower boiling reaction products by careful distillations, was further separated into solid and liquid isomers by low-temperature fractional crystallization from methanol. The nmr spectra of these isomers are similar, and each exhibits an A:B ratio of about 8:4. The infrared spectra of the isomers are nearly the same but differ sufficiently at $10\text{--}11\ \mu$ for quantitative analysis. By comparison of the infrared spectra of the original $\text{C}_8\text{H}_{14}\text{Cl}_4$ product mixtures and standard mixtures prepared from the separated isomers, the original mixtures were estimated to consist of about 30% solid and 70% liquid isomers.¹⁴

When either the liquid or the solid isomer, or a mixture of them, was dehydrochlorinated with 1 molar equiv of potassium hydroxide in a mixed solvent, the same olefin, identified by infrared and nmr spectra as a chloro(dichloromethylene)cyclooctane, was produced. This result clearly identifies the solid and liquid isomers as geometrical, not position, isomers. Further identification of the olefin product as 1-chloro-4-(dichloromethylene)cyclooctane (6) was accomplished by ozonolysis of it to 4-chlorocyclooctanone, an authentic sample of which was synthesized independently from 9-oxabicyclo[4.2.1]nonane (8). This identification is com-



pletely in accord with the nmr A:B ratio for the original

$\text{C}_8\text{H}_{14}\text{Cl}_4$ products and establishes that the radical addition of CCl_4 to cyclooctene proceeds mainly to give 5 (*cis* and *trans*).¹⁵

Bromotrichloromethane, on the other hand, adds equally exclusively to give *cis*- and *trans*-1-bromo-2-trichloromethylcyclooctane (3, $\text{X} = \text{Br}$).¹⁰ Clearly the relative activation free energy requirements of the

(9) (a) M. Fisch and G. Ourisson, *Chem. Commun.*, 407 (1965); (b) G. Ourisson, *Proc. Chem. Soc.*, 281 (1964).

(10) J. G. Traynham, T. M. Couvillon, and N. S. Bhacca, *J. Org. Chem.*, 32, 529 (1967).

(11) F. Reicheneder and H. Suter, German Patent 1,036,847 (Aug 21, 1958); *Chem. Abstr.*, 54, 22416c (1960). Our experiments duplicated the reaction conditions described here as closely as possible.


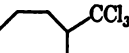

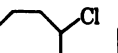
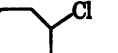
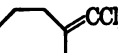



(12) All chemical shifts are relative to internal tetramethylsilane reference.

(13) Analytical use of nmr signal ratios similar to A:B has been described independently by C. L. McGehee and C. H. Sommers in "Developments in Applied Spectroscopy," Vol. 4, E. N. Davis, Ed., Plenum Press, New York, N. Y., 1965, p 405.

(14) The liquid fractions were subsequently shown to contain about 2–5% of the 1,2 isomer along with the 1,4 isomer.

(15) We have not yet firmly matched the labels *cis* and *trans* with the descriptions *solid* and *liquid* for isomeric 5.

Product Distribution Data for CCl_4 Additions to *cis*-Cyclooctene

											
	9	10	11	12	13	14	15	16			
	Yield, mole %										
itions ^a	5s ^d	5l ^d	9 ^b	10	11	12	13	14	15	16	17 ^c
initiated	26	41	3.8	0.7	0.6	1.3	2.6	3.4	5.0	0.07	3.0
ally	20	38	1.2	0.9	8.2	1.2	0.36	8.0	0.3	0.07	5.1
ited											
initiated in	22	46	5.0	0.13	1.1	1.7	5.1	1.5	0.9	0.9	3.3
ene solution											
2Cl	19	37	25	0.05	0.16	1.0	1.3	1.0	0.08	0.08	4.3
tion											

Experimental Section for details. ^b Both *cis* and *trans* isomers were obtained. ^c Other unidentified products. These figures exclude polymer and undistillable material. ^d 5s = solid isomer, 5l = liquid isomer.

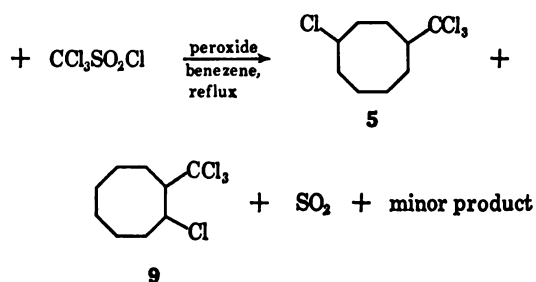
the reactions of intermediate 2-(trichloromethyl)-cyclooctyl radicals (2), steps 2 and 3, determine the course of the overall reaction. Abstraction of chlorine from tetrachloride requires more energy than abstraction of bromine from bromotrichloromethane. An allylic reagent with a radical chain transfer constant less than those for $\text{Cl}-\text{CCl}_3$ and $\text{Br}-\text{CCl}_3$ ¹⁶ would be expected to give more nearly equal amounts of products corresponding to 3 and 4.

Peroxide initiated addition of trichlorosulfonyl chloride¹⁶ to 1 gave an 81% yield of 1,2-dichloro-1-(trichloromethyl)cyclooctane product which was found by gas chromatography and nmr and infrared spectroscopic analyses to be 70% 5 (67% liquid and 33% solid isomers) and 30% 9. The nmr spectrum of the 1,2 isomer shows the expected A:B ratio of 4:8 and includes two signals for HCCl , separated by 18 cps and each

Once the gas chromatography retention time and spectra for the 1,2-isomer mixture were at hand, careful reexamination of the data for the liquid 1,4 isomer from each CCl_4 addition revealed that it was contaminated by small amounts of 9 (2% from thermal addition, 5–7% from photoinitiated additions).

The yields of the major products (as well as the yields of the minor products described in the next section) obtained from the four additions to 1 are summarized in Table I.

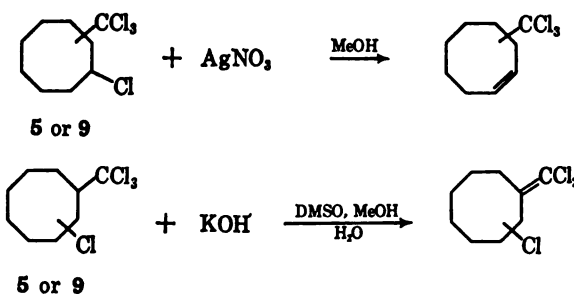
In addition to the dehydrochlorination which established the geometrical isomerism of solid and liquid 5, other selective dehydrochlorinations were carried out with both 5 and 9. When dehydrochlorination is effected by alcoholic silver nitrate, a (trichloromethyl)cyclooctene is the major product formed from both 5 and 9, but with potassium hydroxide in mixed solvent a chloro(dichloromethylene)cyclooctane is the major one (different olefins from 5 and 9). When mixtures of 5 and 9 were used with limited amounts of dehydrochlorinating reagent, 9 was consumed the more rapidly



is due to one H. These signals are virtually identical to those for the 1-bromo-2-trichloromethylcyclooctane (3, X = Br) obtained from BrCCl_3 addition;¹⁰ in experiments with that product identified as a 1:1 mixture of *cis* and *trans* isomers.¹⁰ Because of the correspondence of the spectra for 9 and 3 (X = Cl) we conclude that 9 is also a 1:1 mixture of geometrical isomers (which was not resolved by gas chromatography).

This unexpected composition is apparently completely independent of the reagent (BrCCl_3 or CCl_4) involved in the product-forming step.

C. Walling, "Free Radicals in Solution," John Wiley and Sons, New York, N. Y., 1957, pp 95, 157. The chain-transfer constant for $\text{CCl}_3\text{SO}_2\text{Cl}$ is not accurately known but is apparently between values for BrCCl_3 and CCl_4 . (b) The relative ease of chain transfer by $\text{CCl}_3\text{SO}_2\text{Cl}$ and CCl_4 is illustrated by the report that a 1:1 product is formed from $\text{CCl}_3\text{SO}_2\text{Cl}$ and styrene, but only low weight polymers are obtained with CCl_4 and styrene: E. C. L. Y. Kily, U. S. Patent 2,606,213 (Aug 5, 1962); *Chem. Abstr.*, 6440h (1962).



by potassium hydroxide, but 5 was consumed the more rapidly by silver nitrate. The differences in rates of reactions are apparently sufficiently large to offer promise for purification of one isomer at the expense of the other.

Minor Products. Several chlorine-containing products boiling lower than the $\text{C}_8\text{H}_{14}\text{Cl}_4$ isomers were obtained in very small amounts in each addition reaction. Although there were some differences among the four additions, the general picture for these minor products was consistent. These products were identified primarily by comparison of spectra and gas chromatography retention times with those of authentic samples (see Experimental Section for details). The product distribution data are summarized in Table I.

All of these products can be written as products of conventional radical reactions involving cyclooctene, CCl_4 , and derived radical intermediates. The similarity of distribution among the four additions is not particularly helpful for considerations of mechanism details. Chlorocyclooctane is formed in significantly higher yield in the thermal addition than in the others, however, and this difference may stem from the fact that by-product HCl (which can add to 1) was trapped in the sealed apparatus used for thermal addition but was lost by continuous nitrogen sweep in the others.

The extent to which allylic hydrogen abstraction accompanies addition of $\cdot\text{CCl}_3$ to cyclooctene is small (2–9% with CCl_4 , 1% with $\text{CCl}_3\text{SO}_2\text{Cl}$). By contrast, radical reaction of CCl_4 with cyclohexene gives about equal amounts of addition and hydrogen abstraction.¹⁷ Since the transition state for $\cdot\text{CCl}_3$ addition presumably resembles reactants while that for hydrogen abstraction is more like products,¹⁸ the low extent of hydrogen abstraction from cyclooctene may signal relatively poor allylic stabilization for 2-cyclooctenyl radical compared to 2-cyclohexenyl radical.¹⁹

In connection with identification of one of the minor products, chloroform was added under radical conditions (photoinitiation) to cyclooctene with low conversion. The expected product,²⁰ (trichloromethyl)cyclooctane, was formed in about 20% yield and accompanied by chlorocyclooctane (10%) and (dichloromethyl)cyclooctane (41%). The predominance of this last product in the mixture is unexpected on the basis of previous reports of chloroform additions to olefins,²⁰ and we plan to investigate such additions further.

Energy Considerations. The driving force for the transannular rearrangement of 2 is the destabilization of a radical center by neighboring trichloromethyl substituent. This destabilization, which is relieved by the rearrangement, is estimated to amount to more than 3.5–4.0 kcal/mole. A tertiary radical is more stable than a secondary one by about that amount,²¹ and rearrangement of the tertiary 1-(2,2,2-trichloroethyl)cyclodecyl radical to a secondary one has been reported.²²

The relative extents of transannular and vicinal radical addition depend on addend, temperature, and relative concentrations of cyclooctene and addend. The intermediate 2-substituted cyclooctyl radical is trapped effectively by good chain-transfer agents such as chlorine and bromotrichloromethane but not by carbon tetrachloride. The ratio of transannular 3 to vicinal 4 products was 17:1 for CCl_4 addition and about 1:34 for BrCCl_3 addition (addend:olefin molar ratio 4:1). These ratios lead to a calculated ratio of rate constants for bromine abstraction (from BrCCl_3) and for chlorine abstraction (from ClCCl_3) by 2-(trichloromethyl)cyclooctyl radical of 578:1, and the corresponding difference in free-energy change ($\Delta\Delta G^\ddagger$) is 4.04 kcal/mole ($T =$

317°K). The entropies of activation for the two processes should be quite similar except for the difference in symmetry numbers of CCl_4 (12) and BrCCl_3 (4), and ΔE_a is calculated to be about 5.5 kcal/mole. This amount of energy, 5.5 kcal/mole, is about 29% of the difference in bond energies (19 kcal/mole²¹) of the Cl-CCl_3 and Br-CCl_3 bonds being broken in the two processes.²² The well-known Hirschfelder rule predicts that the activation energies for a series of similar exothermic radical-abstraction reactions should be proportional to the bond-dissociation energy of the bond being broken.²³ If the proportionality is extended for reactions of 2-(trichloromethyl)cyclooctyl radical to include not only halogen abstraction from X-CCl_3 but also (intramolecular) transannular hydrogen abstraction, ΔE_a for hydrogen and chlorine abstractions is estimated to be about 5.8 kcal/mole (0.29×20^{21b}). Data for a good model of radical transfer involving 2 are not available, but activation energies for Cl-CCl_3 abstractions by polystyrene and poly(methyl acrylate) radicals are 12.3 and 13.3 kcal/mole, respectively.^{16a} Using these energies as an approximation of E_a for 2 reacting with CCl_4 , we estimate that E_a for transannular hydrogen abstraction in this system is about 18–19 kcal/mole.^{24–27}

Although the amount of 4 from Cl-CCl_3 addition is small under any circumstances, the ratio of 4:3 is smaller at 150° (1:99) than at 44° (1:17), indicating that the transannular hydrogen migration does indeed have the higher activation energy.

Experimental Section

Gas chromatographic analyses were obtained with a Barber-Colman Model 20 instrument equipped with a hydrogen flame detector and a 100-ft capillary column coated with SE-96 silicone. Preparative gas chromatography was performed with a Wilkens Aerograph Autoprep Model A-700 instrument equipped with a $\frac{1}{8}$ in. \times 20 ft silicone column. Nmr spectra were obtained with the assistance of Mr. R. Seab and Mr. W. Wegner on a Varian Associates HA-60 spectrometer, and all chemical shifts cited refer to tetramethylsilane as internal reference. Infrared spectra were obtained with Beckman IR-5 and IR-7 and Perkin-Elmer Models 21 and 137 instruments. Capillary melting points were obtained with a Thomas-Hoover apparatus and are uncorrected. Element microanalyses were performed by Mr. R. Seab in these laboratories.

(22) The activation energies for few chain-transfer reactions are accurately known.^{16a}

(23) J. O. Hirschfelder, *J. Chem. Phys.*, **9**, 645 (1941).

(24) This estimate depends importantly on the proportions of products 3 and 4 from the additions of Br-CCl_3 and CCl_4 . The proportions we report were obtained in several experiments, and product ratios outside what we consider reasonable limits of experimental error do not drastically change the estimated activation energy for transannular hydrogen abstraction. For example, even if the ratio of 3:4 from CCl_4 addition were actually 9:1 and that from BrCCl_3 addition were actually 1:9, the same kind of calculation leads to an estimate of 17 kcal/mole for hydrogen abstraction.

(25) H. S. Johnson and C. Parr, *J. Am. Chem. Soc.*, **85**, 2544 (1963), have calculated that the potential activation energy for hydrogen transfer between Me_2CH_2 and Me_2CH is 12 kcal/mole. This calculated energy however is slightly lower than the apparent activation energy for chlorine abstraction from CCl_4 by polystyryl radical^{16a,23} and would be inconsistent with the product distribution data from our experiments.

(26) The activation energy for transannular hydride transfer between oxygenated carbons ($\text{O-C-H} \cdots \text{C=O}$) in the seven-membered ring of a dihydropleiadene has very recently been estimated to be about 24 kcal/mole: private communication from Professor P. T. Lansbury, Sept 1966. See P. T. Lansbury and F. D. Saeva, *J. Am. Chem. Soc.*, **89**, 1890 (1967).

(27) The activation energy (E_a) for transannular hydrogen abstraction is higher than E_a for halogen abstraction from XCCl_3 by the 2-(trichloromethyl)cyclooctyl radical, but because of the more favorable entropy of activation for the unimolecular (transannular) reaction, the free energy of activation (ΔG^\ddagger) for the hydrogen-abstraction process is in between those for the two bimolecular, halogen-abstraction reactions.

(17) (a) E. C. Kooyman and E. Farenhorst, *Rec. Trav. Chim.*, **70**, 867 (1951); (b) S. Isralashvili and J. Shabatay, *J. Chem. Soc.*, 3261 (1951); (c) ref 16a, p 261; (d) E. S. Huyser, *J. Org. Chem.*, **26**, 326 (1961).

(18) M. M. Martin and G. J. Gleicher, *J. Am. Chem. Soc.*, **86**, 242 (1964).

(19) Addition to cyclooctene is apparently favorable, however. In a preliminary study of relative rates by competitive reactions, cyclooctene was consumed by $\cdot\text{CCl}_3$ 1.8 times as rapidly as cyclohexene: unpublished experiments by D. B. Stone.

(20) C. Walling and E. S. Huyser, *Org. Reactions*, **13**, 91 (1963).

(21) (a) Reference 16a, p 51; (b) J. A. Kerr, *Chem. Rev.*, **66**, 496 (1966).

Initiated Addition of CCl_4 . A solution of freshly distilled cyclooctene (75 g, 0.68 mole) in carbon tetrachloride (75 g, 0.68 moles) was placed in a 500-ml quartz flask, deoxygenated with gas stream for 10 min, suspended in a Rayonet photochemical reactor, and irradiated with 2537-A light for a total of 40 hr. An atmosphere of nitrogen was maintained over the reaction mixture during irradiation, and a cooling fan in the reactor kept the mixture at 44° . After 20 hr, irradiation was interrupted so that the flask, which had become coated with a dark polymeric material, could be cleaned. The reaction mixture was returned to the flask, with nitrogen for 5 min, and irradiated for another 20 hr. The solution was concentrated on a rotary evaporator and then distilled at reduced pressure. Besides recovered cyclooctene (8 g), there were obtained 18.5 g of low-boiling products containing chlorine (fraction A) and 124 g (72%) of 1:1 addition product, bp $97\text{--}116^\circ$ (0.2 mm) (fraction B).

l. Calcd for $\text{C}_8\text{H}_{14}\text{Cl}_4$: C, 40.95; H, 5.34. Found: C, 41.5; H, 5.75.

Portion of the distillate fraction B was dissolved in twice its volume of absolute methanol and chilled to -60° . The solid that separated was collected and recrystallized three times from methanol (-10 to -30°), mp $64\text{--}65.5^\circ$. It was subsequently recrystallized as 1-chloro-4-(trichloromethyl)cyclooctane, 5s.

l. Calcd for $\text{C}_8\text{H}_{14}\text{Cl}_4$: C, 40.95; H, 5.34. Found: C, 41.7; H, 5.78.

The liquid remaining from the crystallizations was distilled at 10 mm pressure to give a liquid isomer of the solid product, bp 10° (2 mm).

l. Calcd for $\text{C}_8\text{H}_{14}\text{Cl}_4$: C, 40.95; H, 5.34. Found: C, 41.5; H, 5.58.

The proportions of solid and liquid $\text{C}_8\text{H}_{14}\text{Cl}_4$ products isolated were 36% liquid:64% solid. The infrared spectra of both fractions exhibit strong absorptions for CCl_2 ($12.8\text{--}13.5\ \mu$) and absorptions for C—Cl ($14.9\ \mu$ for solid, $14.81\ \mu$ for liquid). The spectra differ primarily in the relative intensities of peaks in the $10\text{--}12\ \mu$ region. Two absorption peaks proved useful for quantitative analysis: $10.2\ (\text{liquid})$ and $10.5\ \mu$ (solid). A plot of mole fraction of liquid isomer vs. the ratio of absorbance ($A_{10.2}/A_{10.5}$) of standard mixtures prepared from the separated solid and liquid products was a smooth curve. The ratio of absorbance for the unseparated distillate B corresponded to 64% liquid:36% solid products (5l and 5s, respectively).

Gas chromatography indicated that the liquid product contained isomeric products, the major one (92%) being subsequently recrystallized as 1-chloro-4-(trichloromethyl)cyclooctane (5l) and the minor one (8%) as 1-chloro-2-(trichloromethyl)cyclooctane (9). Relative amounts of the three isomeric 1:1 addition products were 6% 5s, 58.5% 5l, and 5.5% 9.

The reaction was carried out with a solution of *cis*-cyclooctene (0.25 mole), carbon tetrachloride (3.2 moles), and benzene (100 ml). Little dark polymer was formed, the irradiation was not interrupted during 41 hr, and the conversion of cyclooctene to products was 93%. Product distribution nearly duplicated that obtained without benzene solvent. The yield of 1:1 addition product was 73%, and the distribution among the three isomers was 5% 5s, 63% 5l, and 7% 9.

Photochemically Initiated Addition of CCl_4 . A mixture of *cis*-cyclooctene (61 g, 0.55 mole) and carbon tetrachloride (470 g, 3.1 moles) was placed in a Parr medium-pressure apparatus at 155° for 4.5 hr at 1000 psig. The mixture was concentrated on a rotary evaporator and distilled at reduced pressure. After a low-boiling product (15.1 g, 30– 108° (1.4 mm)) had been collected, the major product, consisting of isomeric $\text{C}_8\text{H}_{14}\text{Cl}_4$ compounds, was obtained; bp $108\text{--}130^\circ$ (1.4 mm). Infrared analysis (see above) of the fraction indicated that it consisted of 67% liquid and 33% solid products, which were subsequently separated by crystallization from methanol. The solid obtained was identical with that obtained from the photochemical experiments (mp $64\text{--}65.5^\circ$; literature melting point showed no depression). A gas chromatogram of the liquid portion indicated the presence of a small amount of isomer 2. The distribution of the three isomeric 1:1 addition products was 33% 5s, 65% 5l, and 2% 9.

Purification of 1:1 Addition Products. Nmr Spectra. The nmr spectrum of the liquid portion of the major product from the additions consisted of multiplets centered near -4.23 ppm (equivalent to one proton, HCCl), -2.6 ppm (1 H, HCCCl_2), 1.7 ppm (7.5 H, CH_2CCl and CH_2CCl_2), and -1.65 ppm (4.5 H, I_2CH_2).²⁹ The nmr spectrum of the solid isomer isolated

consisted of multiplets centered near -4.20 ppm (1 H, HCCl), -2.75 (1 H, HCCCl_2), -2.2 ppm (8 H, CH_2CCl and CH_2CCCl_2), and -1.65 ppm (4 H, $\text{CH}_2\text{CH}_2\text{CH}_2$). These spectra exclude 1,2-addition products 9, which would give a signal at -1.65 ppm equivalent to 8 H, and one at about -2.2 ppm, equivalent to 4 H, exactly opposite to those obtained here. The fractional equivalence of these two signals for the liquid fraction is consistent with the gas chromatographic analysis, indicating contamination by a small amount of the 1,2 isomer.

Dehydrochlorination with KOH. A solution of the mixed 1:1 addition product (50 g, 0.19 mole) in DMSO (120 ml), methanol (35 ml), and water (5 ml) was added to a solution of potassium hydroxide (0.20 mole), water (10 ml), methanol (25 ml), and DMSO (25 ml). The mixture was stirred at 28° for 5 hr, methanol (50 ml) was added to obtain a homogeneous solution, and the solution was stirred for 3 hr more. It was poured into 300 ml of water and extracted with four 150-ml portions of petroleum ether. The combined organic material was washed thoroughly with water and concentrated by rotary evaporation. Gas chromatography indicated that some $\text{C}_8\text{H}_{14}\text{Cl}_4$ remained, but nearly all (about 82%) had been converted to a single olefinic product with detectable amounts of other products. Distillation gave a center cut at bp $121\text{--}123^\circ$ (3.5 mm).

Anal. Calcd for $\text{C}_8\text{H}_{14}\text{Cl}_2$: C, 47.50; H, 5.76. Found: C, 47.53; H, 5.73.

The infrared and nmr spectra of the product were devoid of absorptions for olefinic hydrogens. The infrared spectrum did include intense absorptions for $\text{C}=\text{CCl}_2$ (6.23 and $11.1\ \mu$) but none for CCl_2 . The nmr spectrum included a quintet ($J = 5.5$ cps) at -4.1 ppm (1 H, HCCl) whose resolution was better at 60° than at room temperature. These data indicate that the dehydrochlorination product is a chloro(dichloromethylene)cyclooctane. The same product was obtained in approximately equal yields from equivalent but smaller scale dehydrochlorinations of the separated solid and liquid fractions.²⁹

Ozonolysis of 6. Ozone (52 mmoles, about 5% in a stream of oxygen from a Welsbach T-23 ozonator) was passed during 5 hr into an ice-chilled CCl_4 solution of the chloro(dichloromethylene)cyclooctane (6, 10.0 g, 44 mmoles). The saturated solution was then allowed to stand for several hours at 0° before the solvent was removed on a rotary evaporator (temperature kept below 45°). The gummy residue was dissolved in 100 ml of acetic acid and reduced by the gradual addition at room temperature of powdered zinc (6.5 g) with vigorous stirring. The mixture was diluted with 200 ml of water and extracted three times with petroleum ether. The combined organic material was washed with water and sodium bicarbonate solution, dried, and concentrated. Gas chromatographic analysis indicated some starting olefin (varying amounts up to 30% in different experiments) together with the ozonolysis products. (In some experiments, the reaction mixture was separated by reduced pressure distillation; in others, it was examined directly by infrared spectroscopy and derivatization.) The ozonolysis mixture consisted of a minor product, a cyclooctenone (not conjugated, λ_{max} $1705\ \text{cm}^{-1}$), and a chlorocyclooctanone, the major product. The chlorocyclooctanone exhibited intense infrared absorption at $1706\ \text{cm}^{-1}$, clearly excluding 2-chlorocyclooctanone ($\text{C}=\text{O}$ at 1714 and $1725\ \text{cm}^{-1}$).³⁰ The 2,4-dinitrophenylhydrazone was recrystallized three times from 95% ethyl alcohol, mp $150\text{--}152^\circ$. The infrared spectrum and melting point of this derivative were identical with those of the 2,4-dinitrophenylhydrazone of authentic 4-chlorocyclooctanone (synthesis described below).

Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_4\text{O}_4\text{Cl}$: C, 49.34; H, 5.03. Found: C, 49.42; H, 5.54.

Independent Synthesis of 4-Chlorocyclooctanone (7). Addition of a small amount of zinc chloride (about 0.5 g) to a mixture of 9-oxabicyclo[4.2.1]nonane (8)^{31,32} (2.6 g, 18 mmoles) and acetyl

(29) Dehydrochlorinations with potassium hydroxide in aqueous ethanol or methanol were slow and gave complex mixtures of products. Potassium *t*-butoxide in DMSO gave a rapid, exothermic reaction which also led to a complex mixture of products. These product mixtures, which were unhelpful for structure identification, contained about 15–20% of the chloro(dichloromethylene)cyclooctane.

(30) C. Castinel, G. Chiurdoglu, M. L. Josien, J. Lascombe, and E. Vananduyt, *Bull. Soc. Chim. France*, 807 (1958).

(31) Prepared by the oxidation of cyclooctanol with lead tetraacetate: (a) R. M. Moriarty and H. C. Walsh, *Tetrahedron Letters*, 465 (1965); (b) A. C. Cope, M. Gordon, S. Moon, and C. H. Park, *J. Am. Chem. Soc.*, 87, 3119 (1965).

Cyclooctane gives a single nmr signal at -1.65 ppm.

chloride (15 g) initiated a vigorous reaction³⁴ which was moderated by cooling the reaction flask in a water bath. After the initial reaction had subsided, the mixture was refluxed for 20 min. Gas chromatographic analysis indicated that no 8 remained in the mixture.³⁵ The mixture was diluted with petroleum ether, and the excess acetyl chloride was hydrolyzed with ice. Conventional separation and work-up gave a low-boiling fraction (about 1 g) whose infrared spectrum was characteristic for cyclooctenyl acetate and another fraction [2.5 g, bp 85–115° (2 mm)] whose spectrum was consistent with 4-chlorocyclooctyl acetate (λ_{max} 5.78, 8.1, and 14.9 μ). This chloro acetate (2.5 g, 12 mmoles) was reduced in ethyl ether solution with lithium aluminum hydride (0.35 g, 9 mmoles). Conventional work-up (acidic hydrolysis) and removal of solvent left crude 4-chlorocyclooctanol which was dissolved in acetone (25 ml) and oxidized directly at 0° with a chromic acid solution (1.5 g, 15 mmoles, of CrO_3 in 9 ml of 30% H_2SO_4). After the mixture was diluted with water and extracted with petroleum ether, the organic solution was washed thoroughly with water, dried with calcium chloride, and concentrated. Gas chromatographic analysis indicated that the principal constituent of the residual liquid had a retention time identical with that of the ketone obtained from the ozonolysis of 6. The infrared spectrum (λ_{max} 1706 cm^{-1}), nmr spectrum (quintet at -4.15 ppm), and 2,4-dinitrophenylhydrazone derivative (mp 149–151.5°, the mixture melting point showed no depression) of this sample of 4-chlorocyclooctanone also matched the corresponding data for the ozonolysis product.

Reaction of Trichloromethanesulfonyl Chloride with Cyclooctene. During 1.5 hr, a solution of *cis*-cyclooctene (38 g, 0.35 mole) and benzoyl peroxide (8 g, 0.04 mole) in benzene (150 ml) was added to a refluxing solution of trichloromethanesulfonyl chloride (100 g, 0.45 mole, Eastman Practical Grade) in benzene (150 ml). Titration of evolved SO_2 with iodine indicated that 38% of the sulfonyl chloride had decomposed in 30 min after addition was complete. The mixture was refluxed for 15 hr to ensure complete decomposition of the peroxide. A gas chromatogram of the reaction mixture before distillation showed two principal products (85%) of relative area 30:70 and at least 18 minor components. Distillation at reduced pressure gave a small amount of low-boiling material and 75 g (81%) of mixed $\text{C}_8\text{H}_{14}\text{Cl}_4$ products, bp 90–114° (0.5 mm). The conversion of cyclooctene was greater than 96%. The mixture of products was analyzed by gas chromatography and infrared and nmr spectroscopy. The product distribution data are summarized in Table I.

The 1,2 and 1,4 isomers of $\text{C}_8\text{H}_{14}\text{Cl}_4$ (5 and 9) are resolved by gas chromatography (140°, 100-ft SE-96 silicone capillary column). The nmr spectrum of the $\text{C}_8\text{H}_{14}\text{Cl}_4$ mixture was used to confirm the gas chromatographic analysis. The integrated absorption centered at -4.75 ppm (HCCl , 1,2 isomer) was compared with that at -4.25 ppm (HCCl , 1,4 isomer), and the relative intensities of the absorptions to the left and right of -1.83 ppm were estimated (a 5:8 ratio is expected for the pure 1,2 isomer, a 9:4 ratio for the 1,4 isomer). The three analyses gave concordant results: 31% 1,2 isomer and 69% 1,4 isomer.

The infrared spectrum of the highest boiling $\text{C}_8\text{H}_{14}\text{Cl}_4$ fraction indicated that both the liquid and solid 1,4 isomers were present. The solid isomer was separated by fractional crystallizations, mp and mmp 64.5–65°. The liquid 1,4 and 1,2 isomers could not be separated cleanly by distillation, but repeated distillations through a 12-in. packed column gave fractions enriched in 1,2 isomer (77% purity) and 1,4 isomer (86% purity). The identity of the liquid 1,4 isomer was confirmed by comparison of its nmr and infrared spectra with those of previously identified samples (CCl_4 additions above). The nmr spectrum of the 1,2 isomer is almost identical with that of 1-bromo-2-(trichloromethyl)cyclooctane (1:1 *cis-trans* mixture);¹⁰ it includes a pair of triplet-like signals ($J = 5.5$ cps) centered at -4.90 ppm (HCCl , *cis* isomer) and -4.60 ppm (HCCl , *trans* isomer). The ratio of signal intensity at -2.2 ppm to that

at -1.65 ppm was 5:8 (after correction for 23% 1,4 isomer). The infrared spectrum of the 1,2 isomer was similar to the spectra of the two 1,4 isomers in the 7–11- μ region; the C–Cl absorption frequency was recorded at 690 cm^{-1} compared to 675 and 672 cm^{-1} for the liquid and solid 1,4 isomers, respectively.

Minor Products from Addition Reactions. The lower boiling fraction from the distillations of the addition reaction mixture were fractionally distilled at reduced pressure and analyzed primarily by gas chromatography. Few of the components responsible for the 11–14 gas chromatography peaks were isolated in sufficient quantity for complete identification, but seven have been rather firmly identified by comparisons of gas chromatographic retention times and infrared spectra with those of authentic samples. These minor products are described in order of increasing gas chromatography retention times; the estimated yields for the several addition reactions are summarized in Table I.

Hexachloroethane was identified by sublimation temperature (184°) and infrared spectrum.³⁶

3-Chloro-1-cyclooctene had the same retention time as authentic chloride prepared from 2-cycloocten-1-ol and thionyl chloride. The distillate fraction rich in this component gave an immediate precipitate with cold alcoholic silver nitrate.

Chlorocyclooctane showed the same retention time as an authentic sample prepared by the addition of HCl to cyclooctene.

trans-1,2-Dichlorocyclooctane showed the same retention time as an authentic sample prepared by the addition of chlorine to cyclooctene.^{37,38}

Dichloromethylenecyclooctane was separated in about 91% purity by preparative gas chromatography; the infrared spectrum included only trace absorptions for $\text{C}=\text{CH}$ and intense ones for $\text{C}=\text{CCl}_2$ (6.21 and 11.1 μ).

Anal. Calcd for $\text{C}_8\text{H}_{14}\text{Cl}_2$: C, 56.0; H, 7.3. Found: C, 55.3; H, 7.4.

A (trichloromethyl)cyclooctene was separated in low purity by preparative gas chromatography; the infrared spectrum included absorptions for $\text{C}=\text{CH}$ (3.3 and 6.03 μ) and CCl_3 (13 μ , intense). The gas chromatographic retention time and infrared spectrum of this product were different from those of the 4-(trichloromethyl)-1-cyclooctene obtained by AgNO_3 dehydrochlorination of 5.

(Trichloromethyl)cyclooctane was obtained in about 91% purity by preparative gas chromatography; the infrared spectrum included no absorptions for $\text{C}=\text{CH}$ but an intense one at 13 μ for CCl_3 . The nmr spectrum consisted of multiplets centered at -2.6 (1 H, HCCCl_2), -2.2 (4 H, CH_2CCCl_2), and -1.6 ppm (8 H, $\text{CH}_2\text{CH}_2\text{CH}_2$). Data for this product correspond to those of an authentic sample of (trichloromethyl)cyclooctane, prepared from chloroform and cyclooctene.

Dehydrohalogenation of 5 with AgNO_3 . A mixture of 5s (9.04 g, 34.2 mmoles), silver nitrate (6.00 g, 35 mmoles), and aqueous methanol (50 ml, 90 vol. % MeOH) was stirred at 45° for 4 hr, filtered from precipitated silver chloride, and diluted with ethyl ether. The ether solution was washed thoroughly with water, dried, and distilled. In addition to recovered starting material [4.0 g, 44%, bp 105–107° (0.2 mm)], a dehydrochlorination product was obtained in 93% yield (based on 5s consumed), bp 74–80° (0.15–0.2 mm).

Anal. Calcd for $\text{C}_8\text{H}_{12}\text{Cl}_2$: C, 47.50; H, 5.76. Found: C, 47.40; H, 5.93.

The infrared spectrum of this product included absorptions for $\text{C}=\text{CH}$ (3.30 μ), $\text{C}=\text{C}$ (6.02 μ), and CCl_2 (12.8–13.6 μ , intense). The nmr spectrum included multiplet signals centered at -5.7 (2 H, $\text{C}=\text{CH}$ with splitting virtually identical with the signal for *cis*-cyclooctene),³⁹ -2.6 (1 H, HCCCl_2), -2.2 (6 H, CH_2CCCl_2 and $\text{CH}_2\text{C}=\text{C}$), and -1.6 ppm (4 H, $\text{CH}_2\text{CH}_2\text{CH}_2$). The ratio of the signals at -5.7 , -2.2 , and -1.6 ppm is consistent only with 4-(trichloromethyl)-1-cyclooctene among the four isomeric (trichloromethyl)cyclooctenes. The precision of the integrated areas is such that a small contamination (<4%) by 5-(trichloromethyl)-1-cyclooctene would not be detected.

Similar treatment of 5l with silver nitrate gave a 50% conversion to product whose infrared spectrum and gas chromatographic

(32) The infrared spectrum of our product was identical with the published spectrum for 9-oxabicyclo[4.2.1]nonane³² and gave no indication of contamination by the [3.3.1] isomer.

(33) A. C. Cope and B. C. Anderson, *J. Am. Chem. Soc.*, **79**, 3892 (1957).

(34) A. C. Cope and A. Fournier, *ibid.*, **79**, 3896 (1957), describe the comparable reaction between the oxide and acetyl bromide. We find that the reaction with the less-reactive acetyl chloride is facilitated by zinc chloride catalyst.

(35) In a previous experiment without zinc chloride, the 9-oxabicyclo[4.2.1]nonane was not consumed after 24-hr reflux with excess acetyl chloride.

(36) "Sadler Index-Midget Edition," Sadler Research Laboratory, Philadelphia, Pa., Spectrum No. 4546.

(37) E. A. Forbes, B. R. Gofton, R. P. Houghton, and E. S. Waigh, *J. Chem. Soc.*, 4711 (1957).

(38) P. W. Havinga, *Rec. Trav. Chim.*, **81**, 1053 (1962). This reference includes the infrared spectrum, which is identical with that of our authentic sample.

(39) G. V. Smith and H. Kriloff, *J. Am. Chem. Soc.*, **85**, 2016 (1963).

retention time were identical with those of the 4-(trichloromethyl)-1-cyclooctene obtained from 5s. The conversion of $C_8H_{14}Cl_4$ to dehydrochlorination product by silver nitrate solution was not increased substantially by prolonged heating.

Dehydrohalogenations of Mixed 1,2 and 1,4 Isomers of $C_8H_{14}Cl_4$.

A. KOH in Mixed Solvent. A mixture prepared by adding a solution of potassium hydroxide (1.1 g, 21 mmoles) in 18 ml of solvent (DMSO-MeOH- H_2O , 10:5:3) to a solution of $C_8H_{14}Cl_4$ (4.4 g, 16.7 mmoles, 65% 1,2 isomers, 35% 1,4 isomers) in 5 ml of methanol and 35 ml of DMSO was stirred at room temperature for 6 hr. It was diluted with water and worked up as was the previous basic dehydrochlorination. After removal of solvent, the product mixture (3 g) was shown by gas chromatography to consist of five components (relative peak areas 9:5:54:18:13). The last two peaks corresponded in retention times to 1-chloro-4-(dichloromethylene)cyclooctane and 1-chloro-4-(trichloromethyl)cyclooctane, respectively. A peak corresponding to the starting 1,2 isomers was completely absent.

The major component (area 54) had a retention time indicative of 3 chlorine atoms per molecule.⁴⁰ The infrared spectrum of the product mixture showed only trace absorption for olefinic hydrogen, intense absorptions for $C=CCl_2$ at 6.23 and 11.02 μ , and weak absorption for CCl_2 . Since 6 absorbs at 11.10 μ , the absorption at 11.02 μ can be attributed to the major component of the product mixture. This product is tentatively identified as 1-chloro-2-(dichloromethylene)cyclooctane. On the basis of retention time, the first product is tentatively identified as a (dichloromethylene)cyclooctene. The 1,2 isomers of $C_8H_{14}Cl_4$ apparently undergo dehydrochlorination more rapidly under these conditions than do the 1,4 isomers.

B. Alcoholic $AgNO_3$. A mixture of $C_8H_{14}Cl_4$ (3.6 g, 13.6 mmoles, 65% 1,2 isomers, 35% 1,4 isomers) and silver nitrate (2.47 g, 16.6 mmoles) in aqueous methanol (50 ml, 90 vol. % MeOH) was refluxed for 5 hr, filtered, and diluted with water. Work-up as previously described gave 3 g of a product mixture shown by gas chromatographic analysis to consist of four components (relative peak areas 25:5:60:10). The last two peaks corresponded in retention times to the 1,2 and 1,4 isomers of $C_8H_{14}Cl_4$, respectively, and the first peak to 4-(trichloromethyl)-1-cyclooctene. On the

basis only of retention time and product expected from 4, the intermediate peak is tentatively associated with 3-(trichloromethyl)-1-cyclooctene. The 1,4 isomers undergo dehydrochlorination about six times more rapidly under these conditions than do the 1,2 isomers.

Photoinitiated Addition of Chloroform to Cyclooctene. A mixture of freshly distilled *cis*-cyclooctene (42 g, 0.38 mole) and chloroform (360 g, 3.0 moles) was placed in a quartz tube, deoxygenated with a stream of nitrogen for 15 min, and irradiated with 2537-A light for 65 hr. A slow stream of nitrogen swept over the mixture during the irradiation and into a trap containing a 10% aqueous sodium hydroxide solution. Distillation of the irradiated mixture gave recovered chloroform, cyclooctene (35 g, 83%), and a higher boiling product mixture (8 g) shown by gas chromatography to consist of three components. The most volatile of the three was separated by distillation [bp 40–42° (0.6 mm)] and identified as chlorocyclooctane by comparison with an authentic sample. Its nmr spectrum consisted of a well-resolved quintet ($J = 5.0$ cps) centered at -4.14 ppm (1 H, $HCCl$) and multiplets centered at -2.02 ppm (4 H, CH_2CCl), and -1.65 ppm (6 H, $CH_2CH_2CH_2$). The other higher boiling components were separated by preparative gas chromatography. The major one gave an analysis for $C_8H_{14}Cl_2$; its infrared spectrum showed absorption at 13.4 μ and none for $C=C$; its nmr spectrum consisted of a sharp doublet ($J = 3.0$ cps) at -5.07 ppm (1 H, $CHCHCl_2$) and multiplets at -2.1 ppm (1 H, $CHCHCl_2$) and -1.65 ppm (14 H, CH_2). This product is identified as (dichloromethyl)cyclooctane.

Anal. Calcd for $C_8H_{14}Cl_2$: C, 55.41; H, 8.25. Found: C, 55.77; H, 8.29.

The third product was identified by its analysis for $C_8H_{14}Cl_3$, its infrared spectrum (intense absorption at 13 μ), and its nmr spectrum (see above) as (trichloromethyl)cyclooctane.

The approximate yields of these three products, based on cyclooctene consumed, were 10% chlorocyclooctane, 41% (dichloromethyl)cyclooctane, and 20% (trichloromethyl)cyclooctane. Traces of hexachloroethane, *trans*-1,2-dichlorocyclooctane, and dichloromethylenecyclooctane were detected by gas chromatography. Treatment of the alkaline trap solution with acetic acid and silver nitrate gave silver chloride in molar amount, equivalent to the sum of the three major products.

Acknowledgment. The authors are grateful for helpful discussions with Professor W. A. Pryor during the preparation of the manuscript.

(40) Ranges of retention times for cyclooctane derivatives containing one, two, and three chlorines per molecule (C_8 or C_9), respectively, were separated by several minutes in our gas chromatographic analyses.

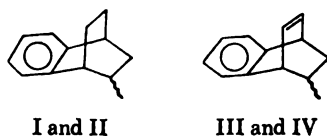
Wagner–Meerwein Rearrangements in the Solvolyses of Benzobicyclo[2.2.2]octenyl and -octadienyl Brosylates and Nuclear Magnetic Resonance Spectra of the Benzobicyclo[3.2.1]octadiene and Benzo[3,4]tricyclo[3.2.1.0^{2,7}]octene Systems

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Abstract: Rate constants and products in the acetolyses of *endo*- and *exo*-benzobicyclo[2.2.2]octen-2-yl (I-OBs and II-OBs) and -octa-5,7-dien-2-yl brosylates (III-OBs and IV-OBs) were determined. The rates of I-OBs, II-OBs, III-OBs, and IV-OBs at 25° relative to that of bicyclo[2.2.2]octan-2-yl brosylate were 0.92, 2.6, 11, and 2.9, respectively. The reaction with I-OBs proceeds with complete rearrangement forming quantitatively a mixture of axial and equatorial benzo[3,4]bicyclo[3.2.1]octen-2-ol acetates. The product from II-OBs is an 83:17 mixture of benzo-bicyclo[2.2.2]octen-2-ol acetate and rearranged benzo[6,7]bicyclo[3.2.1]octen-2(axial)-ol acetate. Only in this case is the reaction stereospecific. In the acetolysis of III-OBs, the major products are axial and equatorial benzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-ol acetates, and the minor products are *exo*- and *endo*-benzo[3,4]tricyclo[3.2.1.0^{2,7}]octen-6-ol acetates. The acetolysis of IV-OBs yields a mixture of axial and equatorial benzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-ol acetates with complete rearrangement. The nmr spectra of the newly formed benzobicyclo[3.2.1]octadienyl and benzo[3,4]tricyclo[3.2.1.0^{2,7}]octenyl derivatives were examined for structural elucidation. Several long-range spin couplings found in these systems are described.

The chemistry of bridged benzocyclenes is one of the research interests in our laboratory. Synthesis of the smallest bridged benzocyclene ever known, benzo-bicyclo[2.1.1]hexene, was recently achieved.¹ Some reported parts of our studies of carbonium ion reactions in the benzonorbornenyl system demonstrated the advantage of discussing the participation effect and the structure of the transition state involved in reactions of this kind.² Along this line, this paper reports a comprehensive study of the rates and Wagner–Meerwein rearrangements in the acetolyses of benzobicyclo[2.2.2]octen-2-yl and -octa-5,7-dien-2-yl brosylates. Rearrangements in the dienyl derivatives produced compounds having new bridged unsaturated systems. The structure elucidation of these compounds leaned heavily on their nmr spectra, and the proton spin-decoupling experiments (nmr and nmtr spectroscopy) performed here are considered to be a model technique for the structure determination of molecules of these kinds.



Preparations. Syntheses and properties of *endo*- and *exo*-benzobicyclo[2.2.2]octen-2-ols (I-OH and II-OH) used in this study are already known.^{3–5} Lithium aluminum hydride reduction of benzobicyclo[2.2.2]octa-5,7-dien-2-one³ led to a mixture of the *endo*-

and *exo*-dienols, III-OH and IV-OH, each of which was isolated in the pure state by elution chromatography. The brosylates of these four alcohols were prepared by standard procedures. The brosylates, III-OBs and IV-OBs, were rather unstable and could be stored for a few days in a dry ether solution at 0°.

Solvolysis Rates. The rates of acetolyses were carried out in glacial acetic acid containing equivalent sodium acetate by the standard procedure.^{2b,6} In each experiment the reaction was followed to at least 80% completion. Good first-order kinetics were observed in the reactions of all the brosylates, and the infinity titers corresponded to theory. The solvolysis rates are summarized in Table I, together with the derived activation parameters and the data of relevant compounds. For comparison, the rate constants at 25.0° were calculated from Arrhenius plots. The relative rates are determined taking that of the parent bicyclo[2.2.2]octyl brosylate (V-OBs) as unity. Table I also lists, for discussion, the *exo:endo* rate ratios in the bicyclo[2.2.2]octenyl, benzobicyclo[2.2.2]octenyl, and benzobicyclo[2.2.2]octadienyl series.

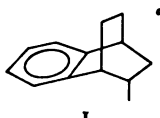
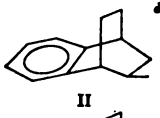
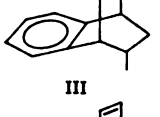
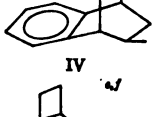
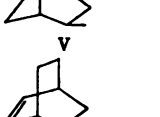
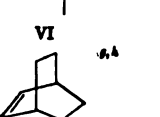
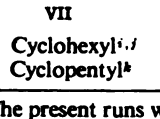
Ethanolyses of I-OBs and II-OBs also followed good first-order kinetics and the rate constants are presented in footnotes to Table I.

Solvolysis Products. For product determination, the acetolyses were carried out under the same conditions used for the rate studies. In all cases, the brosylates quantitatively produced mixtures of acetates. The product composition was examined by vpc analysis of the acetate mixtures and, in addition, of the alcohol mixtures derived therefrom by lithium aluminum hydride reduction. Each component of the acetate mixtures was isolated by preparative vpc. The yields of products were determined by vpc with the isolated pure

- (1) H. Tanida and Y. Hata, *J. Am. Chem. Soc.*, **88**, 4289 (1966).
- (2) (a) H. Tanida, *ibid.*, **85**, 1703 (1967); (b) H. Tanida, T. Tsuji, and H. Ishitobi, *ibid.*, **86**, 4904 (1964); (c) H. Tanida and H. Ishitobi, *ibid.*, **88**, 3663 (1966).
- (3) K. Kitahonoki and Y. Takano, *Tetrahedron Letters*, 1597 (1963).
- (4) The terms axial and equatorial in this paper are abridged as ax and eq. The *endo* and *exo* are defined as follows: substituents on the side of the benzene ring are *endo* and those on the other side are *exo*.
- (5) The numbering used in this paper is shown in the charts.

- (6) E.g., S. Winstein, C. Hanson, and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 812 (1948); S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

Table I. Acetolyses of Bicyclo[2.2.2]octyl Brosylates^a

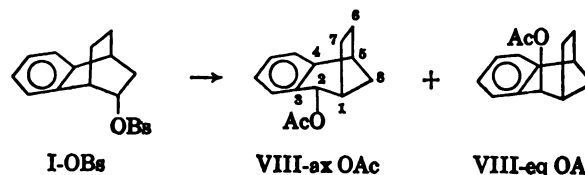
R-OBs	Temp, °C ^b	k_1 , sec ⁻¹	Calcd at 25.0°		k_1 , sec ⁻¹	Rate rel to bicyclo- [2.2.2]octyl	<i>exo:endo</i> ratio
			ΔH^\ddagger , kcal	ΔS^\ddagger , cal/deg			
	{ 34.97 54.94	3.12×10^{-6} 3.45×10^{-6}	23.5	-2.9	8.38×10^{-6}	0.92	2.8
	{ 34.97 54.94	8.94×10^{-6} 1.00×10^{-5}	23.7	-0.1	2.37×10^{-5}	2.6	
	{ 24.97 25.06	9.60×10^{-6} 1.03×10^{-5}			1.01×10^{-4}	11	0.26
	{ 25.03 35.02 54.93	2.68×10^{-6} 1.04×10^{-6} 1.11×10^{-6}	24.8	3.7	2.61×10^{-6}	2.9	
	{ 25.00 50.97	9.07×10^{-6} 2.61×10^{-6}	24.6	1.2	9.07×10^{-6}	1	
	{ 30.07 42.06	2.97×10^{-6} 1.32×10^{-6}	23.0 ⁱ	-3.3 ⁱ	4.57×10^{-6} ^m	5.0	52
	25.00	2.40×10^{-6}			2.40×10^{-6}	260	
Cyclohexyl ^{i,j}			26.8	0.6	1.84×10^{-7}	0.02	
Cyclopentyl ^k			22.7	-6.3	6.28×10^{-6}	0.69	

^a The present runs were conducted in glacial acetic acid containing equivalent sodium acetate. ^b Controlled to 0.02° in the present work. In ethanolysis, k_1 at 35.02° was 6.40×10^{-6} sec⁻¹. ^c In ethanolysis, k_1 at 35.02° was 3.44×10^{-6} sec⁻¹. Thus the *exo:endo* ratio was 5.4. Reference 19a. ^d For the tosylate, Goering, and Sloan^{20b} reported the values of 6.8×10^{-6} sec⁻¹ at 30.07° and 7.4×10^{-6} at 49.03°. Extrapolation gave k_1 (25°) = 3.41×10^{-6} , ΔH^\ddagger = 23.9 kcal, and ΔS^\ddagger = -3.9 cal/deg. ^e Reference 21. ^f The rates of tosylate were reported 6.1×10^{-6} sec⁻¹ at 25.0 (see ref 21) and 2.4×10^{-6} sec⁻¹ at 18.2° in ref 22. ^g Extrapolated from the data for other temperatures taken from H. C. Brown and G. Ham, *J. Am. Chem. Soc.*, **78**, 2735 (1956). ^h S. Winstein, *et al.*, *ibid.*, **74**, 1127 (1952), reported the values of 1.71×10^{-7} sec⁻¹ at 25.0°, ΔH^\ddagger = 26.6 kcal, and ΔS^\ddagger = -0.3 cal/deg. ⁱ The observed value in footnote i. ^j Data of the tosylate cited from ref 2b. ^k Calculated from the rate of tosylate with ROBs/ROTs = 3.

etates and a proper compound being used as an internal reference. The estimated error in the yields is 2%. For discussion, it was considered important to check, in all the acetolyses, the products of retention of configuration and those of inversion. These experiments were also performed by vpc. Demonstration of the absence of such a compound means that it was not formed in amounts greater than 0.5% yield. The product mixtures contained derivatives of benzyl acetate and cyclopropylcarbinyl acetate. They are anticipated to undergo acid-catalyzed isomerization in the acetolysis medium. Therefore, in order to verify that the products and their ratios were, in fact, those of kinetically controlled solvolyses, those isolated pure were treated with acetic acid and acetic acid-sodium acetate under the same conditions used for the product analyses (actually for more than the corresponding ten half-lives). The products were recovered unchanged.⁷

7) It seems likely that such epimerization requires much more severe conditions. For example, treatment of VIII-axOAc in the acetolysis solvent at 150° for 3 hr led to a mixture consisting of 85% VIII-axOAc and 15% VIII-eqOAc. A related example, the epimerization and rearrangement of dibenzobicyclo[3.2.1]octadien-2-ol acetate studied by Stol, *et al.*,⁸ required such a strong condition at HClO₄-CH₃COOH.

The acetolysis of I-OBs for ten half-lives produced in quantitative yield a mixture consisting of 98% of benzo[3,4]bicyclo[3.2.1]octen-axial-2-ol acetate (VIII-axOAc) and 2% of its epimer VIII-eqOAc. The retained product I-OAc and the inverted product II-OAc were absent. Hydrolysis of both acetates with lithium aluminum hydride, followed by Oppenauer oxidation, afforded the same reported benzo[3,4]bicyclo[3.2.1]-



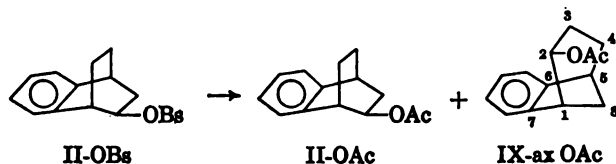
octen-2-one, the semicarbazone of which was identified by comparison with an authentic sample.⁹ This fact proves the ring system of both acetates. It has been reported in nmr studies of bicyclo[3.2.1]oct-3-en-2-yl,

(8) S. J. Cristol, F. P. Parungo, D. E. Florde, and K. Schwarzenbach, *J. Am. Chem. Soc.*, **87**, 2879 (1965).

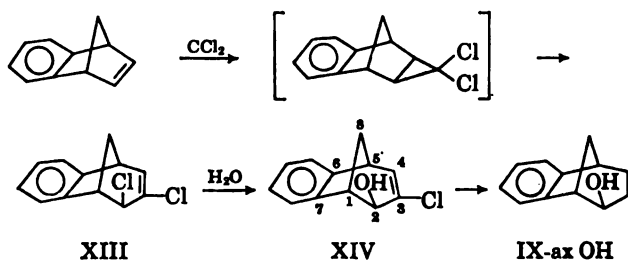
(9) We thank Professor W. Baker for providing the sample. Refer to W. Baker and W. G. Leeds, *J. Chem. Soc.*, 974 (1948).

benzo[3,4]bicyclo[3.2.1]octen-2-yl, and dibenzobicyclo[3.2.1]octadien-2-yl derivatives that the eqH₂ shows a coupling constant of 1.4–2.9 Hz with the bridgehead H₁, whereas the corresponding coupling constant of the axH₂ is 4.3–5.4 Hz.^{10–12} Thus the coupling constants, 2.8 and 4.6 Hz, observed for VIII-axOH and VIII-eqOH, respectively, confirmed the configuration of the hydroxyl groups.

Acetolysis of II-OBs led to a nearly quantitative yield of an acetate mixture containing 83% of the retained II-OAc and 17% of the rearranged IX-axOAc.



Vpc demonstrated the absence of the inverted acetate I-OAc and IX-eqOAc. The structure of IX-axOAc was identified with an authentic sample which was prepared, as shown in the following chart, by the *exo* addition of dichlorocarbene (prepared from chloroform and potassium *t*-butoxide) to benzonorbornene, followed by hydrolysis and then hydrogenation. Substantially the same reaction route has been reported by several workers for the synthesis of bicyclo[3.2.1]oct-3-en-2-yl derivatives.^{10,12,13} Hydrolysis of the intermediate XIII was indicated by nmr spectroscopy to yield predominantly the ax-allylic alcohol XIV, in which *J*_{1,2}



is 2.2 Hz. This stereospecific result was similarly observed in the hydrolysis of ax-2,3-dichlorobicyclo[3.2.1]oct-3-ene.^{10b,12–15} An authentic sample of IX-eqOAc was prepared by Oppenauer oxidation of IX-axOH, followed by lithium aluminum hydride reduction¹⁷ and then acetylation.

Acetolysis of III-OBs resulted in a mixture consisting of the four compounds, ax- and eq-benzo[3,4]bicyclo[3.2.1]octa-3,6-dien-2-ol acetates (X-axOAc and -eqOAc) and *exo*- and *endo*-benzo[3,4]tricyclo[3.2.1.0^{2,7}]octen-6-ol acetates¹⁸ (XI-*exo*-OAc and -*endo*-OAc).

(10) (a) W. R. Moore, W. R. Moser, and J. E. LaPrade, *J. Org. Chem.*, **28**, 2200 (1963); (b) R. C. DeSelms and C. M. Combs, *ibid.*, **28**, 2206 (1963).

(11) A. R. Katritzky and B. Wallis, *Chem. Ind. (London)*, 2025 (1964).

(12) C. W. Jefford, S. Mahajan, J. Waslyn, and B. Waegell, *J. Am. Chem. Soc.*, **87**, 2183 (1965).

(13) (a) E. Bergman, *J. Org. Chem.*, **28**, 2210 (1963); (b) C. W. Jefford and R. Medary, *Tetrahedron Letters*, 2069 (1966).

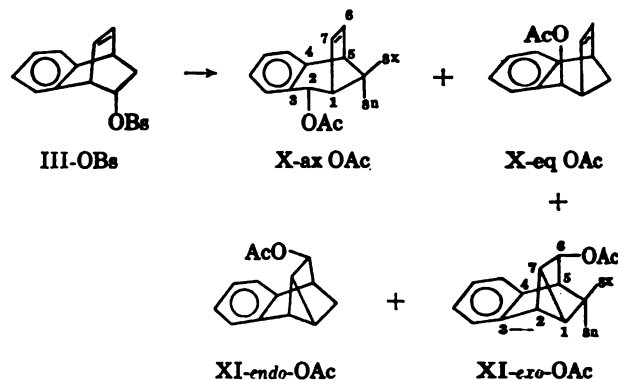
(14) A related result has been reported by Cristol in the reaction of dibenzobicyclo[3.2.1]octadien-2-yl cation which reacts from the *exo* (quasi-ax) side reversibly most rapidly to give (generally) the *exo* product as that of kinetic control.⁹

(15) Results of this kind are reasonable since in allylic cyclohexenyl systems formation and cleavage of quasi-ax bonds is stereoelectronically favored over formation and cleavage of quasi-eq bonds.¹⁶

(16) (a) H. L. Goering and E. F. Silversmith, *J. Am. Chem. Soc.*, **79**, 348 (1957), and also (b) H. L. Goering and D. L. Towns, *ibid.*, **85**, 2295 (1963).

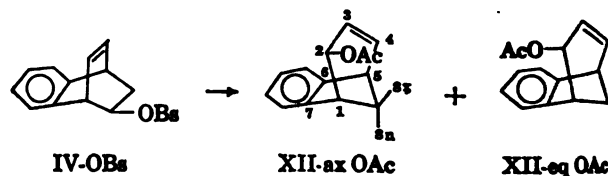
(17) The reduction gave IX-eqOH and IX-axOH in a ratio of 3:2.

At ten half-lives, the relative peak areas of X-axOAc, X-eqOAc, XI-*endo*-OAc, and XI-*exo*-OAc on vpc analysis were 72, 11, 7, and 10, respectively. However,



because only a capillary vpc column could separate X-eqOAc and XI-*endo*-OAc, the errors in these product ratios will be approximately twice as large as those in the other cases. Confirmatory evidence for the indicated structures was provided by detailed examination of their nmr spectra, as described in the following section. In addition, the main products from catalytic reductions of X-axOAc and X-eqOAc over PtO₂ were VIII-axOAc and VIII-eqOAc, respectively. These results chemically confirmed structures of the X derivatives.

Complete rearrangement to the benzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-yl system XII was observed in the acetolysis of IV-OBs. The product for ten half-lives was an 83:17 mixture of XII-axOAc and XII-eqOAc. The structures of the products were convincingly established by the nmr spectra, mentioned below. The structure of XII-axOAc was also chemically confirmed



by the predominant formation of IX-axOAc on catalytic reduction over PtO₂.

It is particularly significant that careful search by vpc demonstrated the absence of the retained and inverted products in the acetolysis mixtures of III-OBs and IV-OBs.

Discussion of Solvolysis Results. Relevant solvolytic studies have been reported by Walborsky, *et al.*,¹⁹ and Goering, *et al.*,^{16b,20} for the bicyclo[2.2.2]octyl system V, by Goering, *et al.*, for the *endo*-2-bicyclo[2.2.2]octenyl system VI, by LeBel, *et al.*,²¹ and Fraser, *et al.*,²² for the *exo*-2-bicyclo[2.2.2]octenyl system VII, and by Cristol and his co-workers²³ for the dibenzo[2.2.2]octadienyl system. With these available data, the present results build up an almost complete set of

(18) The IUPAC name is used according to the suggestion in I. Meinwald and J. K. Crandall, *J. Am. Chem. Soc.*, **88**, 1292 (1966).

(19) (a) H. M. Walborsky, M. E. Baum, and A. A. Youssif, *ibid.*, **83**, 988 (1961); (b) H. M. Walborsky, J. Webb, and C. C. Pitt, *J. Org. Chem.*, **28**, 3214 (1963).

(20) (a) H. L. Goering and M. F. Sloan, *J. Am. Chem. Soc.*, **83**, 1397 (1961); (b) *ibid.*, **83**, 1992 (1961).

(21) N. A. LeBel and J. E. Huber, *ibid.*, **83**, 3193 (1963).

(22) R. R. Fraser and S. O'Farrell, *Tetrahedron Letters*, 1143 (1962).

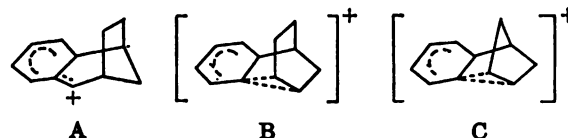
(23) Reference 8 and references cited therein.

solvolytic behavior of bicyclo[2.2.2]octyl and its related derivatives. The ratios $k_{\text{AcOH}}/k_{\text{EtOH}} = 2.6$ at 35° in the solvolyses of I-OBs and II-OBs respectively (footnotes in Table I), suggest that philic participation by solvent is not important; in other words, acetolysis²⁴ (probably also ethanolysis) involves carbonium ion intermediates.²⁵

rates in acetolyses of dehydronorborn- and norbornen-2(*endo*)-yl brosylates drop to 0.022–0.002 that of norborn-2(*endo*)-yl brosylate.^{26–28} In contrast, the rates of VI-OBs and I-OBs were five greater than and nearly equal (a factor of 0.92) to those of V-OBs, respectively. This indicates that the double bond affects the *endo*-norbornenyl and -octenyl ions differently. However, the fact that their ratios, 0.002 and 5.0:0.92, are in the same order of magnitude means that the relative effect of a double bond in the benzene ring is almost the same in each of the cases.²⁹

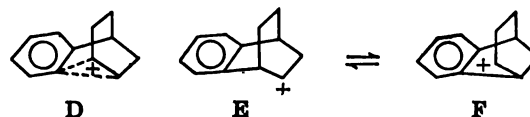
Products in the acetolysis of I-OBs, 98% VIII-axOH and 2% VIII-eqOAc, are comparable with those in the acetolysis of VI-OBs.^{16b} Thus, the combined kinetic and stereochemical results are consistent with formation of the carbonium ion A stabilized by anchimeric resonance, as discussed in the case of VI-OBs. Stereospecific conversion of A to VIII-axOAc would be explained as in similar cases,^{8,16,16b} that is, A electronically favors formation of quasi-ax over eq bonds. Lithium aluminum hydride reduction of the corresponding 2-one leads to an 8:2 mixture of xOH and VIII-eqOH. Since the stereochemical results for the reduction of bridged cyclic ketones by LiAlH₄ are controlled by "steric approach only,"^{30,31} the major formation of VIII-axOH may

suggest that the ax side is sterically more hindered. It is indicated, therefore, that collapse of the ion A to products is predominantly taking place from the sterically unfavorable direction.



The 2.6-fold increase in the rate of II-OBs (relative to V-OBs) and the small *exo:endo* rate ratio (a factor of 2.8) are insufficient values to propose a homobenzylic ion B as an intermediate, in which anchimeric assistance from π electrons in the benzene ring is significantly provided. Similarly, by such a small value as the 2.9-fold increase in the case of IV-OBs, assistance from the benzene ring cannot be considered. The *exo:endo* rate ratios in the norbornen-2-yl and benzonorbornen-2-yl arenesulfonates are both in the same order of magnitude (at 25° , 7000²⁶ and 15,000,²⁷ respectively). Thus, the nonclassical ion C analogous to B has been suggested for the solvolysis of benzonorbornen-2-yl arenesulfonate.^{27,32} The rate-increasing effect of the double bond in VII-OBs has been reported as a factor of 260 and the *exo:endo* rate ratio thus obtained is 52, so that considerable anchimeric assistance by the double bond is demonstrated.²¹ Therefore, the present results are in striking contrast.

The kinetic results and the stereochemical findings (the lack of I-OAc and IX-eqOAc) in the acetolysis of II-OBs could be rationalized by postulating either a nonclassical cation D which may involve participation of the C_{1,6}-methylene bond, but not that of the benzene π electrons, or a rapidly equilibrating set of classical ions E and F which simulate D. A windshield-



wiper effect in this equilibrating set can be invoked in order to explain the observed stereochemistry.³³ It should be noted that the results in the lithium aluminum hydride reduction of the 2-one¹⁷ indicate little difference in the steric factors between ax and eq approach to the open C₂ carbonium ion, if formed.³⁴

In contrast to the acetolyses of the octenyl derivatives, no stereospecific result was obtained in the reactions of the octadienyl derivatives. From the kinetic data, especially from the small rate ratio $k_{\text{III-OBs}}/k_{\text{IV-OBs}} = 3.8$, it can be argued that little, if any, participation by the double bond is being exerted in the acetolysis of III-OBs. Stereochemical results preclude the participation of the classical [2.2.2]dienyl ion G as an intermediate. Absence of products having the [2.2.2] skeleton and lack of stereospecificity also make nonclassical intermediates such as H, I, and J or a rapid and reversible equilibrium between classical ions K and L unsatisfactory. The

S. Winstein, *et al.*, *J. Am. Chem. Soc.*, **79**, 4146 (1957); **75**, 1477, 2700 (1951).

It has been shown that internal return may be an important factor in solvolysis. See S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, D. Robinson, *ibid.*, **78**, 328 (1956). However, any ion-pair return might be involved in the acetolysis of I-OBs, III-OBs, and IV-OBs but not affect the solvolysis rate (*i.e.*, in these cases the solvolysis rate depends on the ionization rate). This is because the expected product-ion-pair return, that is, VIII-axOBs for I-OBs, X-axOBs and OBs for III-OBs, and XII-axOBs for IV-OBs, would solvolyze rapidly. For a similar situation, see A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2767 (1956); footnote 23 in ref 20b; footnote 16 in ref 12 in S. J. Cristol, W. K. Seifert, D. W. Johnson, and J. B. F. *J. Am. Chem. Soc.*, **84**, 3918 (1962). In the remaining case, that is, acetolysis of II-OBs, ion-pair return would conceivably give the starting II-OBs and IX-axOBs. IX-axOBs might be expected to solvolyze more slowly than II-OBs. However, careful first-order experiments give no evidence for this expectation.

S. Winstein, H. M. Walborsky, and K. Schreiber, *ibid.*, **72**, 5795 (1950).

P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960). The constant at 25° originally reported in this paper was 1×10^{-6} sec⁻¹. However, the recalculation by H. C. Brown and G. L. Trillitidis led it to 5.1×10^{-10} sec⁻¹ (a private communication from Professor Brown). We confirmed the recalculation. Therefore, the factor reported widely in reviews is corrected to 0.002, and also the *exo:endo* ratio in the acetolysis of benzonorbornen-2-yl brosylates is corrected to 15,000 from 7500.

a) For a review, see J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1953; (b) for summarized data, see ref 2b.

From this consideration and the rate constant for IV-OBs, we have the rate constant of $\sim 4 \times 10^{-6}$ sec⁻¹ at 25° for the acetolysis of bicyclo[2.2.2]octadien-2-ol brosylate. This value is compatible with that obtained by Cristol and Mohrig. According to a private communication from Professor S. J. Cristol, they obtained an approximate constant of 2×10^{-6} sec⁻¹ for the corresponding tosylate at water-acetic acid (3.6:96.4 mole %) solvent (Ph.D. Dissertation Mohrig, University of Colorado, 1963).

W. G. Dauben, D. G. Fonker, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

I. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).

(32) W. P. Giddings and J. Dirlam, *ibid.*, **85**, 3900 (1963).

(33) H. C. Brown, "The Transition State," Special Publication No. 16, The Chemical Society, London, 1962, pp 140–158, 174–178.

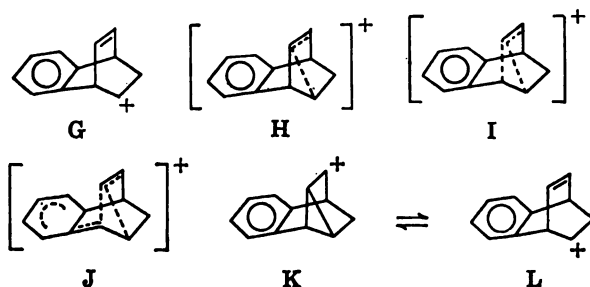
(34) It has been reported by A. A. Yousef, M. E. Baum, and H. M. Walborsky, *J. Am. Chem. Soc.*, **81**, 4709 (1959), that LiAlH₄ reduction of bicyclo[3.2.1]octan-2-one gave the corresponding eq- and ax-2-ols in a ratio of 9:1 and the eq is thermodynamically more stable than the ax.

Table II. Nmr Spectral Data on Some Benzobicyclo[3.2.1]octadienes and Benzotricyclo[3.2.1.0^{3,7}]octenes

Compd	Chemical shift, τ^a	Coupling constant, J , Hz ^b (dihedral angle, θ , deg) ^c			
X-axOAc	H ₁	7.11m(7.11m)	1,2eq = 2.0 (76)	6,7 = 5.8	2eq,8x = 0.8
	H _{2eq}	4.38d(4.10d)	1,8x = 4.7 (40)	5,8x = 4.7 (40)	6,8n ≤ 0.2
	H ₃	6.66m(6.93m)	1,8n = 0.5 (80)	5,8n = 0.5 (80)	7,8n ≤ 0.2
	H ₄	3.53q(3.77q)	1,7 = 2.7	5,6 = 3.1	
	H ₇	4.10q(4.35q)	8x,8n = 10.0		
	H _{ax}	~7.8m(8.00d-t-d)			
	H _{an}	~7.8m(7.78d)			
X-eqOAc	OAc	7.96s(8.27s)			
	H ₁	6.75t-d(6.78t-d)	1,2ax = 5.4 (44)	6,7 = 5.8	2ax,7 ≈ 0.3
	H _{2ax}	4.04d(3.86d)	1,8x = 5.0 (40)	5,8x = 4.7 (40)	6,8n ≤ 0.1
	H ₃	6.77q(7.03q)	1,8n = 0.5 (80)	5,8n ≈ 0.5 (80)	7,8n ≤ 0.1
	H ₄	3.60q(3.73q)	1,7 = 2.8	5,6 = 2.9	
	H ₇	4.29q(4.27q)	8x,8n = 10.3		
	H _{ax}	7.74d-t(7.96d-t)			
XII-axOAc	H _{an}	7.95d(8.26d)			
	OAc	7.96s(8.25s)			
	H ₁	6.76m(6.69m)	1,2eq = 2.0 (76)	3,4 = 9.4	2eq,4 = 1.0
	H _{2eq}	4.99q-d(4.71q-d)	1,8x = 0.9 (80)	5,8x = 0.9 (80)	2eq,8n ≤ 0.3
	H ₃	4.80d-q(4.75d-q)	1,8n = 4.6 (40)	5,8n = 4.2 (40)	1,3 = 1.8
	H ₄	3.60q(3.78q)	2eq,3 = 3.6	4,5 = 6.6	4,8n = 1.0
	H ₅	6.75m(6.97q-m)	8x,8n = 10.1		
XII-eqOAc	H _{ax}	~7.8m(7.75d-t)			
	H _{an}	~7.8m(7.94d-t-d)			
	OAc	7.97s(8.25s)			
	H ₁	6.40t-m(6.49t-m)	1,2ax = 5.5 (44)	3,4 = 9.5	2ax,4 = 2.3
	H _{2ax}	4.50t-d-d(4.39t-d-d)	1,8x = 1.0 (80)	5,8x = 1.0 (80)	1,3 = 1.8
	H ₃	4.93d-q-d(4.92d-q-d)	1,8n = 4.7 (40)	5,8n = 4.2 (40)	4,8n = 1.2
	H ₄	3.70q-t(3.94q-t)	2ax,3 = 2.7	4,5 = 6.2	
XI-exo-OAc	H ₅	6.80q-m(7.16q-m)	8x,8n = 10.0		
	H _{ax}	7.75d-t(8.08d-t)			
	H _{an}	7.62d-t-d(7.90d-t-d)			
	OAc	8.05s(8.37s)			
	H ₁	8.28d-m(8.50q-m)	5,6n = 0.7 (81)	6n,7 = 1.0 (75)	1,5 = 1.0
	H ₂	7.80t(8.10t)	1,8x = 2.8 (45)	5,8x = 4.9 (39)	7,5 = 1.0
	H ₃	7.00d-m(7.02d-m)	1,8n = 0.6 (75)	5,8n = 0.3 (81)	1,6n = 0.4
XI-endo-OAc	H _{an}	5.55s(5.35t)	1,2 = 7.0	2,7 = 7.0	7,8n ≈ 0
	H ₇	8.28d-m(8.38q-t)	1,7 = 5.0	8x,8n = 11.6	2,8x ≤ 0.2
	H _{ax}	7.80m(7.85d-q)			6n,8x ≤ 0.2
	H _{an}	8.96d(9.06d)			
	OAc	8.00s(8.30s)			
	H ₁	~8.25m(8.77m)	5,6x = 5.0 (39)	6x,7 = 3.0 (45)	1,5 ^d
	H ₂	7.78t(8.03t)	1,8x = 2.8 (45)	5,8x = 5.0 (39)	5,7 = 0.7
	H ₃	6.65t(6.70t)	1,8n = 1.0 (75)	5,8n = 0.3 (81)	7,8n ^d
	H _{ax}	4.95q(4.87q)	1,2 = 7.0	2,7 = 7.0	2,6x = 0.4
	H ₇	8.32m(8.36m)	1,7 = 5.5	8x,8n = 11.8	2,8x ≤ 0.2
	H _{ax}	7.95d-q(8.33d-q)			6x,8n ≤ 0.2
	H _{an}	8.96d(9.20d)			
	OAc	8.38s(8.63s)			

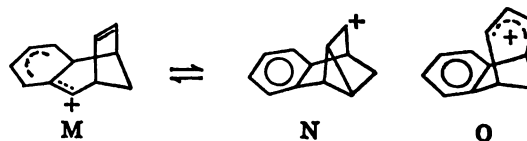
^a Obtained in CCl₄. Values in parentheses are data obtained in C₆D₆. Peak multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). ^b Absolute values. ^c Obtained from Dreiding models. Accuracies are ±2°. ^d Obscured.

combination of kinetic and stereochemical behavior can be accommodated by the direct formation of an equilibrium mixture containing the benzylic cation M and the



cyclopropylcarbiny cation N. The predominant formation of X-axOAc would be accounted for with a stereoelectronic factor as in the above-mentioned case.

As in the case of I-OBs, the direct formation of the classical cation O, stabilized by allylic resonance and not involving participation from the benzene ring, can accommodate all results from IV-OBs.



A summary of related data shows that the relative rates at 25° in acetolyses are for norbornyl, dehydronorbornyl, and benzonorbornenyl *exo*-2-bromides, 1, 0.5, and 0.08; for V-OBs, VII-OBs, and II-OBs, 1, 260, and 2.6; for I-OBs, III-OBs, and dibenzobicyclo[2.2.2]octadienyl-OBs, 1, 12, and ~0.5.²² In each series, ratios of relative rates for the dehydro and the benzo derivatives (0.5:0.08 = 6, 260:2.6 = 100, and 12:0.5 = 24) express the relative effectiveness of double

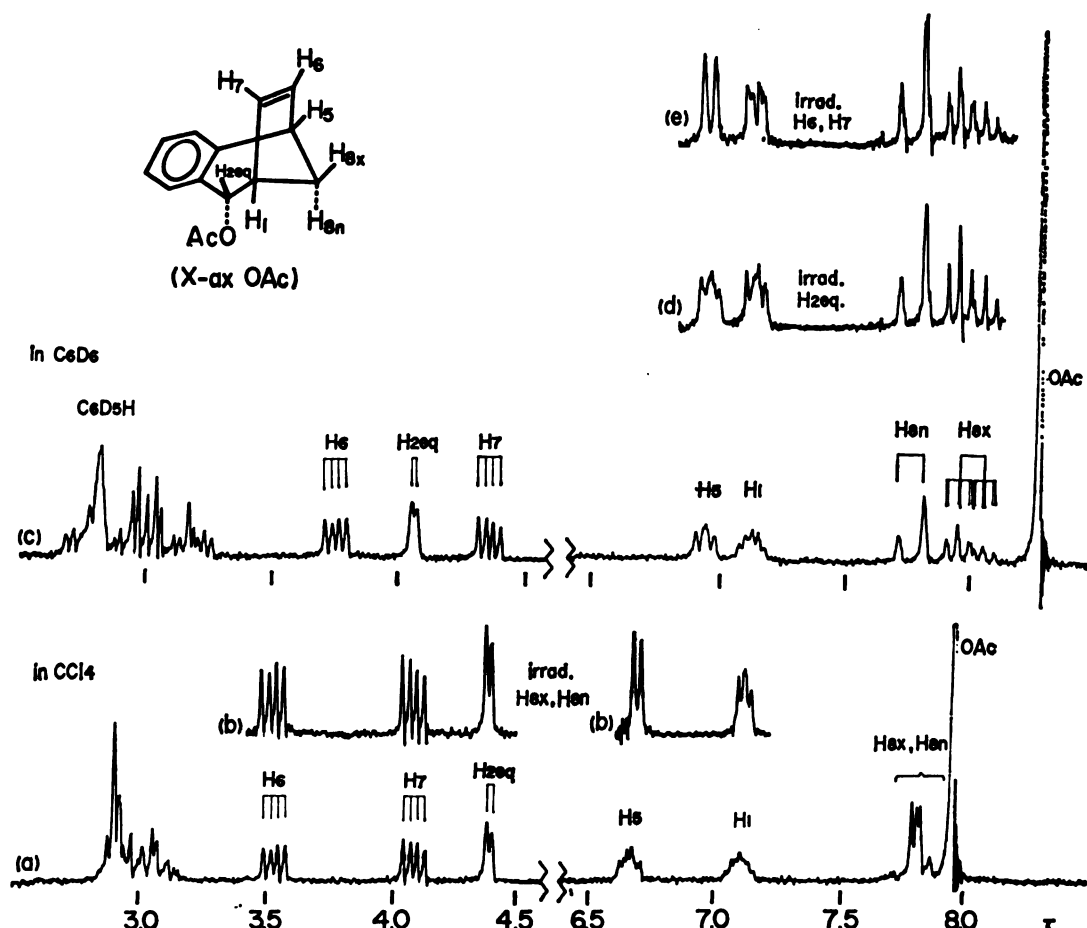


Figure 1. Nmr, nmrd, and nmtr spectra of X-axOAc in CCl_4 and C_6D_6 at 100 MHz. (Spectra shown in b, d, and e were run at increased powers.)

ids vs. benzene rings for participation. Thus, it is clear that the most flexible [2.2.2]octenyl system can achieve the most favorable conformation for participation (the factor of 100). The least participation (the factor of 6) is indicated in the rigid norbornenyl system. However, the present study cannot rationalize the origin of the rate of V-OBs which is 49 times faster than that of cyclohexyl brosylates.

Nmr Spectra of Benzo[3,4]bicyclo[3.2.1]octa-3,6-dien-1-yl (X), Benzo[6,7]bicyclo[3.2.1]octa-3,6-dien-2-yl (XII), Benzo[3,4]tricyclo[3.2.1.0^{2,7}]octen-6-yl (XI) Derivatives. Investigations of the nmr spectra of the six diastereomers X–XII by using double and triple resonance (nmr and nmtr) techniques and the solvent effect of benzene³⁵ at 100 MHz provided evidence for their structures. The nmr spectra with some spin-decoupling experiments are shown in Figures 1–6. In Table II listed the chemical shifts and the coupling constants (solvent values) obtained. The procedure for the central assignments of these compounds is described in the Experimental Section.

The fact that the two bridgeheads H_1 and H_8 are vicinally coupled to the olefinic H_6 and H_7 in the two compounds X indicates that these compounds belong to the

benzo[3,4]bicyclo[3.2.1]octa-3,6-diene system. Applying the Karplus correlation³⁷ to the obtained $J_{1,2}$ values,^{10–12} we confirmed that the acetoxyl at C_2 in X-axOAc and X-eqOAc has an ax and an eq configuration, respectively. Among long-range spin couplings expected by analogy with bicyclo[2.2.1]heptenes,³⁸ a $J_{ax,7}$ of about 0.3 Hz and very small $J_{6,8n}$ and $J_{7,8n}$ were only observed. The overlapping of the back-side lobe of the σ orbital of H_{8n} with π orbitals of the double bond³⁸ might be slight in this system. A long-range $J_{2eq,8x}$ of 0.8 Hz was, however, clearly established, as expected from the “W-letter” rule.³⁸

Decoupling experiments on the two compounds XII showed that only one bridgehead H_8 is vicinally coupled to the one olefinic H_4 . This fact implies that these compounds belong to the benzo[6,7]bicyclo[3.2.1]octa-3,6-diene system. The observed $J_{1,2}$ likewise determined the configurations of the acetoxyls at C_2 in XII-axOAc and XII-eqOAc as ax and eq, respectively. The allylic $J_{2ax,4}$ (2.3 Hz) in XII-eqOAc was greater than $J_{2eq,4}$ (1.0 Hz) in XII-axOAc. This indicates that, as suggested by the molecular models, H_{2ax} has more ax character than H_{2eq} .³⁸ Jefford, *et al.*,³⁹ reported that similar allylic $J_{2,4}$ cannot be observed in several *exo*-

5) Since all the compounds examined here contain an acetoxyl group, their nmr spectra are expected to be fairly changed with an alteration of the solvent from CCl_4 to hexadeuteriobenzene (C_6D_6).³⁶

6) N. S. Bhacca and D. H. Williams, *Tetrahedron Letters*, 3127 (1964); D. H. Williams and N. S. Bhacca, *Tetrahedron*, 21, 1641, 2021 (1965); J. D. Connolly and R. McCrindle, *Chem. Ind. (London)*, 379, (1965); C. J. Timmons, *Chem. Commun.*, 576 (1965).

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in X, and $J_{3,5}$ in XII), benzylic,⁴⁰ homoallylic²⁸ ($J_{1,5}$ in X and $J_{3,5}$ in XII), and homobenzylic couplings⁴⁰ ($J_{3,5}$ in X and $J_{1,5}$ in XII). This substantiates the fact that the σ - π overlapping necessary for these couplings²

Ring system	Subst	Mp ^a or bp, ^c °C (mm)/ <i>m</i> (°C)	Formula	Carbon %		Hydrogen, %	
				Calcd	Found	Calcd	Found
I	OBs	[91-92]	C ₁₀ H ₁₇ BrO ₂ S	54.97	55.18	4.36	4.53
II	OBs	[109-110]	C ₁₀ H ₁₇ BrO ₂ S	54.97	55.00	4.36	4.20
	OAc	120 (1)/1.5389 (24)	C ₁₄ H ₁₈ O ₂	77.95	77.79	7.46	7.58
III	OH	[103.5-104.5]	C ₁₀ H ₁₈ O	83.69	83.46	7.02	7.31
	OBs	<i>d</i>	C ₁₀ H ₁₇ BrO ₂ S	55.25	55.15	3.86	4.05
IV	OH	[96.5-97.5]	C ₁₀ H ₁₈ O	83.69	83.63	7.02	7.03
	OBs	<i>d</i>	C ₁₀ H ₁₇ BrO ₂ S	55.25	55.34	3.86	4.00
VIII	axOH	[83.5-84.5]	C ₁₀ H ₁₈ O	82.72	82.72	8.10	8.09
	eqONB ^a	[112-113]	C ₁₀ H ₁₇ NO ₄	70.57	70.50	5.30	5.46
IX	axOH	[72.5-73.5]	C ₁₀ H ₁₈ O	82.72	82.56	8.26	8.26
	axOAc	125 (5)	C ₁₄ H ₁₈ O ₂	77.76	77.66	7.46	7.43
X	axOAc	125 (3)/1.5457 (27)	C ₁₄ H ₁₈ O ₂	78.48	78.37	6.59	6.74
	eqOAc	125 (3)/1.5445 (26)	C ₁₄ H ₁₈ O ₂	78.48	78.59	6.59	6.98
XI	<i>exo</i> -OAc	[75.5-76.5]	C ₁₄ H ₁₈ O ₂	78.48	78.54	6.59	6.57
	<i>endo</i> -OAc	126-128 (1)/1.5530 (25)	C ₁₄ H ₁₈ O ₂	78.48	78.53	6.59	6.70
XII	axOAc	125-128 (4)/1.5431 (28)	C ₁₄ H ₁₈ O ₂	78.48	78.78	6.59	6.75
	eqOAc	123-126 (2)/1.5421 (28)	C ₁₄ H ₁₈ O ₂	78.48	78.22	6.59	6.81

(40) F. P. Johnson, A. Melera, and S. Sternhell, *Australian J. Chem.*, **19**, 1523 (1966).

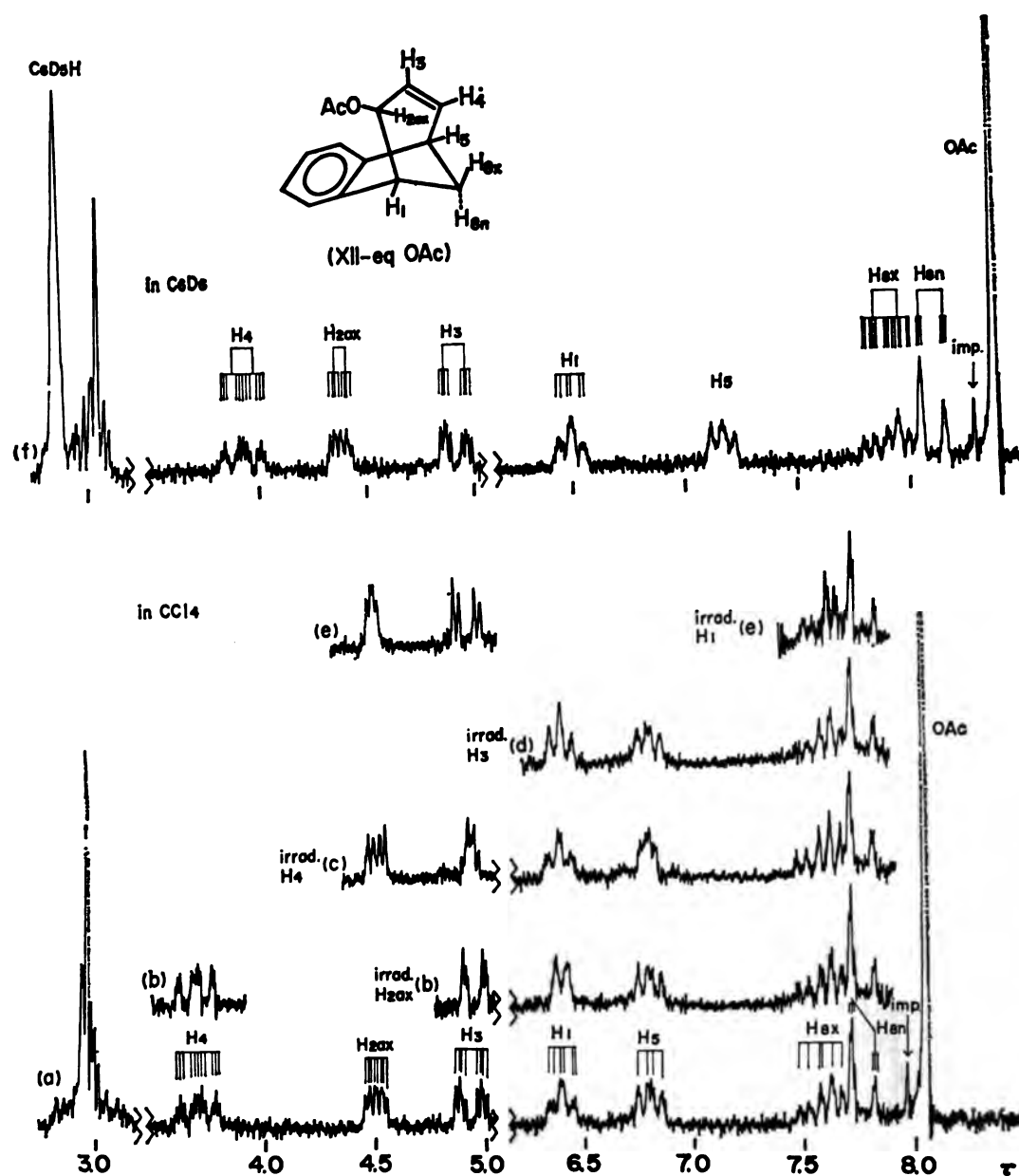


Figure 4. Nmr and nmr spectra of XII-eqOAc in CCl_4 and C_6D_6 at 100 MHz.

suggests an *exo* configuration for the acetoxyl. The nmr and nmtr experiments (see Figure 5 and Experimental Section) confirmed the structure of XI-*exo*-OAc from various approaches. The fact that $J_{8x,8n}$ (≈ 11.6 Hz) falls in a range of magnitudes expected from geminal couplings between methylene protons on a normal sp^3 carbon indicates, in accord with the above assignment, that the C_8 orbital is not highly strained.

Similarly, the nmr and nmtr experiments on XI-*endo*-OAc (see Figure 6 and Experimental Section) led us to conclude that this compound is an epimer of XI-*exo*-OAc. An important change in the spectrum of this compound from that of XI-*exo*-OAc is the appearance of a broad quartet due to H_{8x} ($J = 5.0$ and 3.0 Hz),²¹ instead of the broad singlet due to H_{8n} (see the dihedral angles in Table II).

Except $J_{7,8n}$ and $J_{6n,8n}$, many long-range couplings were observed, as expected from the ring system of XI according to "W-letter rule."³⁸ Besides the expectation, $J_{6n,8x}$ and $J_{6x,8n}$ were obtained, though less than or

equal to 0.2 Hz. It is interesting to note that $J_{1,3}$ and $J_{2,7}$ (7.0 Hz) are not equal to $J_{1,7}$ (5 Hz). This finding may suggest that the strain at C_1 and C_7 is different from that at C_2 .

Experimental Section⁴³

Properties and analyses of the new compounds prepared in the present study are summarized in Table III.

Materials. For the preparation of III-OH and IV-OH the reduction of benzobicyclo[2.2.2]octadien-2-one⁹ was carried out with 4 equiv of lithium aluminum hydride in anhydrous tetrahydrofuran. The usual work-up, followed by separation using elution chromatography over silica gel (Woelm neutral, added with 5% of H_2O), gave pure samples of III-OH and IV-OH in a ratio of 7:3.

Kinetic Measurements. The kinetic procedure for the acetoxylation studies was essentially the same as that employed previously.³⁹ In all cases the initial concentration of brosylate was approximately 0.03 M. The reactions were carried out in glacial acetic acid

(43) Melting points were taken by capillary and are corrected. Boiling points are uncorrected. Ultraviolet spectra were recorded on a Beckman DK-2 spectrometer.

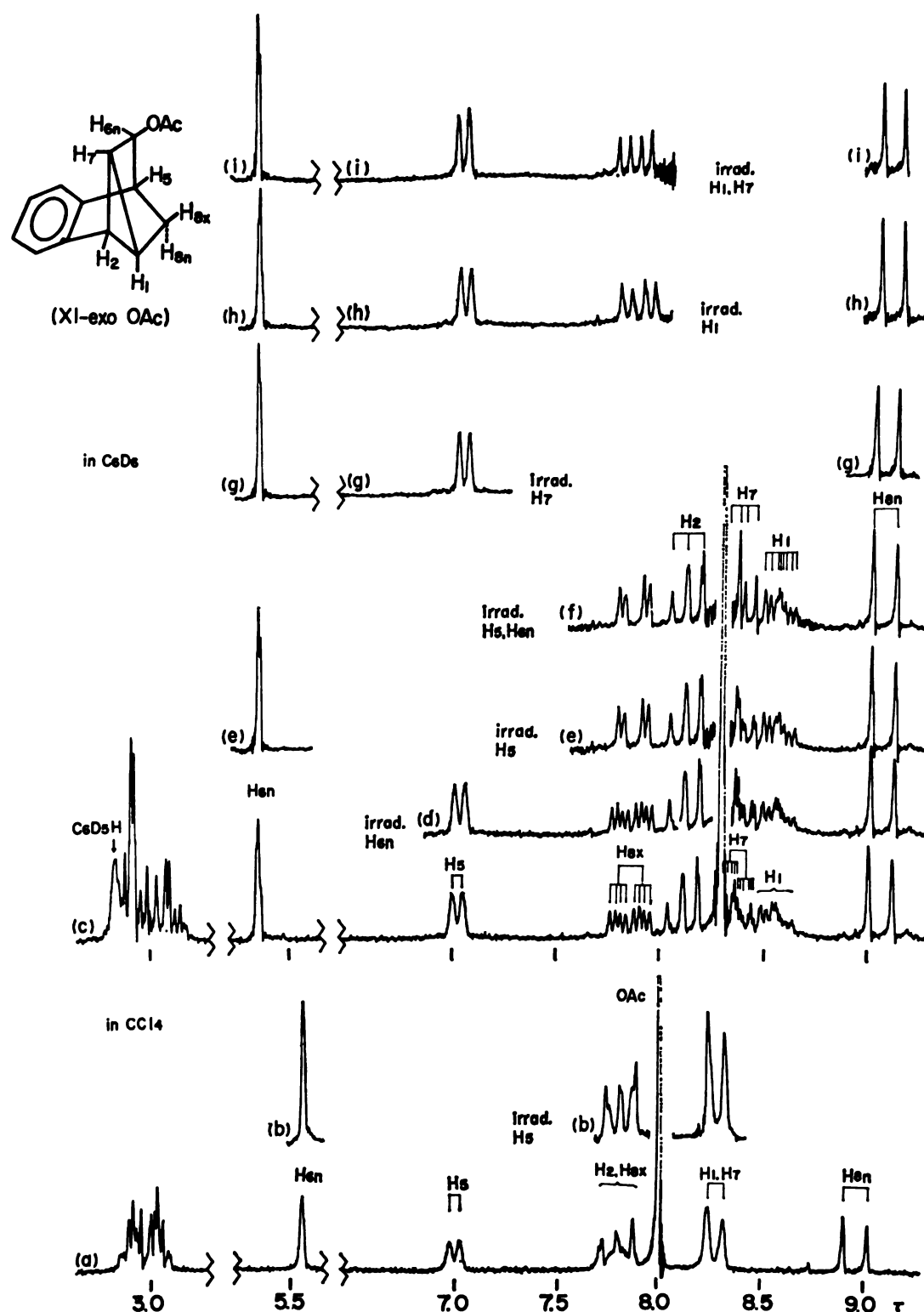


Figure 5. Nmr, nmbr, and nmtr spectra of XI-exo-OAc in CCl₄ and C₆D₆ at 100 MHz.

aining an equivalent of sodium acetate and 1 wt % of acetic anhydride. Rate constants were determined by the infinity titration method. Usually, ten aliquots, 2 ml in volume, were periodically drawn, run into 20 ml of cooled dioxane, and titrated immediately with 0.06 *M* standard perchloric acid solution. Infinity titers were obtained after at least ten half-lives. In all cases observed infinity titers were within $\pm 2\%$ of the calculated values.

The ethanolyses were carried out in anhydrous ethanol. They were followed by titrating usually ten aliquots, 2 ml in volume, which were quenched by adding to 20 ml of ice-cold acetone, with a standard solution of 0.006 *M* sodium methoxide in mixed benzene and methanol (1:3). A methanol solution of methyl red bromocresol green was used as the indicator.

Isolation of Acetolysis Products. The acetolysis solution was allowed to remain in a constant temperature bath for ten half-lives of each of the brosylates, concentrated by distilling the acetic acid, treated with ice-water, and extracted four times with pentane. The pentane solution was washed with aqueous sodium carbonate and dried. After removal of the solvent, the residue was subjected to analytical and preparative vpc.

Analytical Vapor Phase Chromatography. A standard column, 2 m \times 6 mm, of stainless-steel tubing was employed with helium as a carrier gas in a Hitachi gas chromatograph Model F-6. The column was packed with 10 wt % diethylene glycol succinate polymer on 30–60 mesh Chromosorb W. The retention times of I-OAc, II-OAc, VIII-axOAc, VIII-eqOAc, and IX-axOAc were 16.5,

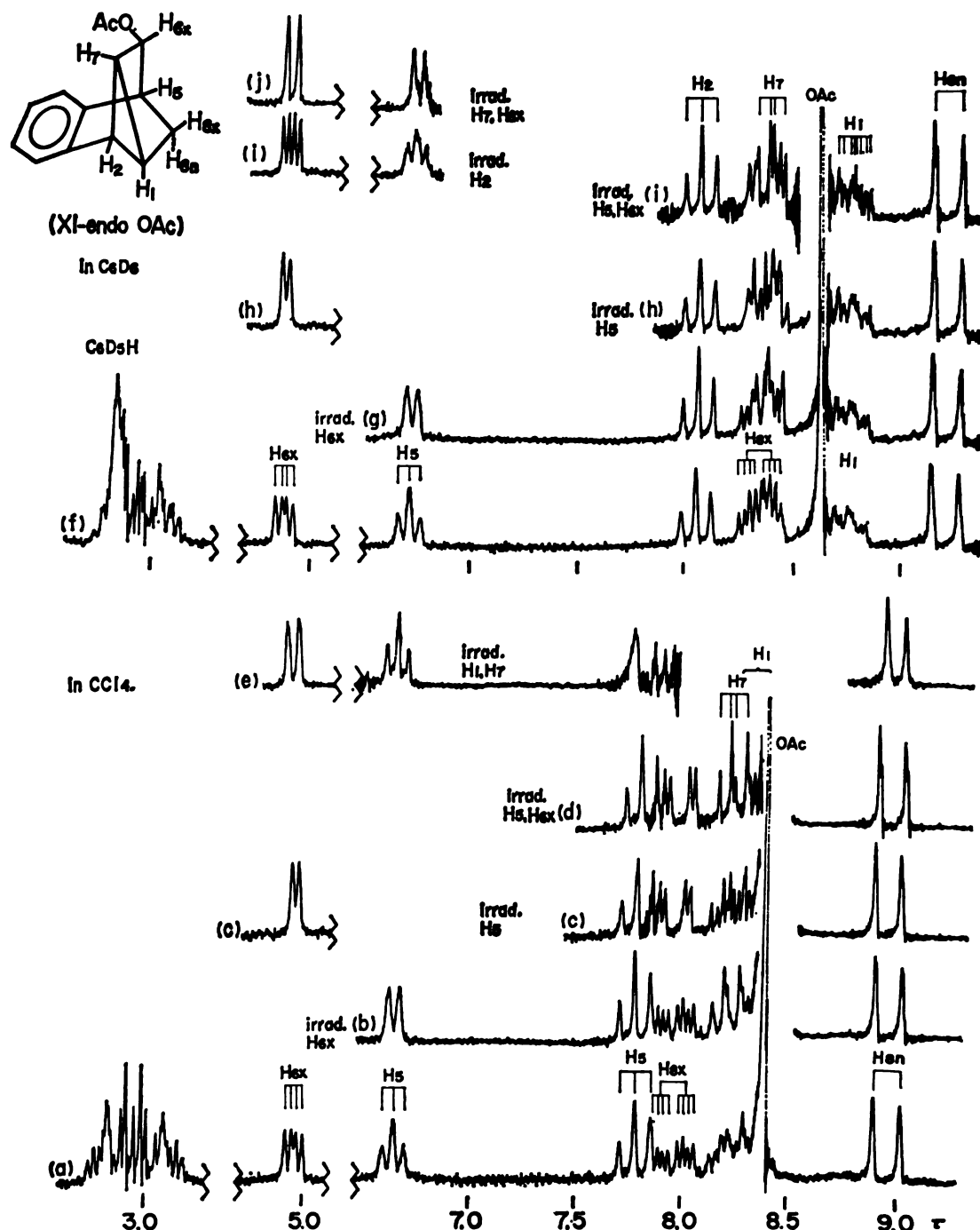


Figure 6. Nmr, nmdr, and nmtr spectra of XI-endo-OAc in CCl₄ and C₆D₆ at 100 MHz.

18.5, 19.2, 17.5, and 13.5 min, respectively, at 200° with 1.5 kg/cm² of He. Those of X-axOAc, X-eqOAc, XI-endo-OAc, and XI-exo-OAc were 15.0, 18.0, 18.0 (overlapped), and 25.0 min, respectively, at 190° with 1.5 kg/cm² of He. Capillary vpc on a 45-m Golay Z-45 at 125° with 1.0 kg/cm² of He showed separated peaks at the retention time of 10.5 for X-eqOAc and 11.0 for XI-endo-OAc. The retention times of III-OAc, IV-OAc, XII-axOAc, and XII-eqOAc were 15.2, 18.3, 16.0, and 18.0 min, respectively, at 190° with 1.5 kg/cm².

Preparative vapor phase chromatography was carried out (a) on a Hitachi gas chromatograph Model F-6, equipped with a 2 m × 21 mm stainless-steel tubing column packed with 10 wt % of diethylene glycol succinate polymer on 30–60 mesh Chromosorb W (column A); (b) on a Yanagimoto gas chromatograph Model GCG-3D, equipped with a 5 m × 14 mm stainless-steel tubing column packed with 5 wt % diethylene glycol succinate polymer on the same support (column B). The retention times were 15.2 and 13.0 min, respectively (200° of column B and 300 cc/min of He),

for II-OAc and IX-axOAc; 19.5, 23.5, 23.5 (overlapped), and 32.0 min, respectively (210° of column A and 600 cc/min of He), for X-axOAc, X-eqOAc, XI-endo-OAc, and XI-exo-OAc; 20.5 and 22.5 min, respectively (210° of column A and 500 cc/min of He), for XII-axOAc and XII-eqOAc.

Benzo[3,4]bicyclo[3.2.1]octen-2-one. A solution of 72 mg of VIII-axOH, 53.6 mg of benzoquinone, and 203.6 mg of aluminum *t*-butoxide in 7 ml of benzene was refluxed overnight. The mixture was washed with dilute sulfuric acid and then with aqueous sodium hydroxide until the inorganic layer was colorless. The benzene solution was dried and evaporated, and the residue was distilled to give 59 mg of the ketone at 132–135° (5 mm), *n*_D²⁰ 1.5684 (lit.⁹ bp 162–163° (23 mm), *n*_D²⁰ 1.577), *λ*_{max}^{200m} 249 mμ (ε 11,600) and 293 (2310).

Anal. Calcd for C₁₃H₁₂O: C, 83.69; H, 7.02. Found: C, 83.59; H, 7.14.

Axial 2,3-Dichlorobenzo[6,7]bicyclo[3.2.1]octa-3,6-diene (XIII). To a stirred solution of 121 g of benzonorbornene in 500 g of dry

form, maintained at 0° under nitrogen, was added 175 g of sium *t*-butoxide during 6 hr. The mixture was added to water neutralized with hydrochloric acid. The organic layer was and distilled to remove *t*-butyl alcohol, chloroform, and most unchanged benzonorbornene. Further distillation under pressure, followed by elution chromatography, gave 10 g II, bp 124–125° (2 mm), n_D^{25} 1.5963, nmr in CCl₄: four aromatic H at τ 2.6–3.0 (m), one vinyl H at 3.61 (d), one C₁ H at 5.74 (d), one C₁ bridgehead H at \sim 6.35 (m), one C₂ bridgehead H at \sim 6.60 (m), two C₃ H at 7.4–8.0 (m), $J_{1,2} = 2.1$ Hz, $J_{1,3} = 6.8$ Hz.

Calcd for C₁₂H₁₀Cl₂: C, 64.02; H, 4.48. Found: C, 64.02; H, 4.48.

1-Chloro-2(axial)-hydroxybenzo[6,7]bicyclo[3.2.1]octa-3,6-diene (X-axOH). A suspension of 2.7 g of XIII, 4.0 g of calcium carbonate, 10 ml of tetrahydrofuran, and 40 ml of water was refluxed under nitrogen for 51 hr. The mixture was extracted with ether. Evaporation of the ether gave 2.2 g of XIV, mp 119–120°; nmr in CCl₄: aromatic H at τ 2.6–3.0 (m), one vinyl H at 3.64 (d), one C₂ H at 6.11 (d), two C₁ bridgehead H at \sim 6.5 (m), two C₃ H at \sim 7.7 (m), $J_{1,2} = 2.2$ and $J_{4,5} = 7.2$ Hz.

Calcd for C₁₂H₁₀ClO: C, 69.74; H, 5.37; Cl, 17.15. Found: C, 70.09; H, 5.76; Cl, 17.32.

Hydrogenation of XIV. A solution of 127 mg of XIV in 3 ml of tetrahydrofuran and 0.7 ml of 1.0 *N* sodium hydroxide was hydrogenated over palladium-charcoal. The hydrogen uptake was 29.0 ml. The usual work-up left 98 mg of crude IX-axOH. Purification was performed by preparative vpc: 10% diethylene glycol succinate polymer on Chromosorb W, column temperature 185°, 30 cc/min, retention time 18.5 min, nmr in CCl₄: four aromatic H at τ \sim 2.9 (m), one CHOH at 6.13 (m), two bridgehead H at 6.9 (m), six H at 7.5–9.0 (m); nmr of the acetate (IX-axOAc) in CDCl₃: four aromatic H at τ \sim 2.9 (m), one CHOAc at 5.17 (m), two bridgehead H at \sim 6.8 (m), six H at 7.6–9.1, three CH₃CO at 7.1.

Nmr Measurements. Nmr spectra were taken with a Varian A spectrometer (60 MHz), calibration of which was checked by the usual side-band method, and/or a Varian HA-100 spectrometer operating at a 100-MHz field in the frequency-swept and tetramethylsilane (TMS) locked mode. The calibration of 100-MHz spectra was made by using a Hewlett-Packard HP-5212A electronic reference. Accuracies of chemical shifts and coupling constants are ± 0.01 and ± 0.1 Hz, respectively. The spectra were recorded by using about 2–5% (w/v) solutions of samples in CCl₄ or C₆D₆ containing TMS as an internal reference. Nmr and nmr experiments were made by using the HA-100 spectrometer and two Hewlett-Packard HP-200ABR audio-oscillators in frequency-swept operation.

Procedure for the Nmr Spectral Assignments of Benzo[bicyclo[3.2.1]octadiene Derivatives X and XII. The spectrum of X-axOAc in CCl₄ (Figure 1a) shows a singlet at τ 7.96 due to the acetoxy methyl protons, a quartet at about τ 7.8 assignable to the bridge methylene H_{2a} and H_{2b}, two multiplets at τ 7.11 and 6.66 due to the bridgehead H₁ and H₄, two quartets at τ 4.10 and 3.53 arising from the olefinic protons H₃ and H₇, a doublet at τ 4.38 corresponding to H₅, and complex multiplets at lower fields due to benzene ring protons. In this spectrum, the signal positions of H_{2a} and H_{2b} are so close that their assignments are difficult and the signals of H₁ and H₄ appear as second-order patterns. Double irradiation at the center of resonance frequencies of H_{2a} and H_{2b} (Figure 1b) made the two quartets at τ 4.10 ($J = 5.8$ and 3.1 Hz) and 4.38 ($J = 5.8$ and 2.7 Hz) and a doublet at τ 4.38 ($J = 2.0$ Hz) relatively sharper, showing the presence of weak long-range couplings, and changed the multiplet at τ 7.11 into a quartet ($J = 2.7$ and 2.0 Hz), which was assignable to H₁, and the multiplet at τ 6.66 into a doublet ($J = 3.1$ Hz), which might be due to H₄. On double irradiation on H₃, one olefinic proton signal at τ 3.53 collapsed to a doublet ($J = 5.8$ Hz), which was therefore assigned to H₇. Decoupling of H₁ resulted in splitting of the H₇ signal at τ 4.10 into a doublet ($J = 5.8$ Hz) and the doublet at τ 4.38 into a somewhat broad singlet, assignable to H_{5a} on the basis of its $J_{1,5}$ value.^{10–12} These experiments showed that no appreciable $J_{1,6}$, $J_{1,7}$, and benzylic couplings^{10,12} are detectable. The spectrum in C₆D₆ (Figure 1c) shows the signals of H₁ and H₄ separately as a doublet of triplets ($J = 10.0$ and 4.7 Hz) and a doublet ($J = 10.0$ Hz), respectively, as expected from the spectrum of benzene.^{10,12} These assignments were made according to the Karplus correlation¹³ (see the dihedral angles in Table II). Double irradiation on H_{2a} (τ 4.10) made each H_{2a} signal peak very sharp (Figure 1d). On triple irradiation on H₁ and H₇ (Figure 1e), the H_{2a} peak clearly appeared as a doublet ($J = 0.8$ Hz), and each

H_{2b} peak changed into a clear triplet ($J = 0.5$ Hz). This irradiation also collapsed the H₁ and H₇ signals into a doublet of quartets ($J = 4.7$, 2.0, and 0.5 Hz) and a quartet ($J = 4.7$ and 0.5 Hz), respectively. These nmr and nmr spectra proved the presence of a long-range $J_{2a,7}$ of 0.8 Hz.^{10,12}

The spectrum of X-eqOAc in CCl₄ (Figure 2a) shows overlapping multiplets at about τ 6.8 due to H₁ and H₄. Double irradiation at τ 6.8 changed two quartets at τ 3.60 and 4.29 due to the two olefinic protons into two doublets ($J = 5.8$ Hz) which are coupled to each other, the doublet at τ 4.04 ($J = 5.4$ Hz) due to H_{2a} into a singlet,^{10–12} a doublet of triplets at τ 7.74 into a doublet ($J = 10.3$ Hz), and a doublet at τ 7.95 ($J = 10.3$ Hz) into a somewhat sharper signal. This irradiation (Figure 2b) also revealed the presence of a weak long-range coupling between H₂ and one olefinic proton which gave the quartet at τ 4.29. On each double irradiation on an olefinic proton at τ 3.60 and the other one at τ 4.29 (Figures 2c and 2d), a doublet ($J = 5.0$ Hz) and a quartet ($J = 5.4$ and 5.0 Hz), respectively, clearly arose from the overlapping multiplets at about τ 6.8, respectively. Triple irradiation on the two olefinic protons resulted in the multiplets changing to the doublet due to H₁ and the quartet due to H₇ simultaneously. This irradiation also made some change in the signals arising from H_{2a} and H_{2b}. Therefore, the quartets at τ 3.60 and 4.29 were assigned to H₃ and H₇, respectively. These observations provided evidence for the structure of X-eqOAc. Applying the Karplus correlation,¹³ we reached the assignments such that the doublet of triplets ($J = 10.3$ and 5.0 Hz) at τ 7.74 and the doublet further weakly split into triplets ($J = 10.3$ and ca. 0.5 Hz) at τ 7.95 arise from H_{2a} and H_{2b}, respectively, from the dihedral angles listed in Table II. Similar nmr and nmr experiments on X-eqOAc in C₆D₆ were made to obtain the same conclusion. As shown in Figure 2e, the signals of H₁ at τ 6.78 and H₄ at τ 7.03 are well separated and supported the above assignments. $J_{1,6}$ and $J_{1,7}$ are too small to be determined from these examinations. In addition, the long-range $J_{2a,7}$, $J_{2b,6}$, and $J_{1,5}$ in X-axOAc and X-eqOAc were found to be weak up to the extent of 0.3 Hz.

The spectrum of XII-axOAc in CCl₄ (Figure 3a) exhibits well-unresolved signals because the differences between the chemical shifts of H₁ and H₄ and of H_{2a} and H_{2b} are very small. The nmr spectrum irradiated simultaneously on H_{2a} and H_{2b} (Figure 3b) showed a distinct octet at τ 3.60 ($J = 9.6$, 6.6, and 1.0 Hz) due to one olefinic proton. On double irradiation at the resonance frequency of the center of the two overlapping multiplets due to H₁ and H₄ (Figure 3c), the signal at τ 3.60 collapsed to a doublet of triplets ($J = 9.6$ and 1.0 Hz), a doublet of quartets at τ 4.80 ($J = 9.6$, 3.6, and 1.8 Hz) to a quartet ($J = 9.6$ and 3.6 Hz) which was therefore assignable to the other olefinic proton signal, a quartet of doublets at τ 4.99 ($J = 3.6$, 2.0, and 1.0 Hz) to a quartet ($J = 3.6$ and 1.0 Hz), and the signals due to H_{2a} and H_{2b} to a broad singlet, which implies the difference between their chemical shifts are small. From these results, we can assign the signals at τ 3.60, 4.80, and 4.99 to H₃, H₇, and H_{2a}, respectively, and, accordingly, XII-axOAc belongs to the benzo[6,7]bicyclo[3.2.1]octa-3,6-diene, and conclude from $J_{1,2}$ of 2.0 Hz that the acetoxy has an *ax* configuration.^{11–13} Long-range J 's were determined by nmr and nmr experiments in C₆D₆, in which the signals of H_{2a} and H_{2b} as well as those of H₁ and H₄ were well separated, as shown in Figure 3d. A doublet of triplets at τ 7.75 ($J = 10.1$ and 0.9 Hz) and a doublet of triplets of doublets at τ 7.94 ($J = 10.1$, ca. 4.5, and 1.0 Hz) were respectively assigned to H_{2a} and H_{2b} from their coupling constants to the bridgehead protons because the models showed that the acute dihedral angle between H₁(H₄) and H_{2a} is larger than that between H₁(H₄) and H_{2b} (Table II). The nmr spectrum irradiated at the resonance frequency of the center of the H_{2a} and H_{2b} signals (Figure 3e) showed a doublet ($J = 4.6$ Hz) at τ 6.69, a doublet at τ 3.60 ($J = 6.6$ Hz), an unchanged quartet of multiplets at τ 6.97 ($J = 6.6$ and 4.2 Hz), and the H_{2a} and H_{2b} signals. Decoupling of H₁ (Figure 3f) resulted in the signal at τ 6.97 changing into a doublet ($J = 4.2$ Hz) which can be assigned to H₇, and each peak of the H_{2a} signal changing into single sharp one. Thus, the long-range $J_{4,5a}$ of 1.0 Hz was confirmed.¹⁰ Triple irradiation on H_{2a}, H₃, and H₇ that changed the H₁ (τ 6.69) and H₄ (τ 6.97) signals into two doublets made it possible to determine $J_{1,2a}$ (4.6 Hz) and $J_{1,2b}$ (4.2 Hz) (Figure 3g). While double irradiation on H₂ did not cause any changes in the signals of H_{2a} and H_{2b}, a coupling ($J = 1.8$ Hz) in the signal of H₇ disappeared in the spectrum irradiated on H₁ (Figure 3h). These experiments provided evidence for the long-range $J_{1,5}$ (1.8 Hz). The second-order patterns of the signals of H₁ and H₄ are due to the close positions of the signals of H_{2a} and H_{2b}.

The nmr spectra of XII-eqOAc in CCl_4 and C_6D_6 are essentially the same except for the signal positions (Figures 4a and 4f). Decoupling experiments similar to the above revealed signal assignments and all J 's (Figures 4b-e). These results are consistent with the structure of XII-eqOAc. Long-range J 's in these compounds are listed in Table II.

Procedure for the Nmr Spectral Assignments of Benzo[3,4]tricyclo[3.2.1.0^{2,7}]octene Derivatives XI. The spectrum of XI-*exo*-OAc in CCl_4 (Figure 5a) shows complicated signals due to two protons at about τ 7.8 and a broad doublet due to two protons at about τ 8.28, so that the signal assignment was difficult. Moreover, the nmrd spectrum irradiated at τ 7.00 (a broad doublet signal) also gave no insight, as shown in Figure 5b. However, the appearance of only one signal at τ 7.00 assignable to the bridgehead proton can exclude the XV structure. Further, a singlet at τ 5.55 indicates a C_6 *exo*-acetoxyl²¹ in the benzo[3,4]tricyclo[3.2.1.0^{2,7}]oct-3-ene system. The spectrum in C_6D_6 (Figure 5c) shows all proton signals separated. Double irradiation on a thin triplet at τ 5.35 assignable to H_{ax} (Figure 5d) made each peak of a doublet at τ 7.02 due to the bridgehead H_a and a multiplet around τ 8.5 fairly sharp, and caused a quartet of triplets at τ 8.38 ($J = 7.0, 5.0, \text{ and } 1.0 \text{ Hz}$) to collapse into a quartet of doublets ($J = 7.0, 5.0, \text{ and } 1.0 \text{ Hz}$). On double irradiation at τ 5.55 (H_a) (Figure 5e), a doublet of quartets at τ 7.85 ($J = 11.6, 4.9, \text{ and } 2.8 \text{ Hz}$), the quartet of triplets at τ 8.38, the multiplet at about τ 8.5, a doublet at τ 9.06 having some broadening ($J = 11.6 \text{ Hz}$), and the thin triplet at τ 5.35 due to H_{ax} were changed into a doublet of doublets ($J = 11.6 \text{ and } 2.8 \text{ Hz}$), a quartet of doublets ($J = 7.0, 5.0, \text{ and } 1.0 \text{ Hz}$), a sharper signal, a doublet of doublets ($J = 11.6 \text{ and } 0.6 \text{ Hz}$), and a thin doublet ($J = 1.0 \text{ Hz}$), respectively. Triple irradiation on H_a and H_{ax} (Figure 5f) gave important changes in the two signals at τ 8.38 and 8.5; the former collapsed to a distinct quartet ($J = 7.0 \text{ and } 5.0 \text{ Hz}$), the lowest field peak of which is overlapped with the acetoxyl signal, whereas the latter multiplet collapsed to a doublet of quartets further split into thin doublets ($J = 7.0, 5.0, 2.8, \text{ and } 0.6 \text{ Hz}$). These decoupling experiments confirmed the assignments given in Figure 5 and determined J 's in Table II. Dredging models suggest that several long-range J 's should be found in this ring system, besides $J_{1,2}$ and $J_{1,7}$ (1.0 Hz) already obtained, according

to the "W-letter rule."²² The absence of $J_{\text{ax},\text{ax}}$ was indicated by no change in the signal shape of H_{ax} suffered from double irradiation on H_{ax} . Double and triple irradiation on H_a and H_a resulted in changes of the signals of H_{ax} , H_a , H_{ax} , and H_{ax} (Figures 5g-i), and showed the presence of $J_{1,\text{ax}}$ (0.4 Hz) and the absence of $J_{1,\text{ax}}$. Although we failed to determine the magnitudes of $J_{2,\text{ax}}$ and $J_{\text{ax},\text{ax}}$ they may be up to the extent of 0.2 Hz.

The spectra of XI-*endo*-OAc in CCl_4 and C_6D_6 (Figures 6a and 6f) show features similar to that of XI-*exo*-OAc in C_6D_6 . However, in XI-*endo*-OAc the signals of H_{ax} and H_a appear as a quartet having some broadening ($J = 5.0 \text{ and } 3.0 \text{ Hz}$) and as a triplet further split into multiplets ($J = 5.0 \text{ Hz}$). Decoupling experiments in CCl_4 (Figures 5b-e) confirmed assignments of the signals and determined the J 's in Table II. In this case, the signals of H_a and H_a overlapped. However, triple irradiation on H_a and H_{ax} revealed the H_a signal. The values of $J_{1,\text{ax}}$ (5.0 Hz) and $J_{\text{ax},7}$ (5.0 Hz) indicate an *endo* configuration²¹ for the acetoxyl (see the dihedral angles in Table II). Similar nmrd and nmtr experiments in C_6D_6 (Figures 5g-j) also confirmed the assignments and J 's. Here, the signals of H_a and H_{ax} overlapped. Double irradiation on H_a and on H_a and H_{ax} , respectively, indicated the presence of $J_{2,\text{ax}}$ (0.4 Hz) and $J_{\text{ax},\text{ax}}$ ($\leq 0.2 \text{ Hz}$). However, we could not determine the magnitudes of $J_{1,2}$ and $J_{1,\text{ax}}$.

Nmr of Benzo[3,4]bicyclo[3.2.1]octene Derivatives in CCl_4 . The spectrum of VIII-*ax*OH showed four aromatic H at τ 2.6-3.0 (m), one CHOH at 5.73 (d), two bridgehead H at 6.94 (m) and 7.47 (m), eight H at 7.9-9.1, and $J_{1,2} = 2.8 \text{ Hz}$. The spectrum of VIII-eqOH showed four aromatic H at τ 2.7-3.4 (m), one CHOH at 5.24 (d), two bridgehead H at 7.12 (m) and 7.55 (m), eight H at 8.0-8.8, and $J_{1,2} = 4.6 \text{ Hz}$. The CHOH in VIII-*ax*OAc appeared at τ 4.46 ($J_{1,2} = 2.5 \text{ Hz}$), and that in VIII-eqOAc appeared at 3.93 ($J_{1,2} = 4.6 \text{ Hz}$).

Acknowledgment. We thank Professor Harold Hart for his kind comments, Messrs. Akio Matsuura, Kensuke Sakurai, and Shuji Teratake for technical assistance, and Miss Masako Ohtsuru for spin-decoupling experiments.

Arylation by Aromatic Nitro Compounds at High Temperatures. II. Nitrobenzene Alone and with Benzene and Benzene- d_6

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Contribution from the Research and Development Department, Amoco Chemicals Corporation, Whiting, Indiana, and the Research and Development Department, American Oil Company, Whiting, Indiana 46394. Received February 13, 1967

Abstract: The nitroarene bond in nitrobenzene and other aromatic nitro compounds breaks above 400°; this provides an easy means of generating phenyl and a great many other aromatic radicals. The decomposition of nitrobenzene alone at 600° seems to parallel rather closely its decomposition under electron impact in the mass spectrometer. With benzene and benzene- d_6 , nitrobenzene yields mainly biphenyl and terphenyl and their deuterated analogs, respectively. Higher yields than calculated on the basis of only one radical indicate the involvement of the NO_2 portion of the original nitrobenzene.

Although nitrobenzene has been known for over 130 years² and has been the subject of innumerable investigations as well as the source of many useful chemicals, its thermal decomposition products have never been adequately described. Smith³ studied the kinetics of its decomposition at 455-515° and 17-92 min in Pyrex, and concluded that the reaction was largely homogeneous, between first and second order,

with an activation energy of 51 kcal/mole. Maksimov⁴ determined the first-order rate constant for nitrobenzene decomposition at 395-445°, and confirmed Smith's value for the activation energy. Neither author proposed a mechanism or determined any nongaseous products.

The discovery that the nitroarene bond in nitrobenzene and other aromatic nitro compounds breaks above 400° made possible the easy generation of phenyl and

(1) (a) Amoco Chemicals Corp. (b) American Oil Co.

(2) E. A. Mitscherlich, *Ann. Physik*, **31**, 625 (1834).

(3) R. E. Smith, *Trans. Faraday Soc.*, **36**, 985 (1940).

(4) Y. Y. Maksimov, *Teoriya Vzrychatykh Veshchestv*, Sb. Sten. 338 (1963); *Chem. Abstr.*, **59**, 15137a (1963).

eat many other aromatic radicals.⁵ Our first con-
clusion was to determine the scope of this new reaction.
Accordingly, nitrobenzene was heated in a flow system
alone, and in admixture with a wide variety of
aromatic compounds, and the major products were
determined by gas chromatography and mass spec-
troscopy. This paper describes the results of thermal
decomposition of nitrobenzene alone and with benzene
benzene-*d*₆.

Experimental Section

Experiments were run in a Vycor tube filled with Vycor beads, in an
electric furnace maintained at $600 \pm 1^\circ$ under pure dry nitrogen
contact times of 5–20 sec. The vapors were condensed in a
trap at -10° . The condensate was distilled to recover unreacted
nitrobenzene, and the residue was analyzed. Noncondensable gases
caught in a gas bulb for analysis.

Analyses were performed with a Consolidated Model 21-103c
mass spectrometer with the inlet system at 250 or 325°; with a
directly coupled gas chromatograph-mass spectrometer com-
bination⁶ also employing a 21-103c instrument with an electron
multiplier in place of the Faraday-cup detector; and by gas chro-
matography on a column of polyethylene glycol sebacate on Chro-
mosorb W. Mass spectra were measured at the conventional 70
eV and at low voltage, 7.5 eV, uncorrected. For the low-
voltage measurements, the repellers were maintained at an average
potential of 3 eV, the exact values being selected to give maximum
sensitivity.

The reagents and standards for gas chromatography were pur-
chased from Aldrich Chemicals and used as received. Where
purity was critical, the reagent was analyzed and, if necessary,
purified by distillation, crystallization, and gas chromatography.

In a typical experiment, a solution of 5.11 ml (0.05 mole) of
benzene in 22.22 ml (0.25 mole) of benzene was passed through
a hot tube at 600° under nitrogen flowing at 45 cc/min. Contact
time was 9 sec. The vapors were condensed in a bulb at -10° ;
the condensate was distilled to recover 15.3 ml of benzene and give
a residue of products, the composition of which is shown in Table III.

Results and Discussion

Nitrobenzene Alone. After 20 sec at 600°, nitro-
benzene was completely decomposed and gave a 30
% yield of the products shown in Table I. To help

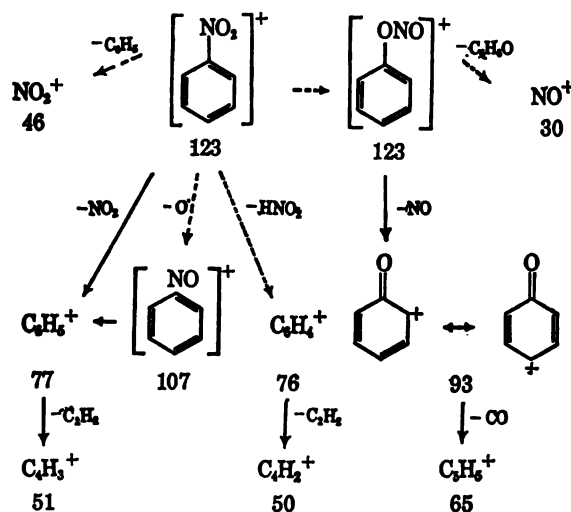
Table I. Products from Nitrobenzene

Product	Rel concn, ^a	Product	Rel concn, ^a
benzene	5.0	Diphenyl ether	0.7
aniline	1.4	Aminobiphenyl	0.7
phenol	27.2	Hydroxybiphenyl	3.7
naphthalene	0.2	Nitrobiphenyl	2.5
quinoline	2.2	<i>o</i> -Terphenyl	1.6
biphenyl	20.1	<i>m</i> -Terphenyl	3.0
carbazole	0.5	<i>p</i> -Terphenyl	3.9
benzofuran	15.1	Quaterphenyl	1.6

^a Determined by gas chromatography.

gain the formation of these products, we also re-
examined the decomposition of nitrobenzene under
electron impact in the mass spectrometer.^{7a} The major
ions in the mass spectrum of nitrobenzene are (solid
lines denote reaction steps supported by metastable
ions)

E. K. Fields and S. Meyerson, *J. Am. Chem. Soc.*, **89**, 724 (1967).
R. S. Gohlke, *Anal. Chem.*, **31**, 535 (1959); L. P. Lindeman and
Annals, *ibid.*, **32**, 1742 (1960); J. T. Watson and K. Biemann, *ibid.*,
35 (1964).
(a) J. H. Beynon, R. S. Saunders, and A. E. Williams, *Ind. Chim.*,
29, 311 (1964); (b) S. Meyerson, I. Puskas, and E. K. Fields,
Preliminary Reports, Division of Petroleum Chemistry, Vol. 11, No. 3, American
Chemical Society, 1966, p 231; *J. Am. Chem. Soc.*, **88**, 4974 (1966).



The relative intensities of the different species, expressed
as fractions of the total ion yield of mass 29 and higher,
are shown in Table II. The major single process thus

Table II. Partial Spectrum of Nitrobenzene

Mass	Species	Rel Inten, % ^a	Mass	Species	Rel Inten, % ^a
123	C ₆ H ₅ NO ₂ ⁺	11.9	65	C ₆ H ₅ ⁺	3.8
107	C ₆ H ₅ NO ⁺	1.0	51	C ₆ H ₃ ⁺	17.9
93	C ₆ H ₅ O ⁺	3.5	50	C ₆ H ₄ ⁺	7.3
77	C ₆ H ₅ ⁺	28.6	46	NO ₂ ⁺	0.6
76	C ₆ H ₄ ⁺	1.0	30	NO ⁺	4.5

^a Not corrected for contributions of species containing naturally
occurring heavy isotopes.

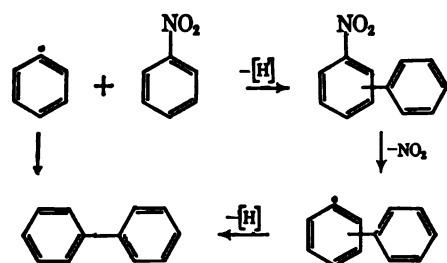
is loss of NO₂, directly and to some extent by a two-step
sequence, to give C₆H₅⁺, accompanied by the comple-
mentary loss of C₆H₅ to give NO₂⁺. The C₆H₅⁺ ion
splits out acetylene and goes to C₆H₃⁺. A significant
fraction of the nitrobenzene parent ions forms phenoxy
ions by loss of NO or NO⁺ by loss of a phenoxy radical,
presumably through an intermediate nitro-nitrite re-
arrangement;⁷ summing the intensities for C₆H₅O⁺,
C₆H₅⁺, C₆H₃⁺, which most likely arises chiefly by
loss of acetylene from C₆H₅⁺,⁸ and NO⁺ leads to an
estimate of 14.8% for the fraction of nitrobenzene
ions that react by this pair of complementary paths.

The thermolysis products can be rationalized in simi-
lar fashion. Phenyl radical, formed by breaking of the
phenyl-nitro bond, can abstract hydrogen from another
molecule of nitrobenzene and give benzene; this is,
however, only a minor reaction. It prefers to dimerize
to biphenyl or to add to the aromatic system, as in
solution chemistry,⁹ to give nitrobiphenyls.

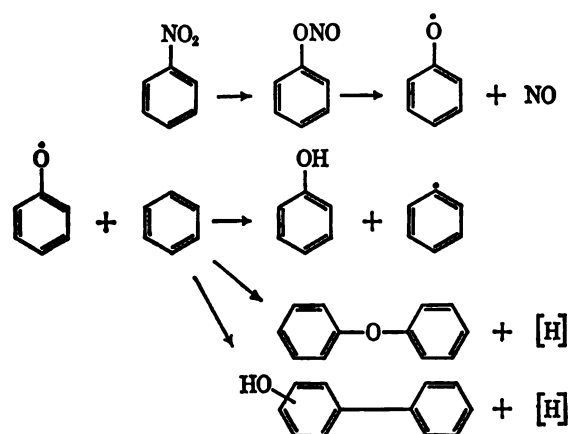
At 600° little nitrobiphenyl survives; it undergoes
decomposition just as nitrobenzene, and gives biphenyl
by hydrogen abstraction, quaterphenyl by dimerization,
and hydroxybiphenyl by rearrangement as well as
by alkylating the nitrobenzene and nitrobiphenyl.

(8) S. Meyerson, J. D. McCollum, and P. N. Rylander, *ibid.*, **83**, 1401
(1961); S. Meyerson, *ibid.*, **85**, 3340 (1963).

(9) D. H. Hey, A. Nechvatal, and T. S. Robinson, *J. Chem. Soc.*, 2892
(1951); T. Inukai, K. Kobayashi, and O. Simamura, *Bull. Chem. Soc.*
Japan, **35**, 1576 (1962); *Chem. Abstr.*, **58**, 5552f (1962).



Phenol, and probably some of the hydroxybiphenyl, arises by a nitro-nitrite rearrangement paralleling the process under electron impact.



Dibenzofuran forms from diphenyl ether, *o*-hydroxybiphenyl, or both, by intramolecular loss of hydrogen. It does not come directly from phenol itself, as phenol alone under identical conditions is converted in only 0.5% yield to a mixture of diphenyl ether, hydroxybiphenyls, and dibenzofuran.

The source of quinoline is not apparent. Quinoline results from the reaction of benzyne with pyridine,¹⁰ and benzyne may well form from nitrobenzene at 600° by elimination of HNO₂, as under electron impact, and indeed may account for all the naphthalene and some of the biphenyl listed in Table I. But whether pyridine forms at all here is uncertain. Intramolecular loss of oxygen at high temperatures has been observed for dibenzothiophene 5,5-dioxide,¹¹ and could conceivably occur in aromatic nitro compounds to give nitrenes; nitrene precursors form pyridine from benzene by insertion.¹² However, the lack of evidence for both pyridine and phenylpyridines among nitrobenzene decomposition products renders this mechanism unlikely. A 3-carbon atom fragment seems called for, to react with aniline in a Skraup-type synthesis, but none of the other products (except benzo-, dibenzo-, and tribenzoquinolines in trace amounts) gives evidence for such fragments. The formation of quinoline, and the detailed steps in nitrobenzene reduction to aniline, remain to be clarified.

Nitrobenzene with Benzene and Benzene-*d*₆. Nitrobenzene with benzene gave the products shown in Table III. Phenol is a minor product, suggesting that the decomposition of nitrobenzene to phenyl radical and nitrogen dioxide is faster than the nitro-nitrite

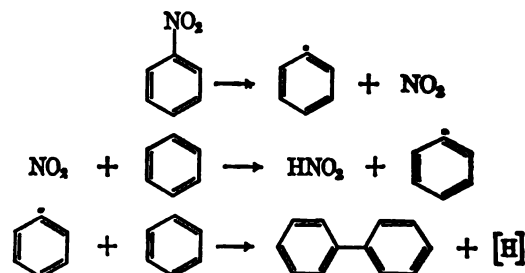
Table III. Reaction of Nitrobenzene with Benzene^a

Product	Rel concn, ^b mole ratio, nitro- benzene : benzene	
	1:5	1:25
Phenol	1.8	1
Naphthalene	0.3	...
Biphenyl	100.0	100
Dibenzofuran	11.5	1
Diphenyl ether, hydroxybiphenyl	3.4	3
Terphenyl	44.4	23
Phenyldibenzofuran	7.3	...
Phenyldiphenyl ether	1.0	...
Quaterphenyl	8.2	2
Diphenyldibenzofuran	1.8	...
Bisbiphenyl ether	0.3	...
Quinquephenyl	0.9	...
Triphenyldibenzofuran	0.3	...

^a At 600°, contact time 9 sec. ^b Relative intensities of the parent peaks of components in the mass spectrum measured at reduced ionizing voltage (7.5 v, uncorrected), normalized to biphenyl = 100 and taken as a first approximation to relative concentrations. Sensitivity, *i.e.*, the proportionality factor between parent-peak intensity and concentration, differs from one compound to another. However, closely related compounds have roughly equal sensitivities at the ionizing voltage employed in our work [G. F. Crable, G. L. Kearns, and M. S. Norris, *Anal. Chem.*, **32**, 13 (1960)]. For example, in the same sample analyzed by both low-voltage mass spectrometry and gas chromatography, the ratios of the concentrations of phenol and biphenyl were 1.37 and 1.35, respectively. In any case, the use of relative intensities is perfectly valid for inter-comparison of concentration ratios of identical components in separate samples [S. Meyerson and E. K. Fields, *Chem. Commun.*, 275 (1966)] within the limits of reproducibility of the low-voltage data.

rearrangement. Most of the biphenyl arises by reaction of benzene with the nitrobenzene rather than dimerization of the phenyl radical from nitrobenzene decomposition, as shown by the increasing proportion of biphenyl with decreasing concentration of the nitrobenzene. The yields of products are considerably different in the reactions at the two different concentration ratios, and thus give a clue to the mechanism of biphenyl formation.

At a nitrobenzene:benzene mole ratio of 1:5, the yield of biphenyl and terphenyl combined, as measured by gas chromatography, was 85 mole % based on 1 mole of phenyl radical produced per mole of nitrobenzene decomposed. At a mole ratio of 1:25, the yield on the same basis jumped to 170%. Both the phenyl radical and the nitrogen dioxide from the nitrobenzene must have been involved. The sequence of reactions is probably



Benzene in nitrogen dioxide at 600° gave a 12% yield of biphenyl plus terphenyl.

The gases from the reaction of nitrobenzene with benzene at 1:5 mole ratio at 600° run under helium

(10) E. K. Fields and S. Meyerson, *Chem. Commun.*, 474 (1965); *J. Org. Chem.*, **31**, 3307 (1966).

(11) E. K. Fields and S. Meyerson, *J. Am. Chem. Soc.*, **88**, 2836 (1966).

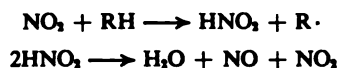
(12) K. F. Schmidt, *Ber.*, **58**, 2409 (1925); T. Curtius and A. Bertho, *ibid.*, **59**, 565 (1926).

e IV. Reaction of Nitrobenzene with Benzene- d_6 ^a

Product	Isotopic distribution ^b	Total concn ^c
Benzene	d_0 0.9	100
	d_1 2.4	
	d_2 1.7	
	d_3 0.8	
	d_4 2.2	
	d_5 17.3	
Phenol	d_0 29.1	4.4
	d_1 19.8	
	d_2 9.9	
	d_3 10.6	
	d_4 11.2	
	d_5 5.2	
Biphenyl	d_0 0.8	20.6
	d_1 0.7	
	d_2 1.3	
	d_3 1.6	
	d_4 1.6	
	d_5 4.4	
	d_6 18.2	
	d_7 16.4	
	d_8 8.5	
	d_9 5.8	
Terphenyl	d_0 14.4	4.2
	d_1 27.1	
	d_2 0.3	
	d_3 0.6	
	d_4 0.9	
	d_5 1.4	
	d_6 2.4	
	d_7 5.6	
	d_8 7.7	
	d_9 7.5	
	d_{10} 8.0	
	d_{11} 12.8	
	d_{12} 16.5	
	d_{13} 11.8	
	d_{14} 7.0	
	d_{15} 7.9	
	d_{16} 9.7	

At 600°, contact time 9.3 sec; mole ratio nitrobenzene:benzene = 1:5; isotopic composition of benzene, 0.2% d_4 , 5.7% d_6 , % d_6 . ^b Estimated from low-voltage (7.5 ionizing v, uncorrected) mass spectrum. ^c Relative intensities in the low-voltage spectrum, normalized to benzene = 100.

the percentage composition:¹⁸ CO₂, 0.3; CO, N₂O, 0.9; NO, 9.8; N₂, 0.7; H₂, 1.4; He, 84.5. NO₂ fragment of the nitrobenzene molecule apparently ends up chiefly as nitric oxide, either by direct action or *via* a series of free radical hydrogen abstractions and decompositions.¹⁴

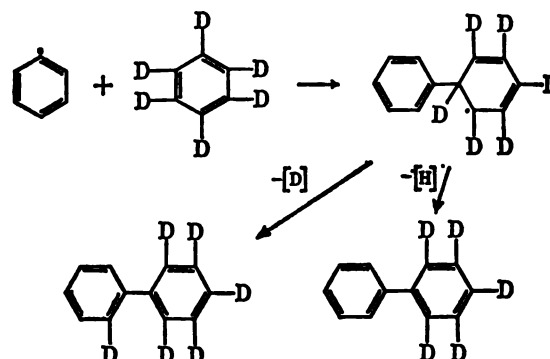


to observe more clearly the interaction of nitrobenzene fragments, nitrobenzene was decomposed at 600° in benzene- d_6 and the isotopic distribution of the products determined, as shown in Table IV. Despite the inevitable scrambling of protium and deuterium,^{15,16} the results are revealing.

(1) Small amounts of NO₂ might have been present and been removed by inadvertent chemical reaction with surface deposits in the mass spectrometer. See R. A. Friedel, A. G. Sharkey, J. L. Shultz, and C. R. Bert, *Anal. Chem.*, **25**, 1314 (1953).

(2) For the structure of nitrous acid in the gas phase and its dissociation products, see A. P. Cox and R. L. Kuczowski, *J. Am. Chem. Soc.*, **88**, 771 (1966), and references cited therein.

Biphenyl consisted mainly of four species: d_6 , d_8 , d_9 , and d_{10} . Only 0.7% was unlabeled; this measures roughly the extent of dimerization of the phenyl radical derived from nitrobenzene. Almost 40 times as much was biphenyl- d_{10} , formed presumably by abstraction of a deuterium atom from the benzene- d_6 by either fragment of the decomposed nitrobenzene, followed by dimerization of the phenyl- d_5 radical or arylation of benzene- d_6 by the phenyl- d_5 radical. The appreciable amount of biphenyl- d_6 probably forms in part, at least, by arylation of benzene- d_6 by the phenyl- d_5 radical. Arylation of benzene- d_6 by unlabeled phenyl radical should give biphenyl- d_6 ; the formation of almost as much biphenyl- d_6 suggests that in the reaction



the intermediate phenylcyclohexadienyl radical has a lifetime sufficiently long to exchange protium and deuterium intramolecularly before it is restored to full aromaticity. This is perhaps not too surprising, in view of the evidence for a phenylcyclohexadienyl intermediate in scrambling of protium and deuterium in the pyrolysis of benzene- d_6 .^{15a}

Isotopic composition of the terphenyl indicates that the bulk of the terphenyl consists of two rings originally derived from benzene- d_6 and one from nitrobenzene. This suggests either of two processes: phenylation of biphenyl- d_6 and - d_{10} by unlabeled phenyl radical, or attack by phenylcyclohexadienyl radical on benzene- d_6 , followed by rearomatization. That the concentration of terphenyl- d_4 is less than half that of terphenyl- d_6 , if these small numbers are significant, may be accounted for by an isotope effect, directing the incoming phenyl radical to the unlabeled, rather than to the deuterated, benzene ring.

Isotopic composition of the phenol is unexpected. Such a reactive aromatic system should exchange ring hydrogens with benzene- d_6 more readily than an unsubstituted benzene, which from the isotopic spread seems to be the case. However, phenol- d would be predicted far to exceed in amount the unlabeled phenol, if abstraction by the phenoxy radical occurred with equal ease from benzene- d_6 or nitrobenzene. Formation of more unlabeled than monodeuterated phenol suggests a reaction involving an intermediate derived from two molecules of nitrobenzene, in which the phenoxy radical site has ready access to a source of hydrogen.

(15) (a) E. K. Fields and S. Meyerson, *ibid.*, **88**, 21 (1966); (b) *ibid.*, **88**, 3388 (1966).

(16) To estimate the extent of scrambling to be expected, an equimolar mixture of benzene and benzene- d_6 was heated at 600° for 9 sec. The percentage isotopic composition of the recovered benzene was: d_0 , 46.2; d_1 , 4.0; d_2 , 0.4; d_3 , 0.1; d_4 , 0.7; d_5 , 6.8; d_6 , 41.8. The scrambling is low enough to justify conclusions drawn from the reaction of nitrobenzene with benzene- d_6 .

Subsequent articles will describe the phenylation of additional aromatic and heterocyclic compounds by nitrobenzene at elevated temperatures.

Acknowledgment. The authors acknowledge with thanks the assistance of D. K. Albert of the American Oil Company in gas chromatographic analyses.

The Participation of Solvent and General Acids in Acetal Hydrolysis. The Hydrolysis of 2-(*para*-Substituted Phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes

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Contribution from the Department of Biochemistry, University of Southern California, Los Angeles, California 90033. Received January 20, 1967

Abstract: The hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane in 0.100 *M* HCl is characterized by a ΔS^\ddagger of -14.2 eu and a D_2O solvent isotope effect of $k_D/k_H = 2.4$. The value of ρ for hydrolysis of a series of 2-(*para*-substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in 0.100 *M* HCl at 30° was found to be -2.0 . The values of ΔS^\ddagger and k_D/k_H are considerably less than normally found in acetal hydrolysis while the ρ value is much more positive than found previously for hydrolysis of the diethyl acetals of *meta*- and *para*-substituted benzaldehydes. The rate constants for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in moderately concentrated HCl solutions are proportional to the stoichiometric acid concentration while a plot of $\log k_{\text{obsd}}$ vs. $-H_0$ shows a pronounced downward curvature. The slope w of a plot of $\log k_{\text{obsd}} + H_0$ vs. the logarithms of the activity of water is $+1.9$. Thus the evidence supports the incursion of an A2 mechanism involving attack of water on the protonated substrate. The rate of hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane is subject to catalysis by increasing concentrations of formic acid at constant pH and ionic strength.

The generally accepted mechanism for the acid-catalyzed hydrolysis of acetals involves a fast pre-equilibrium protonation of the substrate followed by a unimolecular rate-determining decomposition to an alcohol and a resonance-stabilized carbonium ion.¹ The hydrolysis of fully protonated 2-(substituted phenyl)-3-ethyloxazolidines, carbonyl derivatives similar to acetals (1,3-dioxolanes) in which an oxygen has been replaced by an N-ethyl group, is marked however by solvent participation and general catalysis in the ring-opening step.²

It was thought that similar mechanisms might be observable in the hydrolysis of acetals if the A1 transition state could be made sterically unfavorable. Intramolecular participation by various functional groups in acetal hydrolysis has been postulated in several instances.³⁻⁶ The mechanism of such participation, however, has not been established. The clearly unambiguous finding of buffer catalysis and solvent participation in an acetal hydrolysis could lead to insight into the mechanistic possibilities by which glycosidic enzymes effect catalysis since it is likely that functional groups at the active sites of these enzymes are involved in the bond-breaking process.

In preliminary work it was found that the hydronium ion catalyzed hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane proceeded in water at 30° with a second-order rate constant approximately

1030-fold less than that of the corresponding ethylene glycol derivative. There is little doubt that this large observed effect is steric in origin resulting from substitution at the 4 and 5 positions in the 1,3-dioxolane ring system. While this rate effect could be reflecting differences in the dissociation constants for the conjugate acids it is also quite likely that the bond-breaking process is strongly hindered with the tetramethylethylene glycol derivative due to greater steric interactions in the A1 transition state than in the ground state. Since the 1,3-dioxolane ring is normally puckered by carbon-oxygen bond angles of less than 109° ,⁷ a substantial dihedral angle should exist between the methyl groups on adjoining carbons so that ground-state interactions would not be unusually large. A detailed study of the hydrolysis of a series of 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes has therefore been made. It has indeed been found that the hydrolysis reactions of these acetals proceed by an A2 mechanism with general acid catalysis by formic acid being detectable.

Experimental Section

Materials. 2-(*para*-Substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes were prepared by refluxing in benzene or toluene equivalent amounts of the appropriately substituted benzaldehyde and tetramethylethylene glycol. A trace of *p*-toluenesulfonic acid was added as a catalyst. Water was continuously removed from the reaction by azeotropic distillation with the solvent. After collection of a theoretical amount of water the reaction mixture was washed with 1 *M* KOH solution. The benzene or toluene extract was then dried over anhydrous sodium sulfate. The solvent was removed by flash evaporation, and the residue was either distilled or recrystallized from an ether-hexane mixture.

(1) For the evidence which has led to this mechanism and the pertinent references see T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).

(2) T. H. Fife and L. Hagopian, unpublished data.

(3) B. Capon, *Tetrahedron Letters*, 911 (1963).

(4) B. Capon and M. C. Smith, *Chem. Commun.*, 523 (1965).

(5) B. Capon and D. Thacker, *J. Am. Chem. Soc.*, **87**, 4199 (1965).

(6) J. C. Speck, Jr., D. J. Rynbrandt, and I. H. Kochevar, *ibid.*, **87**, 4979 (1965).

(7) R. U. Lemieux, J. D. Stevens, and R. R. Fraser, *Can. J. Chem.*, **48**, 1955 (1960).

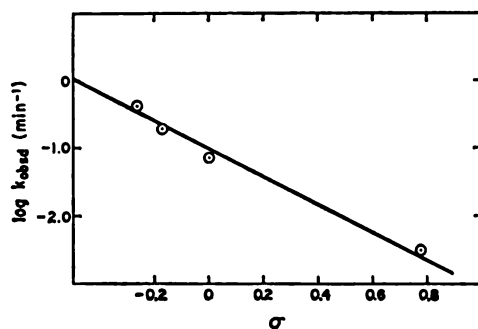


Figure 1. Plot of $\log k_{\text{obsd}}$ for hydrolysis of 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in 0.100 M HCl at 30° vs. σ .

(*p*-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane had bp 115° (1.2 mm), n_D^{20} 1.5090. *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 70.90; H, 8.37. Found: C, 70.90; H, 8.37. 2-(*p*-Methylphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane had bp 99° (1.8 mm), n_D^{20} 1.4975. *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 76.32; H, 9.15. Found: C, 76.48; H, 9.01. 2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane had bp 82–83° (1.4 mm), n_D^{20} 1.4975. *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 75.69; H, 8.80. Found: C, 75.47; H, 8.99. 2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane had mp 85–87°. *Anal.* Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.98; H, 6.98; N, 5.87. Dioxane was purified by the method of Fife¹ and was stored frozen.

Kinetic Measurements. The rates of appearance of the aldehyde products in water as the solvent were measured spectrophotometrically with a Zeiss PMQ 11 spectrophotometer. The dioxolane, dissolved in dioxane, was added to the aqueous solution in a thermostated cuvette in the cell compartment of the spectrophotometer means of a calibrated dropping pipet. The solution was then stirred vigorously. The rates were generally followed to 75–90% completion, and infinity points were taken at 10–20 half-lives. Pseudo-first-order rate constants (k_{obsd}) were obtained from the slopes of plots of $\log (OD_{\infty} - OD_t)/(OD_{\infty} - OD_0)$ vs. time. Constant temperature ($\pm 0.1^\circ$) was maintained in kinetic runs by circulating water from a Haake Model F constant-temperature circulating bath through a Zeiss constant-temperature cell holder. All pH measurements were made with a Radiometer PHM 22 pH meter.

In work utilizing 99.8% D_2O as the solvent, the glass electrode correction formula of Fife and Bruce² was employed in the determination of a_{D^+} .

The determination of activation parameters for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in 0.100 M HCl points obtained at four temperatures (20, 30, 40, and 50°) $\pm 0.1^\circ$. Rates were measured in triplicate at each temperature with an average deviation of less than 2% in the rate constants in all cases.

Results

The rate constants for hydrolysis of the series of 2-(*para*-substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in 0.100 M HCl at 30° are presented in Table I.

Table I. Rate Constants for Hydrolysis of 2-(*para*-Substituted Phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in 0.100 M HCl at 30°

Substituent	k_{obsd} , min ⁻¹	l. mole ⁻¹ min ⁻¹	
		k_H^a	k_D^b
<i>p</i> -OCH ₃	0.400		
<i>p</i> -CH ₃	0.199		
H	0.0739	0.739	1.80
<i>p</i> -NO ₂	0.00324		

$k_{\text{obsd}}^{H_2O}/C_{H_2O}^{+}$. $k_{\text{obsd}}^{D_2O}/C_{D_2O}^{+}$.

¹ L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston Mass., 1955, p 284.

² T. H. Fife and T. C. Bruce, *J. Phys. Chem.*, **65**, 1079 (1961).

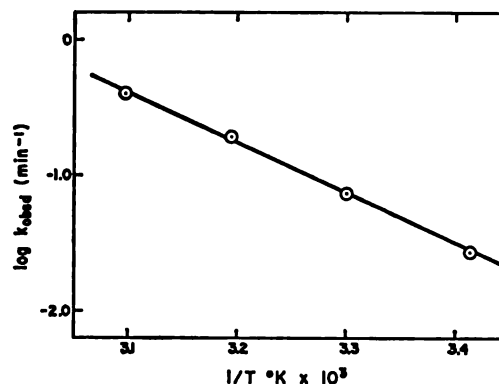


Figure 2. Plot of $\log k_{\text{obsd}}$ for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane in 0.100 M HCl vs. $1/T^\circ K$.

The logarithms of these rate constants are plotted in Figure 1 vs. σ , the Hammett substituent constant.¹⁰ A straight line relationship is obtained with a ρ of -2.0 . Also reported in Table I is the rate constant determined in D_2O as the solvent. The ratio k_D/k_H is 2.4 for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane.

The rate constants for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane were determined as a function of temperature and are given in Table II. In

Table II. Rate Constants for Hydrolysis of 2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane at Various Temperatures in 0.100 M HCl

Temp, °C	k_{obsd} , min ⁻¹
20	0.0275
30	0.0739
40	0.197
50	0.384

Figure 2 is shown a plot of the logarithms of these rate constants vs. $1/T^\circ K$. The value obtained for ΔH^\ddagger is 16.1 ± 0.5 kcal/mole and ΔS^\ddagger has the value -14.2 ± 1.7 eu calculated at 30° with the rate constant having the units l. mole⁻¹ sec⁻¹. The errors reported in ΔH^\ddagger and ΔS^\ddagger were calculated from the standard error of the regression coefficient of a plot of $\ln k_{\text{obsd}}$ vs. $1/T^\circ K$.

The hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane was studied as a function of increasing concentrations of HCl. The rate constants are reported in Table III. It can be seen in Figure 3

Table III. Rate Constants for Hydrolysis of 2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in HCl Solutions at 30°

HCl concn, M	k_{obsd} , min ⁻¹
1.0	0.0429
1.22	0.0586
1.84	0.121
2.45	0.226
3.65	0.525
4.90	1.11
5.51	1.41

(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

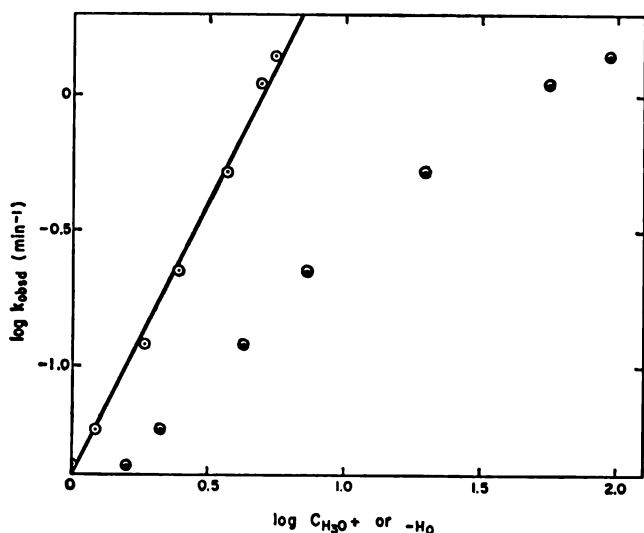


Figure 3. Plot of $\log k_{\text{obsd}}$ for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane at 30° vs. the logarithms of HCl concentration ($\log C_{\text{H}_3\text{O}^+}$), ○, or $-H_0$, ●.

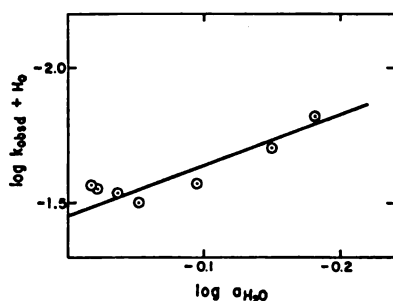


Figure 4. Plot of $\log k_{\text{obsd}} + H_0$ for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane at 30° vs. the logarithms of the activity of water.

that the logarithms of the rate constants are proportional to the logarithms of the stoichiometric acid concentration while curvature is obtained in a plot vs. $-H_0$. It will be noted, however, that the slope of the plot of $\log k_{\text{obsd}}$ vs. $\log C_{\text{H}_3\text{O}^+}$ is 2.0 rather than 1.0 as might be expected. In Figure 4 is presented a plot of $\log k_{\text{obsd}} + H_0$ vs. the logarithms of the activity of water in these solutions.¹¹ A straight line through these points has a slope, w ,¹¹ of +1.9.

The rate of hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane was found to be catalyzed by increasing concentrations of formate buffer at 40°. The observed catalysis is weak, but it is well outside the range of possible experimental error. The observed rate constants obtained at two pH values are plotted in Figure 5 vs. total formate concentration ($\text{HCOOH} + \text{HCOO}^-$). The slopes of the lines increase as pH is decreased showing a kinetic dependence upon the concentration of the acid species. The rate constant for the general acid catalyzed reaction is $0.0026 \text{ l. mole}^{-1} \text{ min}^{-1}$.

Discussion

Mechanisms designated A2 involving attack of solvent on the protonated substrate have been postulated in the hydrolysis of several different types of acetals.^{5,12,13} In none of these cases, however, was more

(11) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4978 (1961).

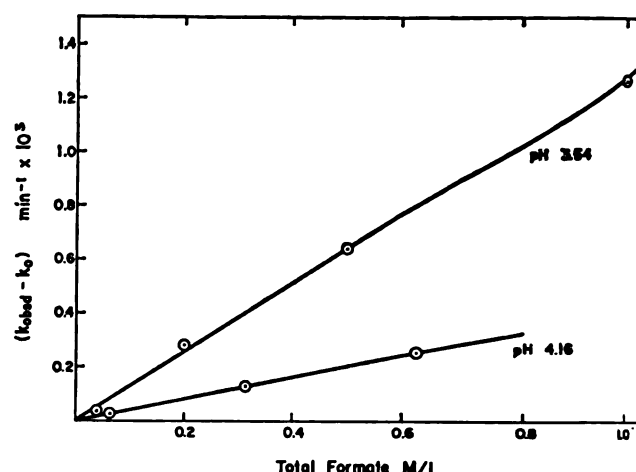


Figure 5. Plot of $(k_{\text{obsd}} - k_0)$ for hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane vs. total formate concentration ($\text{HCOOH} + \text{HCOO}^-$) at 40° and $\mu = 0.5 \text{ M}$. The values of the intercept rate constants, k_0 , are 0.00407 min^{-1} at pH 3.54 and 0.0010 min^{-1} at pH 4.16.

than one criteria of mechanism applied, and in each case some doubt exists as to the correctness of the assigned mechanism. Thus Kreevoy and Taft¹⁴ have pointed out that the data of Kaeding and Andrews¹² on the hydrolysis of the diethyl ketal of *p*-nitrobenzophenone in ethanol-water mixtures is also compatible with an A1 mechanism. Kwart and Price¹³ suggested that the hydrolysis of 2,2-diphenyl-1,3-dioxolane was A1, and a series of similar 2,2-disubstituted 1,3-dioxolanes all have D_2O solvent isotope effects characteristic of an A1 mechanism.¹⁵ Capon and Thacker⁵ postulated on the basis of slightly negative values of ΔS^\ddagger that furanoside hydrolysis has an A2 mechanism, but it has been found that the hydrolysis of 2-ethoxytetrahydrofuran, a model furanoside, is characterized by a ΔS^\ddagger of +3.3 eu¹⁶ which although considerably more negative than that for hydrolysis of 2-ethoxytetrahydropyran is still in the range normally associated with an A1 mechanism.¹⁷ In addition, a D_2O solvent isotope effect characteristic of an A1 reaction was found.¹⁸

In the present study several mechanistic criteria have been applied to the hydrolysis of 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes and some point strongly to incursion of an A2 mechanism in the hydrolysis of these compounds. A ratio of $k_{\text{D}}/k_{\text{H}}$ of 2.4 was found for the hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane. Ratios of $k_{\text{D}}/k_{\text{H}}$ in the range 1.3–1.7 are normally associated with A2 reactions while ratios greater than this can be considered as indicative of an A1 mechanism.¹⁸ The D_2O solvent isotope effects found in A1 acetal hydrolysis reactions vary generally from approximately 2.7 to 3.0.^{1,15} Thus the value of $k_{\text{D}}/k_{\text{H}}$ of 2.4 found in the present study is considerably less than is usually found for A1 acetal hydrolysis.

The value of ΔS^\ddagger for hydrolysis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane, -14.2 eu , is not as highly

(12) W. W. Kaeding and L. J. Andrews, *ibid.*, **74**, 6189 (1952).

(13) H. Kwart and M. B. Price, *ibid.*, **82**, 5123 (1960).

(14) M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, **77**, 3146 (1955).

(15) T. H. Fife and L. Hagopian, *J. Org. Chem.*, **31**, 1772 (1966).

(16) T. H. Fife, unpublished data.

(17) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).

(18) F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

negative as one might expect to find in an A2 reaction where values in excess of -15 eu are commonly observed¹⁷ but is still more in accord with a mechanism involving solvent participation than with a unimolecular mechanism. The A1 cleavage of the 1,3-dioxolane ring system is characterized by ΔS^\ddagger values 8–10 eu more negative than for hydrolysis of the analogous open-chain diethyl acetals,^{1,18} but the ΔS^\ddagger for hydrolysis of 2-phenyl-1,3-dioxolane in 50% dioxane–H₂O is still only -8.9 eu,¹ so the value observed in the case of tetramethylethylene glycol acetal is much more negative.

The logarithms of the rate constants for hydrolysis of the series of 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes are a linear function of σ with a ρ of -2.0 in contrast to the upward curvature obtained in the plot of $\log k_H$ for hydrolysis of the diethyl acetals and ethylene glycol acetals of substituted benzaldehydes vs. σ .¹ Employing *meta*-substituted benzaldehyde diethyl acetals ρ was found to be -3.35 ,¹ so the value obtained in the present study is much more positive. Electron withdrawal should hinder protonation, make departure of the leaving group more difficult, and destabilize a carbonium ion intermediate in an A1 reaction. Nucleophilic attack by solvent, however, should be facilitated by electron withdrawal. Solvent participation therefore should result in a less negative value of ρ . The linear relationship with σ shows there to be much less carbonium ion character in the transition state for hydrolysis of the tetramethylethylene glycol acetals than in the case of the diethyl acetals or ethylene glycol acetals since it is undoubtedly resonance interaction of the *p*-methoxy group with the incipient carbonium ion in the transition state that causes positive deviation in the latter series of compounds.

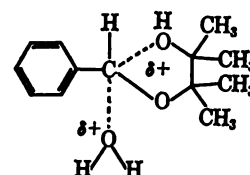
A classic method for distinguishing between A1 and A2 mechanisms has been to determine whether the observed rate constants are proportional to the stoichiometric acid concentration or to h_0 .¹⁹ Bearing in mind the criticisms that have been made of this method and the possible exceptions that have been found,²⁰ the linear relationship between $\log k_{\text{obsd}}$ and \log acid concentration $C_{\text{H}_3\text{O}^+}$ would strongly suggest an A2 mechanism for the hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane. The w value of $+1.9$ is also in the range associated with solvent participation in the Bunnett classification,¹¹ water acting as a nucleophile. This w value is, of course, only approximate because of the scatter of points about the line in Figure 4, but there is no question that the slope is quite positive for hydrolysis in the more concentrated acid solutions. The positive value of w can be contrasted with the highly negative values that are generally observed for acetal hydrolysis.¹¹

(19) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).

(20) R. W. Taft, Jr., N. C. Deno, and P. S. Skell, *Ann. Rev. Phys. Chem.*, **9**, 306 (1958); E. Whalley, *Trans. Faraday Soc.*, **55**, 798 (1959); J. Koskikallio and E. Whalley, *ibid.*, **55**, 815 (1959); H. Kwart and A. L. Goodman, *J. Am. Chem. Soc.*, **82**, 1947 (1960); A. J. Kresge and Y. Chiang, *ibid.*, **81**, 5509 (1959); R. H. Boyd, R. W. Taft, Jr., A. P. Wolf, and D. R. Christman, *ibid.*, **82**, 4729 (1960).

A complication in the interpretation of the data obtained in moderately concentrated HCl is the high slope of 2.0 found in the plot of $\log k_{\text{obsd}}$ vs. $\log C_{\text{H}_3\text{O}^+}$. Slopes considerably greater than unity have been observed in plots of $\log k$ vs. $-H_0$ for acetal hydrolysis in HCl solutions although such plots are linear.^{14,21} Possible explanations for this behavior are salt effects on the activity coefficients^{19,22} or nucleophilic participation by chloride ion.¹¹ The best straight line through the present H_0 plot has a slope of 0.84.

Each piece of evidence cited in the present study contains some ambiguity, but taken together a consistent picture is presented of a reaction in which water is participating as a nucleophile but in which either the bond being formed in the transition state is not well developed or in which an A1 mechanism is still making



some contribution to the observed rate.

If water can participate in the reaction it is reasonable that buffer catalysis might also be observed. The catalysis observed in formate buffer (Figure 5) is small but certainly real. This then is the first reported example of buffer participation in acetal hydrolysis. No rate enhancements were observed for hydrolysis of benzaldehyde diethyl acetal in the same series of buffers at 25°. Thus the observed catalysis is very likely not due to medium effects caused by increasing buffer concentrations.

The different mechanisms observed in the present study can be seen because the normally favored A1 mechanism has been made unfavorable by the increased steric bulk. The rates of hydrolysis of the tetramethylethylene glycol acetals are many times slower than those of the corresponding ethylene glycol acetals even though solvent and buffer are involved. It would appear, however, that glycosidic enzymes probably function by extremely facile general acid–general base mechanisms in which the participating groups catalyze the reactions near neutrality at rates much greater than can be observed in simple acid-catalyzed reactions at the same pH values. Before mechanisms of this type can be understood it must, of course, be demonstrated that they are indeed chemically feasible, and the structural features which promote their utilization must be determined. A step in that direction has now been taken.

Acknowledgment. This work was supported by the National Institutes of Health Research Grant GM-10316-04. The author also acknowledges the able technical assistance of Miss Lily Hagopian.

(21) P. M. Leininger and M. Kilpatrick, *ibid.*, **61**, 2510 (1939).

(22) D. McIntyre and F. A. Long, *ibid.*, **76**, 3240 (1954).

High-Resolution Mass Spectrometry in Molecular Structure Studies. IV. Mechanistic Aspects of the Fragmentation of Widdrol^{1,2}

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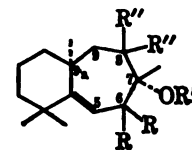
Abstract: The mass spectrum of the sesquiterpenol widdrol is dominated by the peak at m/e 151, corresponding to the charged species formed by loss of 71 mass units from the molecular ion. The mass spectra of a series of deuterium-labeled analogs and the complete high-resolution mass spectrum indicate that most of the $M - 71$ ions arise from a rearranged molecular ion, rather than from that of the original alicyclic alcohol. The presence of homoallylic unsaturation allows postulation of extensive rearrangement to a ketonic molecular ion.

In spite of their broad occurrence in nature, their chemical and biogenetic importance, their volatility, and the ample functional variation of basic skeletal moieties in this class of natural products, the sesqui- and also diterpenes have received little attention in the mass spectrometry literature thus far. A few complete low-resolution mass spectra and comparatively little mechanistic work toward their interpretation have been reported,⁴ although the low-resolution mass spectrum of widdrol (Figure 1) and a suggestion for the composition and the origin of the dominating fragment⁵ are among them.

This situation is clearly a result of the usual difficulties experienced in interpreting spectra of alicyclic compounds, even those of quite simple structure, without having at hand the necessary high-resolution data and supplemental information from labeled analogs. The demand for utilization of high-resolution techniques plus proper deuterium labeling as minimum requirements in the case of monoterpenes has only recently been emphasized by several authors.⁶ Complete high-resolution mass spectra of the sesquiterpene lactone gaillardin and its derivatives have recently been presented by this laboratory in support of its structural elucidation.⁷

The structure and absolute configuration of widdrol (I) were established after extensive discussion in 1961.⁸

Subsequently, in 1964, Dauben and Friedrich⁹ elucidated the mechanism of conversion of thujopsene to widdrol in aqueous acidic media, the analogs 6,6-*d*₂-widdrol (III) (Figure 3) and 8,8-*d*₂-widdrol (IV) (Figure 4) being of primary importance in that context. The availability of these labeled compounds and that of widdrol-OD (II) (Figure 2) led to this mass spectral examination of the major modes of decomposition for this naturally occurring sesquiterpenol. Complete high-resolution data were determined for these compounds and presented in the format of heteroatomic plots⁹ for ease of evaluation of labeling data.



I, R, R', R'' = H
 II, R, R'' = H; R' = D
 III, R = D; R', R'' = H
 IV, R, R' = H; R'' = D

The Fragmentation of Widdrol

If widdrol is viewed as a cyclic alcohol, it would be expected to undergo the characteristic fragmentation outlined for alicyclic alcohols by Natalis¹⁰ and substantiated by use of deuterium-labeled analogs for cyclopentanol¹¹ and cyclohexanol.¹² Thus, the molecular ion M_0 should suffer allylic bond scission α to the hydroxyl group, followed by transfer of an α -hydrogen and cleavage of the β, γ bond.

That this fragmentation sequence yielding ion a does occur to a certain extent is borne out by the high-resolution mass spectrum of widdrol (Figure 5), which shows that virtually all of the peak at m/e 71 arises from ions having the composition C_4H_7O . In the spectrum of 8,8-*d*₂-widdrol (IV) (Figure 4), most of the peak appears at m/e 72,¹³ the corresponding ion retaining only one deuterium atom as expected. Similarly, in the low-resolution mass spectrum of widdrol-OD (II) (Figure

(1) For part III in the Berkeley series, see A. L. Burlingame, D. H. Smith, and W. J. Richter, *J. Am. Chem. Soc.*, in press. Financial support was provided in part by the National Aeronautics and Space Administration, Grant NSG 101.

(2) A portion of this material was presented at the 14th Annual Conference on Mass Spectrometry and Allied Topics, May 1966, Dallas, Texas.

(3) (a) Recipient of a fellowship from the American Association of University Women, 1965-1966. (b) F. Hoffmann-LaRoche & Company, Aktiengesellschaft, Basel, Switzerland.

(4) R. I. Reed in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, pp 672-676; R. T. Aplin and T. G. Halsall, unpublished work in H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, Inc., San Francisco, Calif., 1964, pp 151-153; R. Hodges, E. P. White, and J. S. Shannon, *Tetrahedron Letters*, 371 (1964); G. Lukas, J. C. N. Ma, J. A. McCloskey, and R. E. Wolff, *Tetrahedron*, 20, 1789 (1964); G. L. K. Hunter and W. B. Brogden, *J. Org. Chem.*, 29, 982 (1964); N. Wasuda and T. Tsuchiya, 13th Annual Conference on Mass Spectrometry and Allied Topics, St. Louis, Mo., 1965, p 455; D. G. B. Boocock and E. S. Waight, *Chem. Commun.*, 90 (1966).

(5) C. Enzell, *Acta Chem. Scand.*, 16, 1553 (1962).

(6) D. S. Weinberg and C. Djerassi, *J. Org. Chem.*, 31, 115 (1966); A. F. Thomas and B. Willhalm, *J. Chem. Soc., Phys. Org.*, 219 (1966).

(7) S. M. Kupchan, J. M. Cassady, J. E. Kelsey, H. K. Schnoes, D. H. Smith, and A. L. Burlingame, *J. Am. Chem. Soc.*, 88, 5292 (1966).

(8) W. G. Dauben and L. E. Friedrich, *Tetrahedron Letters*, 2675 (1964).

(9) A. L. Burlingame and D. H. Smith, in preparation.

(10) P. Natalis, *Bull. Soc. Roy. Sci. Liege*, 31, 790 (1962).

(11) P. Natalis, *Bull. Soc. Chim. Belges*, 69, 224 (1960).

(12) H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh. Chem.*, 95, 158 (1964); C. G. McDonald, J. S. Shannon, and G. Sugowdz, *Tetrahedron Letters*, 807 (1963).

(13) All intensities of peaks discussed are corrected for isotopic purity.

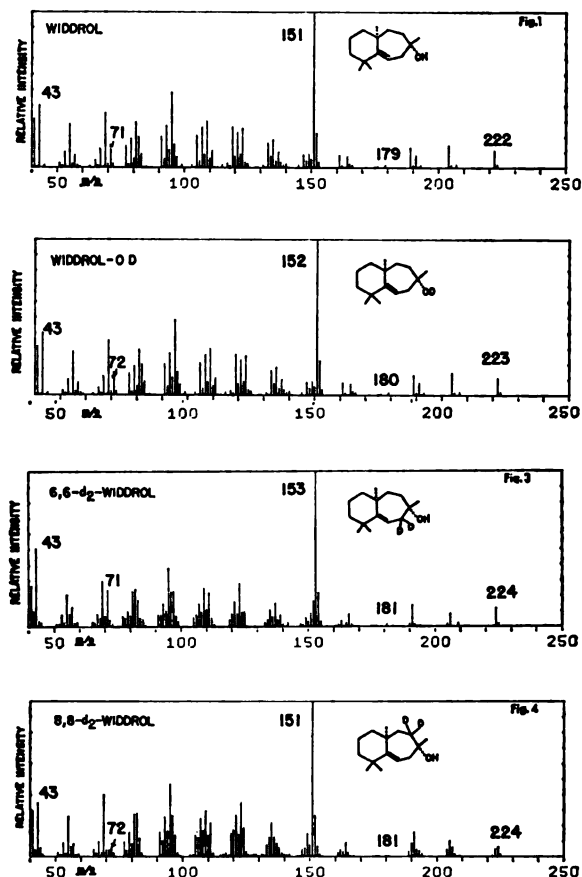
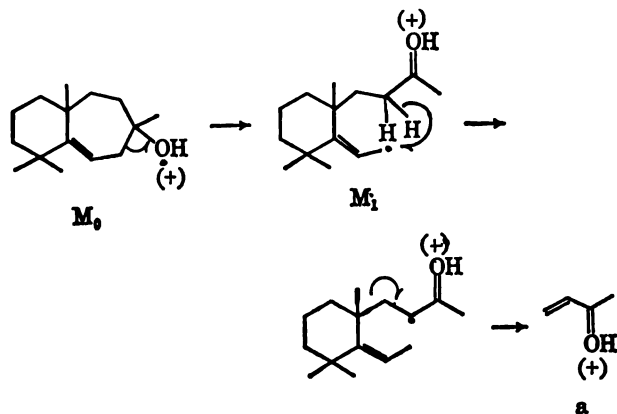


Figure 1. Mass spectrum of widdrol (I).
 Figure 2. Mass spectrum of widdrol-OD (II).
 Figure 3. Mass spectrum of 6,6- d_2 -widdrol (III).
 Figure 4. Mass spectrum of 8,8- d_2 -widdrol (IV).

2), at least 70% of the peak at m/e 71 is shifted to m/e 72 owing to predominant retention of the hydroxyl hydrogen atom.¹³



It should be noted, in addition, that some of the charge seems to be transferred to the hydrocarbon moiety in the final step of this fragmentation sequence, leading to ion b. The precursor ion for both modes of final cleavage, namely, the rearranged molecular ion M_2 , can be viewed as a "new" enolic molecular ion.

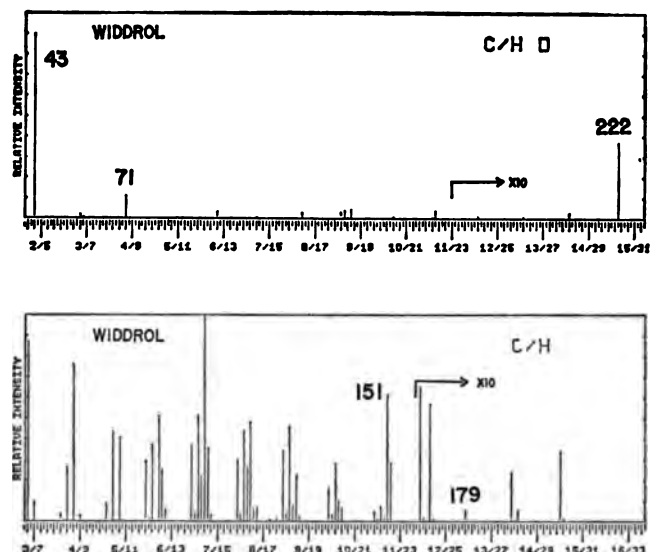
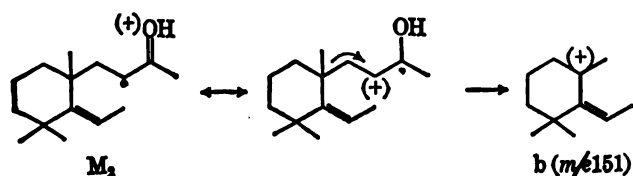
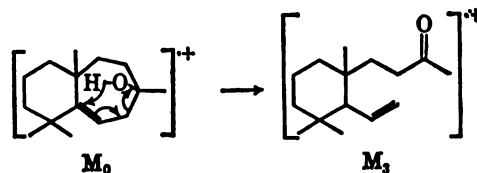


Figure 5. High resolution mass spectrum of widdrol (I).

Such heterolytic cleavage of the 9,9a bond accounts for only a minor portion of the total ion current at m/e 151. Support for a second process contributing to the $C_{11}H_{19}$ ions is shown by noting that (a) 15% of the original peak intensity remains at m/e 151 in widdrol-OD, and (b) a comparable fraction of the $C_{11}H_{19}$ ions shifts to m/e 152 in 8,8- d_2 -widdrol (Figure 4).

As evident from the shift of the major part of the peak at m/e 151 to 152 in the spectrum of compound II (Figure 2), another and much more important mode of fragmentation of the skeleton must be operative in addition to that leading to ion b. The sequence of processes involved seems to be triggered by the presence of the homoallylic bond, since there is no evidence for an analogous sequence in the fragmentation of saturated alicyclic alcohols.

The interpretation presented for the genesis of this main component of the $C_{11}H_{19}$ ion current includes again as the initial step a rearrangement of the original molecular ion M_0 to an "open" isomeric species M_2 , which represents a "ketonic" ion in contrast to the "enolic" ion M_1 . Several mechanistic pathways may be postulated for this rearrangement. One mechanistic possibility ($M_0 \rightarrow M_2$) would depict transfer of the hydroxyl hydrogen to the double bond in M_0 via a six-membered transition state with rupture of the B ring resulting in the generation of a "methyl ketonic" molecular ion, M_2 .

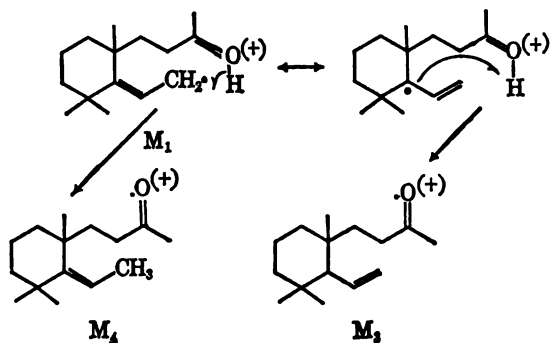


Such a hydrogen transfer with double-bond migration can be regarded as a cyclic analog of the frequently observed McLafferty rearrangement of open-chain olefins or carbonyl compounds containing γ -hydrogen atoms attached to carbon. Djerassi, *et al.*,¹⁴ have suggested from their work on McLafferty rearrangements in steroidal ketones a 1.8-Å maximum allowable distance

(14) C. Djerassi and L. Tokes, *J. Am. Chem. Soc.*, **88**, 536 (1966), and references therein.

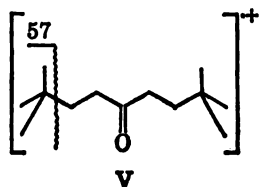
between carbonyl oxygen and the hydrogen atom transferred. Although the steroid model is not strictly analogous, a comfortable conformation of the atoms concerned within 1.8 Å is easily possible for widdrol, as estimated from Dreiding models.

A mechanistic alternative involves initial α -allylic cleavage with subsequent abstraction of the hydroxyl hydrogen *via* a seven- or nine-membered transition state. Again, an open ketonic molecular ion, *e.g.*, M_3 or M_4 , would result. That a predominant prefer-



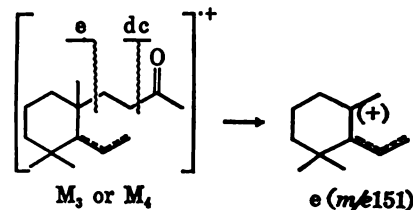
ence exists in the case of M_1 for the abstraction of the hydroxyl hydrogen rather than the activated α -hydrogens, as is the dominant process in the alicyclic alcohol model,¹⁰⁻¹² would not be expected, and the driving force is unclear. Of course, generation of an allylically stabilized radical leads to a less reactive radical site and, as a consequence, higher selectivity rendering preferred abstraction from conformationally less but energetically more favorable sites could result. In contrast to the foregoing discussion, conceptual preference for the hydroxyl hydrogen over that of C-7 methyl hydrogens utilizing a McLafferty-type mechanism is reasonable.

Assuming the formation of such a rearranged molecular ionic species, *e.g.*, M_3 or M_4 , its subsequent modes of fragmentation will then be governed by its methyl ketonic nature. α Cleavage produces ion *c* (C_2H_5O), as expected, from a methyl ketone, which accounts for nearly all of the abundant peak at m/e 43. The corresponding C_2H_5O ions formed from the three labeled derivatives contain no deuterium atoms. A minor portion of the charge is carried by the complementary fragment *d* (m/e 179). This hydrocarbon fragment acquires one deuterium atom in the spectrum of widdrol-OD (Figure 2), two deuterium atoms in 6,6- d_2 -widdrol (Figure 3), and also two atoms in 8,8- d_2 -widdrol (Figure 4).¹³ The classical McLafferty ketone rearrangement of M_3 or M_4 is *a priori* inhibited since the position γ to the carbonyl function is quaternary. A datum from the literature¹⁵ reveals that the major contribution to the total ionization of a model γ -quaternary ketone, *cf.* 2,2,8,8-tetramethylnonan-5-one (V), is borne by the quaternary hydrocarbon moiety upon cleavage of the β,γ bond.



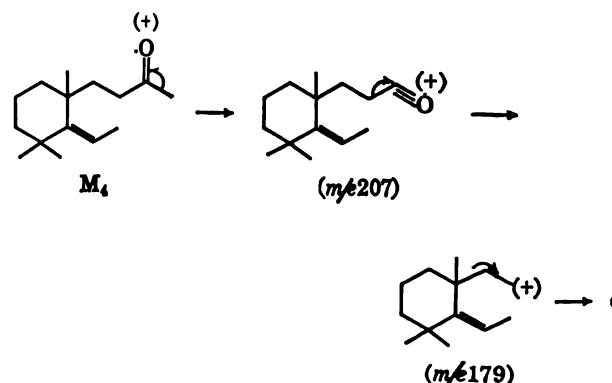
(15) R. Arndt and C. Djerassi, *Chem. Commun.*, 578 (1965).

Formally, this is the exact mechanistic model which is invoked to explain the major contribution to the peak at nominal m/e 151, which dominates the fragmentation pattern of widdrol M_3 or $M_4 \rightarrow e$.



Data from the deuterium-labeled derivatives quantitatively support this discussion, *e.g.*, (a) in widdrol-OD (Figure 2), 85%¹³ of the peak at m/e 151 shifts to m/e 152; (b) in 6,6- d_2 -widdrol (Figure 3), an even more significant portion shifts to m/e 153; and (c) in 8,8- d_2 -widdrol (Figure 4), the peak at m/e 151 remains unshifted, since C-8 and attached deuterium atoms are eliminated in the fragmentation.

This second phase of the fragmentation of the original molecular ion, namely, the final decomposition of the rearranged "ketonic" species to the fragment of mass 151, may, as formulated, proceed *via* a direct cleavage as a one-step process or may comprise a sequence of several steps. Considering the latter case, a sequential loss of methyl radical, carbon monoxide, and ethylene from any of the ketonic intermediates would give ion *e* as well.



There are, however, no metastable peaks in the spectrum of widdrol permitting a decision between these two alternatives. The model ketone V does exhibit a metastable peak for the second step, namely, the loss of carbon monoxide from the acylium ion.¹⁶ The $M - 15$ and $M - 43$ peaks, *e.g.*, m/e 207 and 179, respectively, in the spectrum of widdrol could be interpreted as being intermediates of such a sequential fragmentation.

Several ions of abundance comparable to that of the molecular ion can be defined with regard to their structural origin. The first ion (*f*) occurring at m/e 164 ($M - 58$, $C_{12}H_{20}$) in the natural product shifts unexpectedly to m/e 165 in widdrol-OD and to m/e 166 in 6,6- d_2 -widdrol and remains unshifted in 8,8- d_2 -widdrol. Since the hydroxyl hydrogen is retained in the fragment under discussion, one is required to postulate the occurrence of a "reciprocal" double hydrogen transfer during the lifetime of the molecular ion. This behavior is analogous to that of ion *e* and would suggest, therefore,

(16) Professor C. Djerassi, Stanford University, private communication.

common mechanistic genesis. The neutral species postulated is of composition C_2H_6O and would be consistent with loss of a molecule of acetone from ions or M_4 . Positional origin for the hydrogen transferred back to the carbonyl group cannot be deduced from these data, but it is assumed that a five- or seven-membered transition state is involved.

Thus, fragmentation can be distinguished in the mass spectrum of widdrol from "alcohol" as well as "ketone" molecular ions, which both produce daughter ions of same exact mass in their major fragmentation patterns. In one case, the hydroxyl hydrogen is transferred, and the charge remains primarily on the hydroxyl moiety. In the other, a ring hydrogen is transferred, and most of the charge remains on the ring-containing fragment. Such rearrangement of molecular ionic species prior to fragmentation is not unique to the β,γ -unsaturated alcohol, widdrol.¹⁷ Our observations and suggestions have been recorded in at least six earlier papers, e.g., on 2-phenyl-1-propanol¹⁸ and derivatives,¹⁹ on derivatives of 3-buten-2-ol,²⁰ on β -hydroxy esters,²¹ on several hydroxy ketones,²² and on 19-hydroxy steroids.²³ The thermal

The high-resolution spectra of isopulegol, terpen-4-ol, and their analogs obtained in this laboratory indicate that these homoallylic alcohols also rearrange to carbonyl ions under electron impact.

A. Gilpin, *J. Chem. Phys.*, **28**, 521 (1957).

H. E. Audier, H. Felkin, M. Fetizon, and W. Vetter, *Bull. Soc. Chim. France*, 3236 (1964).

J. W. Cornforth, R. H. Cornforth, G. Popjak, and L. Yengoyan, *J. Chem. Phys.*, 3970 (1966).

A. H. Etemadi, *Bull. Soc. Chim. France*, 1537 (1964).

C. Djerassi, H. Budzikiewicz, R. J. Owellen, J. M. Wilson, W. G. D. J. LeCount, A. R. Battersby, and H. Schmid, *Helv. Chim. Acta*, **46**, 742 (1963); M. Pinar, W. V. Philipsborn, W. Vetter, and H. Schmid, *ibid.*, **45**, 2260 (1962).

equivalent of such a rearrangement is known as well, e.g., in β -hydroxy olefins²⁴ and β -hydroxy esters.²¹

Experimental Section

Widdrol-OD (II) was obtained by exchanging a sample of widdrol on a D_2O -treated vpc column²⁵ and co-inserting it into the mass spectrometer with a microliter of heavy water. Its isotopic purity was calculated from the spectrum to be 83% d_1 and 17% d_0 . The isotopic purity of 6,6- d_7 -widdrol was determined as 93% d_7 and 7% d_1 , and that of 8,8- d_7 -widdrol as 43% d_7 and 43% d_1 .

The low-resolution mass spectra of widdrol, widdrol-OD, 6,6- d_7 -widdrol, and 8,8- d_7 -widdrol were obtained on a modified²⁶ CEC 21-103C mass spectrometer (inlet system 100° , ion source 180° , ionizing energy 70 eV). The high-resolution mass spectrum of widdrol was obtained on a CEC 21-110B mass spectrometer operating with the inlet system at 180° and the ion source at 200° . In the spectra presented (Figure 5), the masses are plotted in methylene units.⁶ On the abscissa, each major division marker corresponds to the saturated ion, e.g., C_nH_{2n+1} , with the number of carbon atoms given in the top row of figures and the number of hydrogen atoms indicated in the bottom row. There are 14 units between each major division, and the number of hydrogen atoms of an unsaturated or cyclic ion is obtained simply by determining the difference from the position of the next higher saturated ion.

Acknowledgment. The authors are indebted to Professor W. G. Dauben for kindly providing the deuterated widdrol analogs II and III and to L. E. Friedrich for valuable discussions.

(23) S. H. Eggers, *Tetrahedron Letters*, 733 (1965).

(24) R. T. Arnold and G. Smolinsky, *J. Am. Chem. Soc.*, **82**, 4918 (1960); R. T. Arnold and G. Smolinsky, *ibid.*, **81**, 6443 (1959).

(25) M. Senn, W. J. Richter, and A. L. Burlingame, *ibid.*, **87**, 680 (1965).

(26) F. C. Walls and A. L. Burlingame, Abstracts of Papers Presented at the 4th Annual Meeting of the Society for Applied Spectroscopy, Denver, Colo., Sept 1-5, 1965.

Structures of the Indole Alkaloids Kopsingine and Kopsaporine

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Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, and from the Department of Chemistry, University of Singapore, Singapore. Received November 4, 1966

Abstract: Structures 4 and 5, respectively, were assigned to kopsingine and kopsaporine, the two major alkaloids of *Kopsia singapurensis*. The carbon skeleton of kopsingine was confirmed by conversion to 17-methoxy-N-methyl-aspidofractinine, and the assignment of functional groups was based on the mass spectra of kopsingine and numerous derivatives. Kopsaporine was shown to be demethoxykopsingine by a comparison of its mass and nmr spectra with data from kopsingine.

Kopsingine, kopsaporine, and kopsingarine have been reported to occur as the major alkaloidal constituents of *Kopsia singapurensis*.² These alkaloids amount for 3% of the dried leaves of this Malayan species, with kopsingine being obtained in 2.2% yield. It will be shown that these compounds are structurally related to several *Kopsia* alkaloids, but their presence

has not been detected in other *Kopsia* species.

Earlier work² on the structure of kopsingine established a molecular composition of $C_{24}H_{28}N_2O_7$, which has now been confirmed by an accurate mass determination (calcd 456.1896, found 456.1860). The ultraviolet spectrum of kopsingine [λ_{max}^{MeOH} 217 m μ (log ϵ 4.56), 253 (4.04), 282 (3.38), 288 (3.36)] is similar to reported N-carbomethoxyindoline spectra [pleiocarpine (1)^{3,4} λ_{max} 207 m μ (log ϵ 4.49), 246 (4.20), 283 (3.51), 290

^{1a} Massachusetts Institute of Technology, Cambridge, Mass. ^(b) University of Singapore, Singapore.

² A. K. Kiang and R. D. Amarasingham, *Proc. Symp. Phyto-Kuala Lumpur*, 165 (1957); *Chem. Abstr.*, **53**, 14131 (1959); ^(b) Amarasingham, M.S. Thesis, University of Malaya, 1961.

⁽³⁾ W. G. Kump and H. Schmid, *Helv. Chim. Acta*, **44**, 1503 (1961).

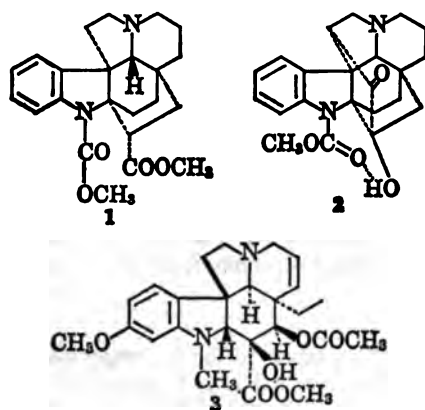
⁽⁴⁾ W. G. Kump, D. J. LeCount, A. R. Battersby, and H. Schmid, *ibid.*, **45**, 854 (1962).

(3.48); kopsine (2)⁵ λ_{\max} 240 m μ (log ϵ 4.08), 278 (3.37), 285–286 (3.35)].

The presence of a hydrogen-bonded urethan group could be deduced from absorption in the infrared at 1670 cm^{-1} . This is analogous to the kopsine (2) infrared absorption at 1679 cm^{-1} ,⁵ whereas a free urethan [e.g., pleiocarpine (1)] absorbs near 1705 cm^{-1} .⁸ The infrared spectrum of kopsingine shows additional absorption at 1740 cm^{-1} , which was attributed to an ester function. These two carbomethoxyl groups could be chemically verified by their reduction with lithium aluminum hydride, a reaction which will be discussed in greater detail later.

Conventional analysis had indicated the presence of three methoxyl groups,² also apparent in the nmr spectrum of kopsingine at 3.77, 3.79, and 3.82 ppm. Two of these were accounted for by the carbomethoxyl groups. The third had the chemical shift of an aromatic methoxyl, an assignment which is consistent with the observation of only three aromatic hydrogens in the nmr spectrum (6.6–7.2 ppm) and which may explain the small differences between the ultraviolet spectra of kopsingine and the unsubstituted reference compounds cited above.

The nmr spectrum of kopsingine showed absorption of two vinyl protons at 5.62 and 5.95 ppm. These signals were absent in the spectrum of dihydrokopsingine (mol wt, 458), obtained by catalytic hydrogenation of kopsingine. The vinyl protons were coupled to each other ($J = 10$ cps), and one of these protons (5.95 ppm) was further split by two adjacent non-equivalent protons ($J = 4$ and 2 cps), the latter appearing as a multiplet at 3.3 ppm. These observations are nearly identical with data on the *Vinca* alkaloid vindoline, to which structure 3 had been assigned.⁶



Kopsingine contained two active hydrogen atoms, as demonstrated by conventional analysis as well as by the incorporation of two deuterium atoms when introduced into the mass spectrometer in the presence of deuterium oxide. The remaining two oxygens of kopsingine, thus far unidentified, may therefore be accounted for as hydroxyl groups. Only one hydroxyl was reactive, since a monoacetate could readily be prepared (mol wt, 498; nmr 1.92 ppm, 3 H). It was also apparent that this hydroxyl was secondary, as the nmr spectrum

(5) T. R. Govindachari, B. R. Pai, S. Rajappa, N. Viswanathan, W. G. Kump, K. Nagarajan, and H. Schmid, *Helv. Chim. Acta*, **45**, 1146 (1962); **46**, 572 (1963).

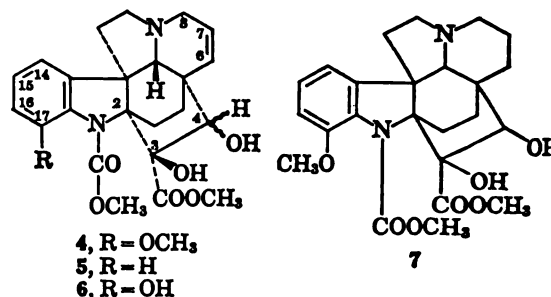
(6) (a) M. Gorman, N. Neuss, and K. Biemann, *J. Am. Chem. Soc.*, **84**, 1058 (1962); (b) J. W. Moncrief and W. N. Lipscomb, *Acta Cryst.*, **21**, 322 (1966).

of kopsingine acetate showed a one-proton signal at 5.15 ppm (a doublet due to long-range coupling, $J = 2$ cps) from the proton on the carbon bearing the acetate group. The infrared absorption of the acetate at 1670 cm^{-1} indicated that the second hydroxyl, probably tertiary, was responsible for the hydrogen bonding of the urethan.

Because of the striking similarity of the data for kopsingine and vindoline (3), structure 4 for kopsingine was proposed as a working hypothesis. Confirmation of this structure, including the exact position of aromatic substitution and the relative stereochemistry, resulted from data discussed in the remainder of this paper.⁷ An alternative location of the double bond at C-7–C-8 was not consistent with the nmr spectrum of kopsingine, which indicated that the methylene group (3.3 ppm) next to the double bond was further deshielded by an adjacent nitrogen atom. A double bond at C-6–C-7 has also been found in vindolinine,⁸ tabersonine,⁹ vindoline,⁶ and venalstonine.¹⁰

Structure 4 is supported by the mass spectra of kopsingine and dihydrokopsingine (7). These spectra however are not very characteristic and involve mainly the losses of elements of the C-3–C-4 bridge.

Conclusive evidence for the proposed structure for kopsingine was obtained by the chemical transformations below.



The Carbon Skeleton and Its C-3 Substituents. A crucial piece of evidence is the conversion of kopsingine to a compound representing a known ring system by a sequence of a few uncomplicated reactions outlined in Scheme I.

On treatment with *p*-toluenesulfonyl chloride, dihydrokopsingine (7) formed a monotosylate 9 (nmr 2.45 ppm, 3 H). Reduction of the tosylate with lithium aluminum hydride yielded two major products: (a) a diol 10 (mol wt, 370) formed by displacement of the tosylate ester, and (b) a triol 11 (mol wt, 386) formed by cleavage of the S–O bond. The number of hydroxyl groups in each derivative was verified by exchange with deuterium oxide which resulted in a shift of the molecular ions of these compounds to m/e 372 and 389, respectively.

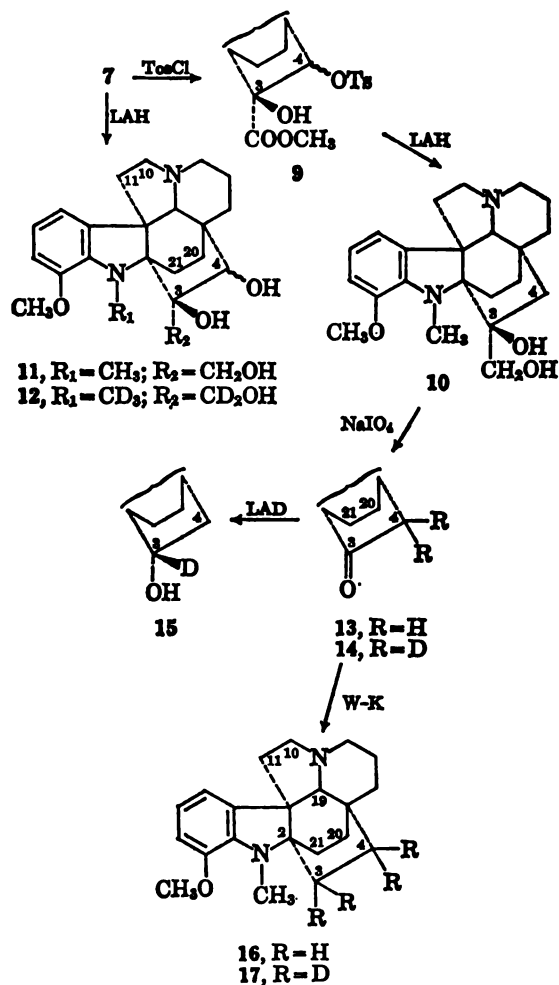
(7) To simplify discussion of the data and arguments, the substituents are always shown at C-3 and C-4 (see structure 4). It should be kept in mind that most of the arguments would hold equally well if they were on C-21 and C-20. The correctness of the former representation will be proven later in this paper.

(8) C. Djerassi, S. E. Flores, H. Budzikiewicz, J. M. Wilson, L. J. Durham, J. LeMen, M.-M. Janot, M. Plat, M. Gorman, and N. Neuss, *Proc. Natl. Acad. Sci. U. S. A.*, **48**, 113 (1962).

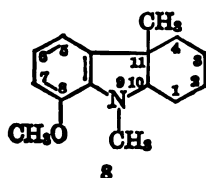
(9) M. Platt, J. LeMen, M.-M. Janot, J. M. Wilson, H. Budzikiewicz, L. J. Durham, Y. Nakagawa, and C. Djerassi, *Tetrahedron Letters*, 271 (1962).

(10) B. Das, K. Biemann, A. Chatterjee, A. B. Ray, and P. L. Majumder, *ibid.*, 2239 (1965).

Scheme I



The triol 11 was also obtained in the hydride reduction of dihydrokopsingine. Conversion of the urethane to an N-methyl group was apparent from the presence of an appropriate signal at 3.12 ppm in the nmr spectrum, and the incorporation of five deuterium atoms (12, mol wt, 391) with lithium aluminum deuteride confirmed the nature of this reaction. The ultraviolet spectrum of the triol 11 [$\lambda_{\text{max}}^{\text{MeOH}}$ 216 m μ (log ϵ 4.40), 260 (3.87), 295 (3.34)], as well as the diol and all other N-methyl derivatives, was similar in both peak positions and shape of curve to spectra of N-methylindolines substituted at the position *ortho* to the nitrogen. A suitable model is 1,2,3,4,10,11-hexahydro-8-methoxy-9,11-dimethylcarbazole (8) which exhibits λ_{max} 253 m μ (log ϵ 3.86) and 293 (3.18).¹¹ This observation established the aromatic methoxyl group of



kopsingine at C-17 (see structure 4 for numbering system).

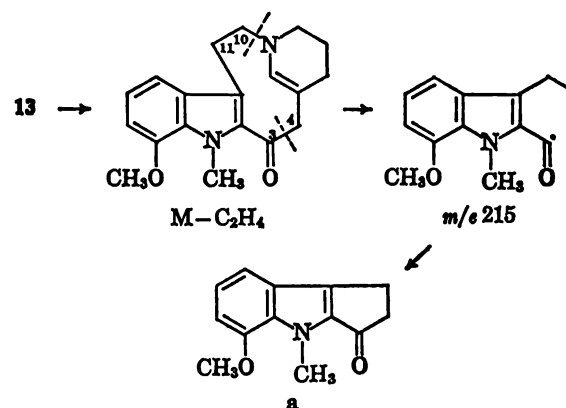
The above-mentioned diol 10 proved to be a 1,2 diol, as it reacted with sodium periodate to give the ketone 13 (mol wt, 338; γ_{max} 1720 cm^{-1}). The latter gave a

(11) M. F. Millson and R. Robinson, *J. Chem. Soc.*, 3362 (1955).

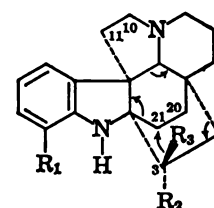
monodeuterated alcohol (15, mol wt, 341) on reduction with lithium aluminum deuteride, and the compound 16 (17-methoxy-N-methylaspidofractinine) on Wolff-Kishner reduction. The evidence on which these assignments are based will be outlined below.

The mass spectrum of the diol 10 (mol wt, 370) was consistent with the structure proposed. In particular, the most intense peak at m/e 110 is characteristic^{12,13} of alkaloids of the aspidofractinine skeleton (18) which have a hydrogen-bearing substituent (such as a hydroxyl group) at C-3, but lack functional groups at C-4.

Ketone 13 gave a mass spectrum which was consistent with the proposed structure. The most abundant fragment of this spectrum was at m/e 215, and did not contain C-4 (m/e 215 from 14 rather than m/e 217). It seemed likely that homolytic cleavage at C-3-C-4 and C-10-N₆ of an $M - \text{C}_2\text{H}_4$ ion could produce an ion of mass 215, which then might cyclize to form the fragment a, as diagrammed below.



The position of the carbonyl group in the ketone 13, and hence of the tertiary hydroxyl and carbomethoxyl functions of kopsingine, was confirmed by conversion to the deuterated alcohol 15. The mass spectrum of the latter is analogous to that of compound 21^{12,13} (except the difference of 14 mass units in some of the peaks) with the most intense peak at m/e 110 (characteristic of a C-3 alcohol) and the second major peak at m/e 125. The occurrence of the latter peak at m/e 125 rather than 124 conclusively proved that deuterium was introduced at C-3, since only the substituent R_1 in 21 was found to be transferred in the formation of this ion.^{12,13}



(12) C. Djerassi, H. Budzikiewicz, R. J. Owellen, J. M. Wilson, W. G. Kump, D. J. LeCount, A. R. Battersby, and H. Schmid, *Helv. Chim. Acta*, 46, 742 (1963).

(13) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Holden-Day, Inc., San Francisco, Calif., 1964.

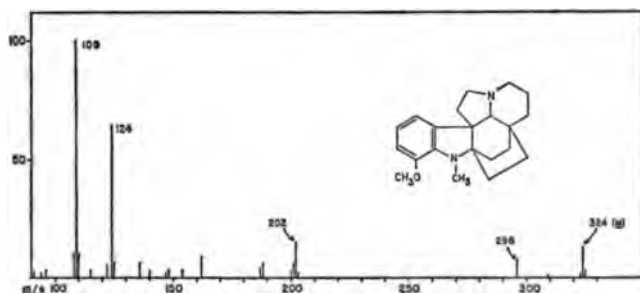


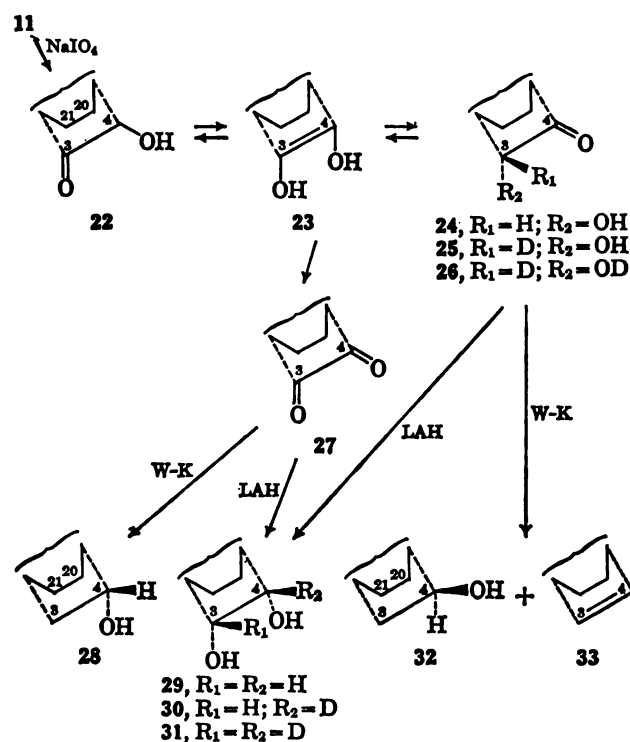
Figure 1. Mass spectrum of 17-methoxy-N-methylaspidofractinine (16).

The relative stereochemistry at C-3 of kopsingine follows from the observation that only the epimer indicated by structure 4 brings the C-3 hydroxyl group and the urethan carbonyl function close enough to form a hydrogen bond.

The most conclusive verification of the skeleton of kopsingine was provided by a mass spectrum of the reduction product 16 (Figure 1), which showed all the peaks characteristic of the aspidofractinine skeleton. This spectrum is very similar to the published spectra of aspidofractinine itself (18) and 17-methoxyaspidofractinine (19),¹⁸ except for the shifts of all ions containing aromatic substituents, occurring at m/e 324 (M), 296, and 202, and the minor differences in relative peak intensities which are to be expected.

Location of the C-4 Hydroxyl Function. Another part of structure 4 which required confirmation was the location of the secondary hydroxyl, suggested to be at C-4, and this was achieved through the reactions of the triol 11 (Scheme II).

Scheme II

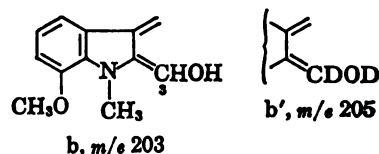


Treatment of triol 11 with sodium periodate gave a mixture of products, the formation of which is unusual in many respects. It was immediately apparent that cleavage at C-3-C-4 had not occurred, probably be-

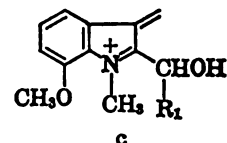
cause the intermediate five-membered periodate ring might interfere with either the 20-21 or the 10-11 bridge. However, the primary alcohol function in 11 was readily lost, resulting in an α -diketone 27, an α -ketol 24, and a comparatively small quantity of an unstable compound thought to be the enediol 23. The properties of these products thus require the presence of a secondary hydroxyl group at a carbon atom next to that bearing the tertiary hydroxyl of kopsingine.

The diketone 27 (mol wt, 352; γ_{\max} 1720, 1755 cm^{-1}) was isolated as orange needles, mp 184-187°. It resulted either from air oxidation of the ketol 24 or, more likely, from the enediol 23, since the latter was observed to give nearly equal amounts of 24 and 27 on standing.

The ketol (mol wt, 354; γ_{\max} 1715 cm^{-1}) was originally thought to have structure 22, with a ketone function at C-3. However, its mass spectrum had a major peak at m/e 124, a result which was shown earlier to require a hydrogen atom at C-3.^{12,13} Furthermore, the monodeuterated derivative 25, obtained by base-catalyzed exchange with deuterium oxide, produced a shift of the major part of this peak to m/e 125. In addition, a significant ion of m/e 203 from the ketol was shifted to m/e 204 in the spectrum of 25 and to m/e 205 when deuterium was also incorporated in the hydroxyl group (26). The fragment at m/e 203 must have structure b, containing C-3 as well as the oxygen function at that carbon. The two deuterium atoms can only be incorporated in this fragment if the C-3 function is a secondary alcohol, and the ketol therefore is best represented by structure 24. Isolation of the ketol in this form suggests that the isomerization of 22 to 24 takes place readily *via* the enediol intermediate, which relieves the steric crowding of a tetrahedral carbon at C-4. The preference for a trigonal carbon at C-4 is also indicated from an examination of Dreiding models.



The diketone and the ketol were directly correlated by hydride reduction of each to the same diol 29. Use of deuteride gave two labeled diols, 30 and 31. The mass spectra of these gave additional confirmation of the structure 24 for the ketol. In particular, the peaks at m/e 124 and 204 (c) in the spectrum of 29 were shifted to m/e 125 and 205 only in the spectrum of the diol-4 31 derived from the diketone, which implied that the deuterium atom in 30, obtained from the ketol, was located at C-4.

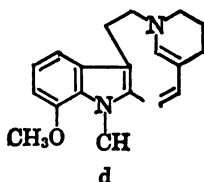


The diketone 27 was originally considered a suitable starting material for the preparation of compound 16 by Wolff-Kishner reduction; however, the single product obtained proved instead to be the alcohol 28. Further investigation of this reaction showed that only a monohydrazone had formed, and the remaining

ketone function at C-4 subsequently became reduced (presumably from the less hindered side) by the alkoxide during pyrolysis. These results again point to an unusual environment of C-4, also noticed in the isomerization of the α -ketols, which could perhaps also be related to the failure of the C-3-C-4 periodate cleavage of the triol 11.

The reluctance of the C-4 ketone function to form a hydrazone may also account for the formation of alcohol 32 by Wolff-Kishner reduction of 24. The mass spectrum of 32 was distinctly different from that of the isomeric alcohol 15 (hydrogen instead of deuterium at C-3), the expected reduction product. In fact, the spectra of 28 and 32 were strikingly similar (peaks at m/e 188, 125, and 124) with only small differences in relative peak intensities, reflecting the epimerization at C-4. If a C-4 carbonyl function is unreactive toward hydrazine, the ketol 24 could have been isomerized to form the hydrazone of 22. The product could then undergo normal Wolff-Kishner reduction to the less hindered C-4 epimer 32.

A second major product of the Wolff-Kishner reduction of the ketol 24 arose by an abnormal reaction, which is also occasionally observed with α -substituted hydrazones,¹⁴ in which the α substituent (a hydroxyl group in this case) is lost to give an olefin 33. The mass spectrum of this compound shows a very pronounced loss of ethylene, facilitated by the extended conjugation of the resulting ion d (m/e 294). The nmr spectrum of 33 exhibited two doublets for the resonance of two olefinic protons (6.08 and 6.45 ppm, $J = 9$ cps), which confirmed the assignment of an isolated double bond on one of the ethylene bridges.



Catalytic reduction of the olefin 33 completed an independent route to the previously derived 17-methoxy-N-methylaspidofractinine (16), thereby verifying all features of the structure of kopsingine, with the exception of the still uncertain relative stereochemistry at C-4.

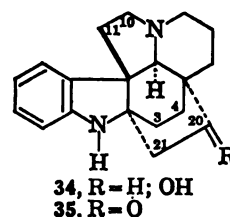
Substituents at C-3-C-4 vs. C-21-C-20. The remaining possibility that the substituents are located at C-21-C-20 is eliminated by the following observations.

It had been noticed in substituted derivatives of aspidofractinine that the unsubstituted bridge (that which is *trans* to the tryptophan bridge) was always lost in the formation of the $M - 28$ ion.^{12,13} This feature, which is also evident in the mass spectra of many kopsingine derivatives, was tentatively taken as an indication that here also the substituents are at the same (*cis*) bridge. The preparation of the deuterated derivative 17 strengthened this hypothesis. Base-catalyzed exchange of ketone 13 with deuterium oxide gave the labeled derivative 14, which was reduced by a Wolff-Kishner reaction in methanol- d . The mass spectrum of the product 17 had peaks at m/e 328 (M), 300, 204, 190, 125, and 111, indicating the exclusive

(14) N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, **74**, 1704 (1952), and references therein.

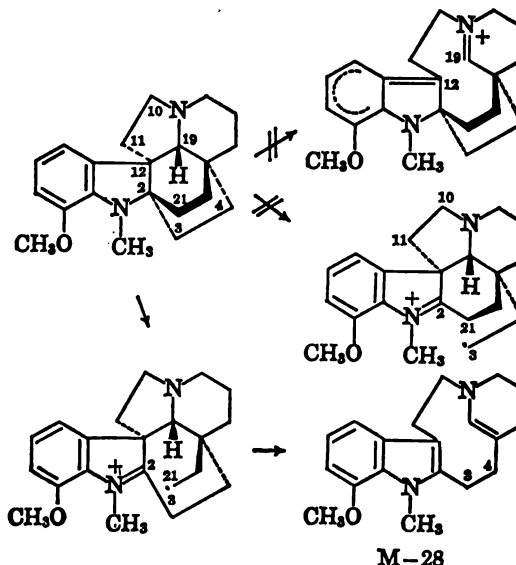
loss of a completely unlabeled bridge. It will be shown by comparison with compounds known to be oxygenated at C-20 that in kopsingine the substituents are at C-3 and C-4, i.e., at the *cis* bridge. As a corollary, the spectrum of 17 implies that the preferred loss of one of the two bridges is controlled by its stereochemistry and not by the presence or absence of substituents.¹⁵

A comparison of the mass spectra of alcohols 28 and 32 [m/e 340 (M), 312 ($M - 28$), 188, 125, 124] with that of compound 34 [m/e 296 (M), 252 ($M - 44$), 140, 109¹⁶] provided additional evidence for the presence of the functional groups of kopsingine at the C-3-C-4 bridge. In each case, only the bridge *trans* to the tryptophan bridge was lost, even though this was the substituted bridge in 34 ($M - 44$) and the unsubstituted bridge in 28 and 32 ($M - 28$). Because of the significant implications of this result, it was necessary to make very certain that the pair 28 and 32 have the substituents indeed on the other bridge in comparison with 34. Three of the four possible alcohols with the hydroxyl groups on the same bridge (15, 28, and 32) have been obtained from kopsingine. The possibility that 23 could be the fourth, and that 28 and 32 could be C-21



alcohols and 15 could be the C-20 epimer of 34, would require the ketones 13 and 35 to be nearly identical.

(15) The exclusiveness of the loss of one bridge eliminates a stepwise process initiated by cleavage of the C-12-C-19 bond (which is both benzylic and α to nitrogen) because both bridges become equivalent if the resulting radical ion has sufficient lifetime for C-12 and C-19 to become planar. On the other hand, a stepwise mechanism involving initial cleavage at C-2-C-21 is not only consistent with all data but also accounts for the stereospecificity of the elimination of ethylene. This cleavage and the subsequent planar configuration of the bonds at C-2 release the considerable strain of the bridged ring system, whereas the alternative cleavage at C-2-C-3 not only leads to increased ring strain, but also greater steric crowding between C-4 and C-10.



(16) H. K. Schnoes and K. Biemann, *J. Am. Chem. Soc.*, **86**, 5693 (1964).

This was ruled out by a comparison of their mass spectra which were dissimilar far beyond the degree attributable to their difference in aromatic substitution [13: m/e 338 (M), 215 (a), 187, 169, 155, 124; 35: m/e 294 (M), 266 (M - CO and M - C_2H_4), 252 (M - C_2H_2O), 138, 109¹⁸]. It follows that the ketone functions of 13 and 35 must be on different bridges, and the kosingine derivatives are therefore substituted at C-3 and/or C-4.

Kopsaporine and Kopsingarine. Kopsaporine, a second major alkaloid of *Kopsia singapurensis*, has a composition of $C_{23}H_{26}N_2O_8$, based on conventional analysis and mass spectrometric molecular weight. The mass spectrum suggested it to be demethoxykopsingine (5) because it was analogous to the spectrum of kopsingine except that all peaks above m/e 200 appeared 30 mass units lower. All other evidence agreed with this assignment. Analysis had indicated the presence of two methoxyl groups which, by analogy with kopsingine, could be attributed to a hydrogen-bonded urethan and an ester (ν_{\max} 1675 and 1740 cm^{-1} ; nmr 3.80 and 3.90 ppm). The nmr spectrum of kopsaporine showed the same olefinic absorption pattern [5.83 ($J = 10$ cps) and 6.02 ppm ($J = 10, 4$, and 2 cps)] as had been observed for kopsingine, and the ultraviolet spectrum [λ_{\max}^{MeOH} 207 $m\mu$ ($\log \epsilon$ 4.53), 246 (4.15), 279 (3.43), 287 (3.39)] was similar to the spectra of pleiocarpine (1)⁸ and kopsine (2).⁵ Three active hydrogens had been indicated by conventional analysis; however, only two deuterium atoms were incorporated by exchange with deuterium oxide in the mass spectrometer.

Further proof is the appearance of a fourth aromatic hydrogen in the nmr spectrum of kopsaporine, which was distinctive in its absorption as a broad doublet (7.53 ppm, $J = 8$ cps) slightly downfield from the remaining aromatic signals. This behavior is characteristic of the C-17 hydrogen atom of other N-carbomethoxyindoline alkaloids (cf. pleiocarpine⁴). Lack of this signal in the spectrum of kopsingine provides, in retrospect, complementary evidence for the assignment of a methoxyl group at C-17 in this alkaloid.

It is suggested that kopsingarine, also isolated from *K. singapurensis*, is 17-hydroxykopsaporine (6). This follows from a comparison of ultraviolet and infrared spectra of kopsingarine with data from kopsingine and kopsaporine.² Structure 6 is also in agreement with the elemental analysis of $C_{23}H_{28-30}N_2O_7$, including the presence of only two O-methyl groups. However, neither chemical nor mass spectral data have yet been obtained.

Experimental Section

Reaction products were usually purified by preparative thin layer chromatography (tlc) on silica gel H (Brinkmann), prewashed with methanol, using chloroform-methanol (9:1) as the solvent system. Compounds were detected with iodine vapor. The small scale on which reactions were frequently performed often precluded crystallization, and thus many compounds were characterized primarily by infrared, ultraviolet, and mass spectra.

Melting points were taken on a Kofler micro hot stage, and are uncorrected. Quantitative ultraviolet spectra were determined with a Cary Model 14 recording spectrophotometer, and those reported without extinction values were determined with a Cary Model 11 spectrophotometer. Infrared spectra were obtained using either a Perkin-Elmer Model 237B or Model 337 spectrophotometer. Nmr spectra were obtained in deuteriochloroform with a Varian A-60 spectrometer, and data are expressed in parts per million downfield from an internal tetramethylsilane standard.

Conventional mass spectra were determined with a CEC 21-103C mass spectrometer, equipped with a vacuum lock for the introduction of compounds of low volatility or thermal instability directly into the ion source. All spectra were recorded at 70 ev ionizing potential. High-resolution data were obtained with a CEC 21-110 double-focusing mass spectrometer, using a photographic plate for recording.

The spectral data reported here for kopsingine and kopsaporine were determined recently and some of them differ slightly from those previously reported,² which is due to the use of different instruments.

Isolation of Alkaloids. The isolation, reported in detail elsewhere,² involved alumina chromatography of the bases, obtained from a methanol extract of the leaves of *Kopsia singapurensis*. After separation of crystalline kopsingine from the early fractions, the remaining residue was subjected to countercurrent distribution giving kopsaporine, kopsingarine, and additional kopsingine.

Kopsingine (4). Recrystallization from chloroform-ethanol gave colorless prisms: mp 270-274° dec; $pK_a = 5.27$; $[\alpha]_D^{25} +75^\circ$; λ_{\max}^{MeOH} 217 $m\mu$ ($\log \epsilon$ 4.56), 253 (4.04), 282 (3.38), 288 (3.36); $\nu_{\max}^{CHCl_3}$ 1670, 1740, 3370 cm^{-1} ; nmr 3.3 [multiplet, (C-8) H_2], 3.7 (singlet, OCH_3), 3.79 (singlet, OCH_3), 3.82 (singlet, OCH_3), 5.62 [doublet, $J = 10$ cps, (C-6) H], 5.73 [singlet, (C-3) OH], 5.95 [octet, $J = 10, 4$, and 2 cps, (C-7) H], 6.6-7.2 (multiplet, 3 H), 7.98 ppm [broad doublet, $J = 4$ cps, (C-4) OH]; mass spectrum, m/e 456 (M), 428, 427, 405, 397, 395, 379, 368, 339, 337, 283, 246.

Kopsaporine (5). Recrystallization from ethanol gave colorless needles: mp 234° dec; $pK_a = 5.63$; $[\alpha]_D^{25} +48^\circ$; λ_{\max}^{MeOH} 207 $m\mu$ ($\log \epsilon$ 4.53), 246 (4.15), 279 (3.43), 287 (3.39); $\nu_{\max}^{CHCl_3}$ 1675, 1740, 3350 cm^{-1} ; nmr 3.4 [multiplet, (C-8) H_2], 3.80 (singlet, OCH_3), 3.90 (singlet, OCH_3), 5.83 [doublet, $J = 10$ cps, (C-6) H], 6.02 [octet, $J = 10, 4$, and 2 cps, (C-7) H], 6.32 [singlet, (C-3) OH], 7.0-7.4 (multiplet, 3 H), 7.53 [complex doublet, $J = 8$ cps, (C-17) H], 8.15 ppm [broad doublet, $J = 5$ cps, (C-4) OH]; mass spectrum, m/e 426 (M), 398, 397, 375, 367, 365, 349, 338, 309, 307, 253, 216, 156, 143, 130, 115, 108.

Kopsingine Acetate. Kopsingine (50 mg) and 50 μ l of acetic anhydride were refluxed for 24 hr in 2 ml of pyridine. The product was evaporated to dryness under vacuum and the residue purified by TLC to give amorphous kopsingine acetate; $\nu_{\max}^{CHCl_3}$ 1665, 1740, 3320 cm^{-1} ; nmr 1.92 (singlet, CH_3CO), 3.67 (singlet, OCH_3), 3.77 (singlet, OCH_3), 3.80 (singlet, OCH_3), 5.15 [doublet, $J = 2$ cps, (C-4) H], 5.63 [(C-6) H], 5.78 [(C-7) H], 6.27 [singlet, (C-3) OH], 6.6-7.2 ppm (3 H); mass spectrum, m/e 498 (M), 479, 455, 439, 421, 379, 337, 283, 123, 120, 107.

Dihydrokopsingine (7). Kopsingine (1.00 g), with 200 mg of platinum oxide in 50 ml of acetic acid-methanol (4:1), was reduced with hydrogen gas for 3 hr at room temperature and atmospheric pressure. After removal of platinum by filtration, the methanol was evaporated and 20 ml of water was added. The solution was made basic with sodium carbonate and then extracted with three 20-ml portions of chloroform. The extracts were combined, evaporated, and crystallized from chloroform-methanol to give 884 mg of dihydrokopsingine (7) as colorless prisms: mp 268-270° dec; λ_{\max}^{MeOH} 216 $m\mu$ ($\log \epsilon$ 4.58), 253 (4.06), 281 (3.38), 288 (3.36); $\nu_{\max}^{CHCl_3}$ 1670, 1740, 3400 cm^{-1} ; nmr 3.80 (singlet, 6 H , OCH_3), 3.82 (singlet, OCH_3), 5.62 [singlet, (C-3) OH], 6.6-7.2 (3 H), 8.44 ppm [doublet, $J = 7$ cps, (C-4) OH]; mass spectrum, m/e 458 (M), 443, 430, 429, 399, 370, 355, 341, 399, 315, 301, 278, 124, 122, 109.

Dihydrokopsingine Tosylate (9). Dihydrokopsingine (7, 50 mg) and 25 mg of *p*-toluenesulfonyl chloride were dissolved in 0.5 ml of pyridine and allowed to stand at room temperature for 24 hr. The solvent was removed under vacuum and the residue taken up in 5 ml of chloroform. This solution was rinsed successively with two 5-ml portions each of water, 0.5 *N* HCl, and saturated aqueous sodium carbonate, then dried over sodium sulfate and evaporated. The amorphous residue was not further purified and was identified as dihydrokopsingine tosylate on the basis of its nmr spectrum: 2.45 (tosylate CH_3), 3.45 (OCH_3), 3.74 (OCH_3), 3.80 (OCH_3), 4.90 [singlet, (C-4) H], 5.90 [singlet, (C-3) OH], 6.6-7.2 (3 H), 7.1-7.9 ppm (quartet, 4 H).

Hydride Reduction of Dihydrokopsingine to Triol 11. Dihydrokopsingine (7, 650 mg) and 350 mg of lithium aluminum hydride were refluxed for 4 hr in 50 ml of tetrahydrofuran. Excess hydride was decomposed with THF containing water, then solvents were removed by evaporation. Saturated sodium potassium tartrate solution (100 ml) was added, and the product was then extracted with three 50-ml portions of chloroform. After evaporation of the combined extracts, crystallization from ether yielded 375 mg of triol 11 as colorless needles. Recrystallization from ether gave:

71°; $\lambda_{\text{max}}^{\text{MeOH}}$ 216 m μ (log ϵ 4.40), 260 (3.87), 295 (3.34); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3400 cm $^{-1}$; nmr 3.12 (singlet, NCH $_3$), 3.75 (singlet, OCH $_3$), doublet, J = 12 cps, one of the two hydroxymethylene hydrogens (C-3 with geminal coupling), 6.70 ppm (singlet, 3 H); mass spectrum, m/e 386 (M), 355, 327, 297, 271, 230, 216, 202, 188, 14, 126, 125, 124, 112, 96.

Triol-*d*₃. When triol 11 was introduced into the mass spectrometer in the presence of deuterium oxide, the mass spectrum at of triol-(O-*d*)₃ with peaks at m/e 389 (M), 357, 329, 298, 11, 217, 203, 189, 174, 156, 128, 126, 124, 114, 97.

Diol-*d*₂ (12). Use of lithium aluminum deuteride in the reduction of dihydrokopsingine gave triol-*d*₃ (12): mass spectrum, m/e 358, 330, 300, 274, 235, 221, 205, 191, 177, 154, 126, 2, 96.

Reduction of Dihydrokopsingine Tosylate to Diol 10. Dihydrokopsingine tosylate (approximate 50 mg) in 5 ml of tetrahydrofuran was refluxed for 2 hr with excess lithium aluminum hydride. The solvent was then evaporated and 50 ml of saturated potassium tartrate solution was added. Two 10-ml portions with chloroform, followed by tlc purification, gave 10 mg of diol 10 as the major product, with a smaller amount of triol. The amorphous diol had $\nu_{\text{max}}^{\text{CHCl}_3}$ 3380 cm $^{-1}$; mass spectrum, m/e 355, 339, 311, 124, 122, 110, 96.

Periodate Cleavage of Diol 10 to Ketone 13. Diol 10 (9 mg) in 10 ml of methanol was added to 2 ml of 0.01% sulfuric acid-methanol which contained 40 mg of sodium periodate and 0.4 ml of water. The mixture was stirred at room temperature for 15 min and then poured into 10 ml of saturated sodium carbonate solution. Extractions of 5 ml of chloroform each, followed by tlc purification, gave 2 mg of ketone 13: $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720 cm $^{-1}$; mass spectrum, m/e 338 (M), 215 (a), 187, 155, 124.

Reduction of Ketone 13 to Ketone 14. Ketone 13 (2 mg) was dissolved in 1 ml of tetrahydrofuran. Deuterium oxide (0.1 ml) and a small piece of sodium metal were added, and the solution was stirred at room temperature for 1 hr. The sodium hydroxide layer was removed and 200 μ l of deuterium oxide and additional sodium were added. After a further 18 hr with stirring, the tetrahydrofuran was evaporated. Deuterium oxide (5 ml) was added and the product extracted with two 5-ml portions of chloroform to give ketone-*d*₂ 14: mass spectrum, m/e 340 (M), 215, 187, 156, 126.

Reduction of Ketone 13 to Alcohol 15. Ketone 13 was dissolved in 0.5 ml of tetrahydrofuran and excess lithium aluminum deuteride was added. After 3 hr at room temperature, the solvent was evaporated and 5 ml of saturated sodium potassium tartrate solution was added. Extraction with 5 ml of chloroform gave the pure deuterated alcohol 15: mass spectrum, m/e 341 (M), 155, 127, 124, 113.

Wittig-Kishner Reduction of Ketone 13 to 17-Methoxy-N-methylfractinine (16). Ketone 13 (2 mg) was dissolved in 200 μ l of ethanol. Hydrazine hydrate (20 μ l) was added, and the solution was heated in a sealed tube for 5 hr at 100°. The ethanol was removed and 100 μ l of 10% sodium hydroxide in ethanol was added. This mixture, sealed, was kept at 190° for 5.5 hr. Water was added, and the product was extracted with two 5-ml portions of chloroform to give pure 17-methoxy-N-methylaspidofractinine (16): $\lambda_{\text{max}}^{\text{MeOH}}$ 218, 258, 293 m μ ; mass spectrum, Figure 1.

Wittig-Kishner Reduction of Ketone 14 to 17-Methoxy-N-methylfractinine-*d*₂ (17). Ketone 14 (2 mg) was dissolved in 100 μ l of methanol-*d* and added to 100 μ l of methanol-*d* containing 10% anhydrous hydrazine. The solution was heated at 100° in a sealed tube for 2 hr and then the solvent was evaporated. A saturated solution (300 μ l) of sodium methoxide in methanol-*d* was added, then sealed and heated at 200° for 4 hr. Water (5 ml) was added, and the product was extracted with two portions of 5 ml of chloroform. A mass spectrum indicated a small amount of product in addition to that at C-3 and C-4, so the product was heated at 200° for 16 hr in 0.5 ml of sodium ethoxide-ethanol. After purification by tlc, the product showed mass spectral peaks at m/e 328 (M), 300, 204, 190, 125, 111.

Periodate Cleavage of Triol 11. Triol 11 (300 mg) in 1 ml of methanol was added to 1.2 g of sodium periodate and 12 ml of water in 60 ml of 0.01% sulfuric acid-methanol. The mixture was stirred at room temperature for 15 min, then poured into 150 ml of saturated sodium carbonate solution. Four chloroform portions of 25 ml each were combined and evaporated, giving 3 mg of amorphous residue. From 300 mg of this residue, after purification by tlc, three fractions were obtained containing diketone 27, ketol 24, and enediol 23, each described below.

Diketone 27. Crystallization from methanol of the least polar fraction from the periodate cleavage of triol 11 gave 45 mg of diketone 27 as orange needles: mp 184–187°; $\lambda_{\text{max}}^{\text{MeOH}}$ 216 m μ (log ϵ 4.48), 256 (3.92), 295 (3.45); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1720, 1755 cm $^{-1}$; mass spectrum, m/e 352 (M), 296, 229, 226, 202, 109.

Ketol 24. The most polar of the three periodate cleavage fractions crystallized with difficulty from acetone to give 41 mg of ketol 24 as colorless prisms: mp 190–193°; $\lambda_{\text{max}}^{\text{MeOH}}$ 217 m μ (log ϵ 4.46), 257 (3.94), 296 (3.41); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1715, 3350 cm $^{-1}$; nmr 3.02 (singlet, NCH $_3$), 3.42 [singlet, (C-19) H], 3.47 [(C-3) OH], 3.75 (singlet, OCH $_3$), 4.22 [singlet, (C-3) H], 6.6–7.1 ppm (3 H); mass spectrum, m/e 354 (M), 337, 326, 297, 203 (b), 124, 110, 96.

Ketol-*d* 25. Ketol 24 was dissolved in 1 ml of tetrahydrofuran with 100 μ l of deuterium oxide. A small piece of sodium metal was added and the solution was allowed to stand at room temperature for 13 hr. The solvent was evaporated, 1 ml of deuterium oxide was added, and the product was extracted with 5 ml of chloroform. After purification by tlc, ketol-*d* 25 was obtained: mass spectrum, m/e 355 (M), 338, 327, 297, 204 (b'), 125, 110, 96.

Ketol-*d* 26. When ketol-*d* 25 was introduced into the mass spectrometer in the presence of deuterium oxide, the following mass spectrum was obtained: m/e 356 (M), 338, 328, 298, 205 (b'), 125, 111, 97.

Enediol 23. The third fraction from the periodate cleavage of triol 11 could not be isolated or characterized in pure form. Even though chromatographic resolution was good, on repeated chromatography this fraction always contained large amounts of diketone 27 and ketol 24, which must have formed by decomposition of the compound in question. The structure of an enediol 23 is postulated for this compound. An alternative ketol structure 22 cannot be ruled out, but it seems that the enediol would be more stable because of the trigonal carbon at C-4, and a stable 3,4 double bond has also been observed in the olefin 33.

Diol 29. a. Diketone 27 (5 mg) with excess lithium aluminum hydride was allowed to stand at room temperature in 1 ml of tetrahydrofuran for 3 hr. The solvent was then evaporated and 5 ml of saturated sodium potassium tartrate was added. The product was extracted with two 5-ml portions of chloroform and crystallized from methanol to give colorless needles: mp 169–171°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3400 cm $^{-1}$; mass spectrum, m/e 356 (M), 297, 204 (c), 154, 126, 124, 112.

b. Ketol 24 (5 mg) was reduced with hydride in the same manner, giving a product identical with the diol 29 from the diketone (mp 169–171°, identical infrared and mass spectra).

Diol-*d* 30. Ketol 24 was reduced as above, using lithium aluminum deuteride, giving diol-*d* 30: mass spectrum, m/e 357 (M), 297, 204 (c), 155, 127, 124, 113.

Diol-*d* 31. Diketone 27 was reduced as above, using lithium aluminum deuteride, giving diol-*d* 31: mass spectrum, m/e 358 (M), 297, 205 (c), 155, 127, 125, 113.

Wittig-Kishner Reduction of Diketone 27 to Alcohol 28. Diketone 27 (5 mg) and 5 μ l of anhydrous hydrazine in 100 μ l of ethanol was heated in a sealed tube at 100° for 3 hr. Evaporation under vacuum gave the monohydrazone: mol wt, 366; $\nu_{\text{max}}^{\text{CHCl}_3}$ 1665 cm $^{-1}$ (chelated carbonyl). The hydrazone was dissolved in 100 μ l of ethanol and 100 μ l of a saturated solution of sodium ethoxide in ethanol was added. The reaction mixture was heated in a sealed tube at 200° for 4 hr. Water (5 ml) was then added, and the major product, alcohol 28, was extracted with two 5-ml portions of chloroform, purified by tlc, and crystallized from methanol as colorless needles: mp 204–205°; mass spectrum, m/e 340 (M), 312, 188, 125, 124.

Wittig-Kishner Reduction of Ketol 24 to Alcohol 32 and Olefin 33. Ketol 24 (60 mg) in 0.5 ml of ethanol was heated at 100° in a sealed tube for 3 hr with 50 μ l of anhydrous hydrazine. A saturated solution of sodium ethoxide in ethanol (0.5 ml) was added, and the mixture was then heated for 4 hr in a sealed tube at 200°. Water (25 ml) was added and the product was extracted with two 25-ml portions of chloroform. Separation by tlc provided two major products, alcohol 32 and olefin 33.

a. Alcohol 32 (9 mg) was crystallized from methanol to give 5 mg of colorless prisms: mp 172–174°; $\lambda_{\text{max}}^{\text{MeOH}}$ 217 m μ (log ϵ 4.41), 259 (3.85), 294 (3.37); mass spectrum, m/e 340 (M), 312, 188, 125, 124.

b. Olefin 33 (8 mg) was obtained in colorless amorphous form: $\lambda_{\text{max}}^{\text{MeOH}}$ 257, 293 m μ ; nmr 3.02 (singlet, NCH $_3$), 3.77 (singlet, OCH $_3$), 6.08 (doublet J = 9 cps), 6.45 (doublet, J = 9 cps), 6.6–7.1 ppm; mass spectrum, m/e 322 (M), 294 (d), 279, 266, 250, 238, 224, 161.

Reduction of Olefin 33 to 17-Methoxy-N-methylaspidofractinine (16). Olefin 33 (5 mg) in 1 ml of methanol was reduced with hydrogen over platinum at room temperature and pressure for 1 hr. Filtration and evaporation, followed by purification by tlc, yielded

a single amorphous compound which gave a mass spectrum identical with that of 17-methoxy-N-methylaspidofractinine (16), previously obtained from the ketone 13.

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Acceleration of Phenyl Ester Cleavage by Cycloamyloses. A Model for Enzymatic Specificity^{1,2}

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Abstract: The cycloamyloses cause a markedly stereoselective acceleration of phenol release from a variety of substituted phenyl acetates in alkaline solution. Unlike methyl glucoside or glucose which produces small uniform rate effects, both cyclohexaamylose and cycloheptaamylose cause large, nonuniform increases in the rate of phenol release from *meta*-substituted phenyl acetates; phenol release from *para*-substituted phenyl acetates is only slightly enhanced. Rate effects due to cyclooctaamylose are smaller and much less stereoselective. The rate accelerations are independent of the electronic nature of the substituents. The cycloamylose system exhibits many characteristics of enzyme-catalyzed reactions, including saturation, competitive inhibition, and nonproductive binding. Dissociation constants of cycloamylose complexes with a variety of guest molecules were obtained using kinetic, spectroscopic, and competitive inhibition methods and are in experimental agreement. The maximal rate effects are independent of the stabilities of the cycloamylose-substrate complexes, as in enzymatic catalysis. The rate accelerations are entirely explained by considering the region of the cycloamylose torus and the secondary hydroxyl groups to be the active site of the cycloamylose. In the complex the *meta* substituents on the phenyl ring fix the carbonyl carbon atom of the ester in close proximity to the secondary hydroxyl groups of the cycloamylose whereas *para* substituents prevent this approximation. The reaction system constitutes a striking model for the lock and key theory of enzymatic specificity proposed by Emil Fischer.

As an aid to the understanding of the mechanism of enzyme action it would be useful to have a relatively simple model system which exhibits some of the important characteristics of enzyme-catalyzed reactions. Such a model system should exhibit substantial catalytic effects which vary in a predictable manner depending upon the substrate. The catalysis should be ascribable to a known reactive group or groups and the structure and geometry of the catalyst should be known. The catalytic effects should be the result of prior complexation of the catalyst and substrate. It must be possible to accurately determine both the stability of the catalyst-substrate complex and its inherent reactivity since there is no necessary relationship between these two factors (for example, although chymotrypsin binds N-acetyl-D-tryptophanamide somewhat better than it binds the L isomer,⁴ the deacylation rates of N-acetyl-D- and -L-tryptophanyl chymotrypsins differ by a factor of 1.6×10^4 in favor of the L isomer⁵).

Stereochemical aspects of both the binding and the subsequent catalysis should be readily explainable on the basis of the geometry of the catalyst and substrate. Other features of enzymic catalysis which should be sought for in a model system include competitive inhibition and nonproductive binding. In addition, it would be preferable if the catalysis proceeded by a mechanism similar to those so far known for enzyme-catalyzed reactions.

It appeared possible that a system incorporating the cycloamyloses⁶⁻⁹ might permit the development of such a model. As the name implies,¹⁰ the cycloamyloses are cyclic α -1,4-linked D-glucose polymers and have 6, 7, or 8 glucose residues per molecule.¹¹ X-Ray crystallographic studies have firmly established the structure⁷

chymotrypsin-catalyzed hydrolyses. Conversely, the k_2 step for chymotrypsin-catalyzed hydrolyses of esters related to specific substrates is too fast to permit a similar measurement.

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(10) The names α -, β -, and γ -Schardinger dextrans and cyclodextrins became established early in the literature, the prefixes referring to cyclohexa-, -hepta-, and -octaamylose, respectively. Now that the structures of these molecules have been unequivocally established it seems appropriate to use the more descriptive amylose names.

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(3) National Institutes of Health Postdoctoral Research Fellow.

(4) The K_s for acetyl-L-tryptophanamide is 5.0×10^{-3} M [R. J. Foster and C. Niemann, *J. Am. Chem. Soc.*, **77**, 1886 (1955)] while the K_1 for acetyl-D-tryptophanamide is 2.3×10^{-3} M [R. J. Foster, H. J. Shine, and C. Niemann, *ibid.*, **77**, 2378 (1955)].

(5) D. W. Ingles, J. R. Knowles, and J. A. Tomlinson, *Biochem. Biophys. Res. Commun.*, **23**, 619 (1966). Qualitatively similar observations may be made for K_s , K_1 , and k_2 values of amide substrates but because reactions of the D isomers are so slow it is not possible to obtain an accurate ratio which describes the kinetic specificity of the k_2 step for

and stereochemistry¹² of the cycloamyloses. They are doughnut-shaped molecules with the glucose units in the C-1 conformation. The primary hydroxyl groups (carbon 6 of the glucose unit) are located on one side of the torus while the secondary hydroxyls (carbons 2 and 3 of the glucose units) are located on the other side of the torus. The interior of the cavity contains a ring of C-H groups, a ring of glycosidic oxygens, and another ring of C-H groups. As a consequence the interior of the cycloamylose torus is relatively hydrophobic¹³ when compared to water.

The cycloamyloses form solid inclusion complexes and complexes in solution with a variety of molecules and ions.⁶⁻⁹ This characteristic has led to their utilization as enzyme models. For example, the cycloamyloses have been shown to act as asymmetric catalysts in the saponification of mandelic acid esters, although the rate effects and optical yields were small.¹⁴ The cycloamyloses catalyze the decarboxylation of substituted cyanoacetic acids, accelerations of up to 15-fold being observed.¹⁵ In neither of these studies was the relationship between complexing and catalysis determined. Cycloheptaamylose was found to inhibit the basic hydrolysis of ethyl *p*-aminobenzoate, the complexed ester being completely unreactive (within experimental error) in 0.04 *N* barium hydroxide solution.¹⁶ The extent of inhibition due to added cycloheptaamylose was consistent with the formation of a 1:1 complex¹⁷ having a dissociation constant of 2.34×10^{-3} *M*. Most pertinent to the present investigation is the work of Hennrich and Cramer where it was found that the cycloamyloses accelerate the decomposition of diaryl phosphates in heterogeneous alkaline mixtures with concomitant phosphorylation of the amylose.¹⁸ The acceleration of the release of phenol from di-*p*-chlorophenyl pyrophosphate was *ca.* 200-fold with cycloheptaamylose, smaller accelerations being observed with cyclohexaamylose and cyclooctaamylose. Furthermore, the acceleration was reduced when phenolic products were present in the reaction mixture. Unfortunately, limitations of the experimental system made it impossible to investigate the relationship between the stability of the complex and its reactivity. The relative importance of steric and electronic effects on reactivity and on complexation could not be determined. The present investigation of the effects of cycloamyloses on the alkaline hydrolysis reactions of phenyl esters was therefore undertaken in an effort to determine these critically important facts.

Experimental Section

Cycloamyloses were initially obtained as a gift from Professor Dexter French. Subsequently cyclohexaamylose was purchased from Applied Science Laboratories. At the present time both

cyclohexaamylose and cycloheptaamylose are available from Pierce Chemical Co. (Rockford, Ill.). Cyclooctaamylose was obtained as the pure crystalline material from Professor French. Cycloheptaamylose was purified by recrystallization from water and dried at 110° for 12 hr. *Anal.* Calcd for $C_{48}H_{76}O_{18}$: C, 44.44; H, 6.22. Found: C, 44.11; H, 6.29.

Cyclohexaamylose was purified by recrystallization from 1-propanol-water⁷ followed by recrystallization from water and drying under vacuum at 80° for 12 hr. *Anal.* Calcd for $C_{36}H_{56}O_{12}$: C, 44.44; H, 6.22. Found: C, 44.16, 44.44; H, 6.32, 6.35.

Both the cyclohexaamylose and cycloheptaamylose were found to be pure and free from cross-contamination as judged by paper chromatography on Whatman No. 1 paper (descending chromatography, 25°, solvent: 1-butanol-dimethylformamide-water, 2:1:1, v/v/v) using 1% alcoholic iodine as a developing spray. The *R_f* values of cyclohexa- and -heptaamylose were 0.23 and 0.20, respectively.

The specific rotation of aqueous cyclohexaamylose was $[\alpha]^{25}_D 150.2 \pm 4.20^\circ$ (concentration varied from 0.0104 to 0.0286 g/ml), in agreement with the literature value¹⁹ of $150.5 \pm 0.5^\circ$. No trend was observed in the specific rotation values as the cyclohexaamylose concentration was varied. A Rudolph Model 200S/655 manual photoelectric spectropolarimeter equipped with an electrical null reading device was used to determine the optical rotations.

The molecular weight of cyclohexaamylose in water at 37° was determined using a Mechrolab Model 301A vapor pressure osmometer with sucrose as a standard. Three samples at concentrations of 58, 132, and 50 g/l. gave molecular weights of 1120, 1090, and 1110, respectively (calculated 972). Since raffinose pentahydrate also gave a somewhat high value of 630 (calculated 594), it is possible that there is some systematic error involved; hydration of the cycloamylose would also lead to high observed values. Both the molecular weight data and the optical rotation data indicate that in aqueous solution cyclohexaamylose is only slightly associated (if at all).

Esters. Phenyl acetates were purchased from commercial sources (Distillation Products Industries or Aldrich Organic Chem. Co.) or were synthesized generally by the method of Spasov.²⁰ The physical properties of the esters prepared as well as the wavelengths used to follow the reactions are shown in Table I. *m*-Carboxy-

Table I. Phenyl Acetates Used as Substrates

Acetate	Bp, °C (mm), or mp, °C	Wavelength,* mμ
3,5-Dimethylphenyl	143 (54)	295
3,4,5-Trimethylphenyl	58.5-59.5	285-300
<i>m</i> -Ethylphenyl	127.5 (31)	280-298
<i>m</i> - <i>t</i> -Butylphenyl	160-161 (61)	290-295
<i>p</i> - <i>t</i> -Butylphenyl	157 (50)	300
<i>p</i> -Methoxyphenyl	160 (55)	315
<i>p</i> -Bromophenyl	154 (45)	305
<i>m</i> -Chlorophenyl	105-109 (15-16)	299-305
<i>p</i> -Chlorophenyl	143 (55)	305
<i>p</i> -Cyanophenyl	56-57	290
<i>m</i> -Carboxyphenyl	131-132.5	330
<i>p</i> -Carboxyphenyl	191-192.5	280-308

* Phenyl acetate and the tolyl acetates were assayed at 298-305 mμ, *m*-nitrophenyl acetate at 390 mμ, *p*-nitrophenyl acetate at 400 mμ, and *o*-nitrophenyl acetate at 470 mμ. (These wavelengths proved to be experimentally convenient but are not necessarily optimal.)

phenyl acetate was prepared by reaction of acetic anhydride with *m*-carboxyphenol in pyridine followed by recrystallization from chloroform. *p*-Carboxyphenyl acetate was synthesized by the method of Renson and Huls²¹ and recrystallized from chloroform. *p*-Carboxyphenyl 2-methylpropionate was prepared in 10% yield by reaction of *p*-carboxyphenol with isobutyl chloride in pyridine followed by recrystallization from chloroform, mp 181.5-183°. *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C,

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63.17; H, 5.85. *p*-Carboxyphenyl 3,3-dimethylbutyrate was prepared in 25% yield by reaction of *p*-carboxyphenol with *t*-butyl-acetyl chloride (Aldrich Chemical Co.) in pyridine followed by recrystallization from chloroform, mp 195–197°. *Anal.* Calcd for $C_{15}H_{18}O_4$: C, 66.10; H, 6.78. Found: C, 65.86; H, 6.72. Reactions of this and the previous compound were followed at 280 m μ .

Kinetics of Hydrolysis of Phenyl Acetates. The reactions were carried out by following the appearance of phenol spectrophotometrically using a Cary Model 14 recording spectrophotometer equipped with a thermostated cell compartment, thermostated cell holder, and 0–1 and 0–0.1 absorbance slide wires. The reaction medium, generally 3.00 ml of pH 10.6 sodium carbonate buffer, was placed in a stoppered 1-cm silica cell and thermostated for 15 min. The reaction was initiated by the addition of 15 μ l of a stock solution of the ester in acetonitrile (Eastman Spectro Grade) using a plastic flat-tipped stirring rod (Calbiochem). The final ester concentration was 1×10^{-4} M and the acetonitrile concentration was 0.5% (v/v). When fast reactions were being followed, the time necessary to complete the mixing of the reactants and begin recording the spectral changes did not exceed 6 sec. The pH determined using a Radiometer 4c pH meter did not change during the course of the reaction. The hydrolysis of the phenyl acetates as determined in these buffered alkaline solutions followed (pseudo) first-order kinetics. Times were determined from the recorded chart divisions by calibration using a Precision Scientific Time-It electric clock and are accurate to $\pm 1\%$. The infinite absorbance values were obtained after at least eight half-lives and reactions were recorded through 70% of completion. The rate constants were calculated by electronic computation of the linear least-squares slope of the line formed by the set of points [time, $\log(\text{absorbance} - \text{infinite absorbance})$] and division of the slope by -0.4343 . The resulting points were checked by examination of a computer-produced graph of the first-order plot in order to eliminate transcription errors. The reported rate constants are averages of two or three determinations which agreed within 3%. The spectra of the products corresponded to the spectra obtained by addition of pure phenol to the buffered cycloamylose solutions.

Determination of Dissociation Constants by Kinetic Methods. The observed first-order rate constants for hydrolysis of phenyl acetates (as measured by phenol release) in the absence (k_{un}) and presence (k_{obsd}) of added cycloamylose were determined. From 5 to 12 points were obtained at cycloamylose concentrations spanning (whenever possible) the value of K_{diss} (the dissociation constant of the cycloamylose-ester complex calculated assuming a 1:1 stoichiometry). The values of $-K_{diss}$ and k_2 (the maximal catalyzed rate due to decomposition of the fully complexed ester) were obtained as the slope and *Y* intercept of the line^{22,23} formed by plotting $k_{obsd} - k_{un}$ against $(k_{obsd} - k_{un})/[\text{cycloamylose}]$. Calculations were carried out using Eadie-type plots rather than the Lineweaver-Burk plot previously used² because the Eadie plot is statistically preferable.²⁴ The slope and intercept were obtained by electronic computation of the least-squares line. This appeared adequate since in an Eadie plot it is relatively easy to choose concentrations so that the experimental points are evenly distributed along the line. Unlike the usual situation in enzyme kinetics, the cycloamylose here is present in large excess over the substrate concentration and may be accurately determined by weight. The range of cycloamylose concentrations (depending on the value of K_{diss}) varied from 6×10^{-4} to 4×10^{-3} M. The error limits of K_{diss} were calculated from the experimental data by application of Student's *t* test for 95% probability of fit to the least-square line. The error in k_2 may be expected to parallel the error in K_{diss} . Graphical estimates of error limits made by drawing extreme lines through Lineweaver-Burk plots were significantly less than the computed values shown in Table IV.

Determination of Dissociation Constant by Spectrophotometric Methods. The increase in absorbance of the aromatic chromophore in the presence of varying amounts of cycloamylose were determined using a Cary Model 14 recording spectrophotometer equipped with a thermostated cell compartment and a 0–0.1, 0.1–0.2 slide wire. To minimize hydrolysis of esters and suppress phenol ionization a pH 2.2 hydrochloric acid–potassium chloride buffer ($I = 0.06$) was employed. Since the cycloamyloses are relatively unstable in acid solution the solutions were used within 1 hr

of preparation. The substrate concentration was held constant at 10^{-4} M. The reference compartment contained phenol or ester and cycloamylose solutions contained in separate 1-cm silica cells. The sample compartment contained a cell with buffer and a cell with combined cycloamylose and phenol or ester. The difference spectrum of 4.4×10^{-3} M glucose plus 5.8×10^{-4} M phenol as phenol was identical with the difference spectrum of phenol as phenol.

In order to calculate the cycloamylose–substrate dissociation constants a linear relationship was employed²⁵ relating the observed spectral changes to the added concentrations of cycloamylose and ester (see Appendix). The slope $1/\Delta\epsilon$ and the intercept $K_{diss}/\Delta\epsilon$ were obtained by electronic computation of the linear least-squares line through the experimental points. The validity of the method of data treatment was checked by using synthetic data available in²⁶ the literature as well as by redetermining the dissociation constant of the methyl orange–cyclohexaamylose complex (see footnotes *d* and *e* to Table VI).

Determination of Inhibition Constants. The dissociation constants of cycloamylose–inhibitor complexes (K_i) were determined by measuring the rate of *m*-nitrophenyl acetate hydrolysis in the presence of a fixed amount of cycloamylose and varying concentrations of added inhibitor. The concentration of the ester was 9.9×10^{-3} M and the cycloamylose was 3.6×10^{-3} M; the inhibitor concentrations were chosen, when possible, to span the value of K_i .

One milliliter of 1.08×10^{-3} M cycloamylose solution in pH 10.05 sodium carbonate buffer was mixed with 2 ml of a sodium carbonate buffer solution of the inhibitor, the pH was adjusted if necessary to 10.05, and the mixture in a 1-cm quartz cell was thermostated for 15 min at $25.0 \pm 0.1^\circ$ in a Cary Model 14 spectrophotometer. The ester was added in 15 μ l of acetonitrile (Eastman Spectro Grade) and the appearance of phenoxide ion was followed at 390 m μ .

Added inhibitor at the highest concentrations used had only small effects on the rate of the uncatalyzed reaction. The pH of the reaction mixture did not vary by more than 0.04 unit during the course of the reaction. The values of k_2 and K_{diss} for the cycloamylose-catalyzed decomposition of *m*-nitrophenyl acetate were previously determined (Table IV). The inhibitor concentration $[I]$ was plotted as a function of $(k_2 - k_{obsd})/(k_{obsd} - k_{un})$. The *Y* intercept is $-K_i$ and the slope is $[\text{cycloamylose}] \times K_i/K_{diss}$ (see Appendix). A sample plot is shown in Figure 5.

Results

Kinetics of Hydrolysis of Phenyl Acetates in the Presence of Glucose and Methyl Glucoside. The pseudo-first-order rate constants for the alkaline hydrolysis of a variety of substituted phenyl acetates are shown in Table II. The hydroxide ion reaction rates vary in the manner expected from the electronic character of the substituents. Data for the various *meta*- and *para*-substituted phenyl acetate hydrolysis rates gives an excellent fit to a Hammett-type relationship. The line formed by plotting $\log(k/k_H)$ vs. the substituent constant²⁷ σ^+ gives a slightly better correlation coefficient than the corresponding plot using ordinary σ values (footnote *c* to Table II), indicating that there is not a significant charge delocalization in the aromatic ring in the transition state.

No unusual effects are observed when 0.06 M α -methyl glucoside is added to the reaction mixture, there being only a 10–20% acceleration of the hydrolysis rates (Table II). Addition of 0.06 M glucose to the reaction mixture causes a two- to threefold increase in the hydrolysis rates. The larger effect due to glucose is presumably the result of reaction with the hemiacetal

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Table II. Hydrolysis of Phenyl Acetates in the Presence of Glucose and Methyl Glucoside^a

Phenyl acetate substituent	Rate with			Substituent constants ^{b,c}	
	Hydroxide ion rate, 10 ⁻³ sec ⁻¹	0.06 M α -methyl glucoside, 10 ⁻³ sec ⁻¹	Rate with 0.06 M glucose, 10 ⁻³ sec ⁻¹	σ	σ^+
H	0.804	0.879	2.39	(1)	(1)
<i>p</i> -OMe	0.749	0.802	2.14	-0.268	-0.111
<i>p</i> - <i>t</i> -Bu	0.607	0.710	1.87	-0.197	
<i>m</i> - <i>t</i> -Bu	0.490	0.582	1.51	-0.10	
<i>p</i> -Cl	1.52	1.69	5.31	0.227	0.238
<i>m</i> -Cl	1.91	2.08	7.07	0.373	
<i>p</i> -CN	4.78	5.12	19.0	0.660	0.674
<i>m</i> -NO ₂	4.64	5.16	19.7	0.710	
<i>p</i> -NO ₂	6.94	7.36	26.8	0.778	0.778

^a Pseudo-first-order rate constants obtained using pH 10.60 sodium carbonate buffer with 0.5% (v/v) acetonitrile added; [ester] $\approx 1 \times 10^{-4}$ M. ^b Taken from ref 27. ^c The correlation coefficients obtained for the least-squares fit to the line formed by plotting log (k/k_H) vs. σ for the uncatalyzed, methyl glucoside, and glucose reaction mixtures were 0.972, 0.977, and 0.980; for the plot vs. σ^+ they were 0.987, 0.989, and 0.992, respectively. The ρ values obtained for the three reaction systems using σ^+ values were 1.10, 1.07, and 1.24.

alkoxide ion derived from glucose. This is consistent with the fact that the Hammett ρ value for the glucose-catalyzed reaction is 1.24 as compared with 1.10 for the pure hydroxide ion reaction (Table II). The alkoxide ion derived from glucose is more sensitive than hydroxide ion to the electronic nature of the substituted carbonyl group.

Kinetics of Hydrolysis of Phenyl Acetates in the Presence of Cycloamyloses. The hydrolysis rates of a variety of substituted phenyl esters in the absence (k_{un}) and presence (k_{obsd}) of 0.01 M added cycloamyloses are shown in Table III. Depending on the structure of

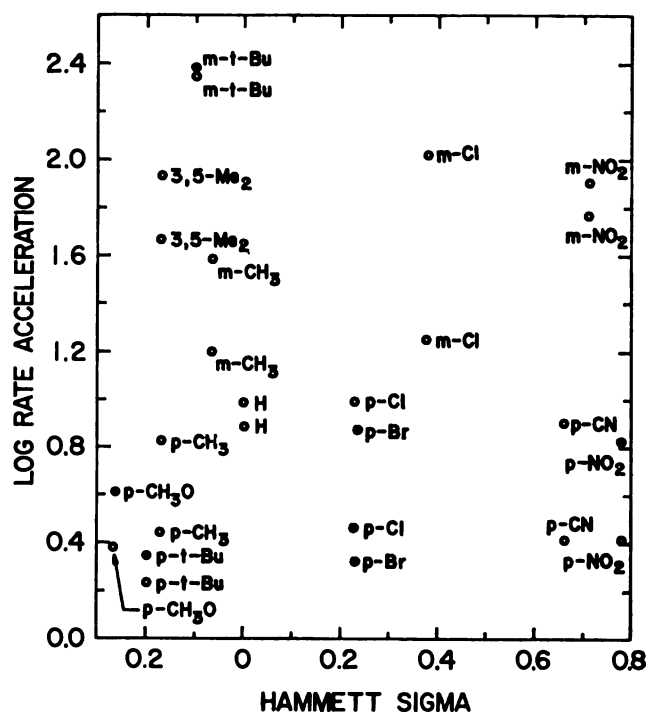


Figure 1. Graph of the logarithm of the acceleration of the rate of phenol release due to 1×10^{-3} M cycloamylose vs. the Hammett substituent constant σ : ●, added cycloheptaamylose; ○, added cyclohexaamylose (for experimental conditions see Table III).

chlorophenyl acetate occurs 113 times more rapidly in the presence of 0.01 M cyclohexaamylose. The acceleration k_{obsd}/k_{un} bears no apparent relationship to the electronic character of the substituents. A Hammett-type plot of log (k_{obsd}/k_{un}) vs. the substituent constant σ shows a tremendous scatter (Figure 1).

Table III. Hydrolysis Rates of Phenyl Acetates at pH 10.60 in the Absence and Presence of Cycloamyloses^a

Acetate ester	Hydroxide ion rate, k_{un} , 10 ⁻⁴ sec ⁻¹	[Cyclohexaamylose (0.01 M)]		[Cycloheptaamylose (0.01 M)]		[Cyclooctaamylose (0.01 M)]	
		k_{obsd} , 10 ⁻³ sec ⁻¹	k_{obsd}/k_{un}	k_{obsd} , 10 ⁻³ sec ⁻¹	k_{obsd}/k_{un}	k_{obsd} , 10 ⁻³ sec ⁻¹	k_{obsd}/k_{un}
Phenyl	8.04	0.779	9.7	0.609	7.6		
<i>o</i> -Tolyl	3.84	0.294	7.7	0.266	6.9		
<i>m</i> -Tolyl	6.96	2.70	39	1.14	16		
<i>p</i> -Tolyl	6.64	0.187	3.8	0.443	6.7		
3,5-Dimethylphenyl	5.80	4.97	86	2.64	46		
3,4,5-Trimethylphenyl	4.31	0.911	21	3.15	73		
<i>m</i> - <i>t</i> -Butylphenyl	4.90	11.1	226	12.1	250	2.65	54
<i>p</i> - <i>t</i> -Butylphenyl	6.07	0.102	1.7	0.135	2.2	2.51	41
<i>p</i> -Methoxyphenyl	7.49	0.174	2.3	0.298	4.0		
<i>p</i> -Bromophenyl	16.4	0.347	2.1	1.23	7.5		
<i>m</i> -Chlorophenyl	19.1	21.5	113	3.49	18	1.48	7.8
<i>p</i> -Chlorophenyl	15.2	0.453	3.0	1.55	10	1.34	8.8
<i>p</i> -Cyanophenyl	47.8	1.20	2.5	3.61	7.6		
<i>o</i> -Nitrophenyl	53.2	5.39	10.1				
<i>m</i> -Nitrophenyl	46.4	47.9	103	25.0	54	4.65	10.0
<i>p</i> -Nitrophenyl	69.4	1.79	2.6	4.66	6.7	4.33	6.2

^a The pseudo-first-order rate constants were determined by following the release of phenol spectrophotometrically: see Experimental Section. All determinations were done at $25.0 \pm 0.2^\circ$ using pH 10.60 sodium carbonate buffer, $I = 0.2$, with 0.5% (v/v) added acetonitrile.

the ester, marked accelerations of the phenol release may occur as the result of addition of the cycloamyloses to the reaction mixture. Thus, *m*-*t*-butylphenyl acetate hydrolyzes 240 times more rapidly in the presence of 0.01 M cycloheptaamylose, and the hydrolysis of *m*-

However, there does appear to be a relationship between the stereochemistry of substitution of the phenyl acetates and the degree of acceleration of the hydrolysis reaction. Figure 1 suggests that phenyl acetates having substituents in the position *meta* to the acetoxy group

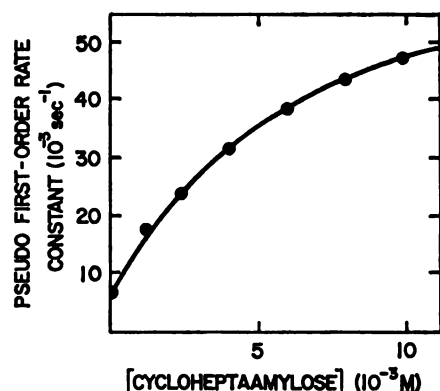


Figure 2. The pseudo-first-order rate constant for release of phenol from *p*-nitrophenyl acetate at pH 10.6 plotted as a function of added cycloheptaamylose; 0.5% (v/v) acetonitrile-water, 25°, [*p*-nitrophenyl acetate] $\approx 1 \times 10^{-4}$ M.

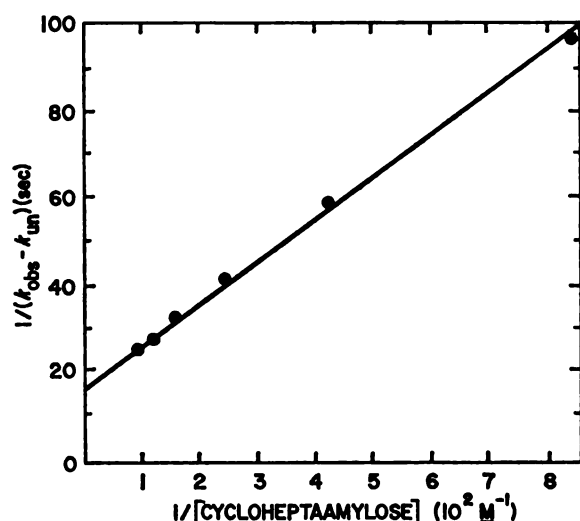


Figure 3. $1/(k_{\text{obs}} - k_{\text{un}})$ for *p*-nitrophenyl acetate decomposition is plotted vs. the reciprocal of the cycloheptaamylose concentration (data from Figure 2).

exhibit the largest rate accelerations. For example, although *m*-chlorophenyl acetate hydrolysis shows a 113-fold acceleration in the presence of cyclohexaamylose, the *para* isomer shows only a threefold acceleration; likewise *m*-*t*-butylphenyl acetate shows a 230-fold acceleration whereas the *para* isomer shows only a 1.7-fold rate enhancement. Similar observations may be made for the effects of added cycloheptaamylose on reaction of substituted phenyl acetates, there being a remarkable stereoselective enhancement of the phenol release reaction favoring the *meta*-substituted compounds.

Because the cycloamyloses form inclusion complexes in solution with a variety of organic and inorganic substances⁶⁻⁹ it appeared likely that the rate increases shown in the data of Table III involved a cycloamylose-ester complex. Such being the case, it is uncertain whether the apparent geometric specificity evident in the accelerations is due to differences in the reactivity of the complexes (or in both). In an effort to resolve this problem the concentration dependence of the catalytic action was examined. The effect of varying (excess) cycloheptaamylose concentration on the pseudo-first-order rate constant for *p*-nitrophenyl acetate hydrolysis (as measured by phenol release) is shown in Figure 2. The rate accelerations approach a

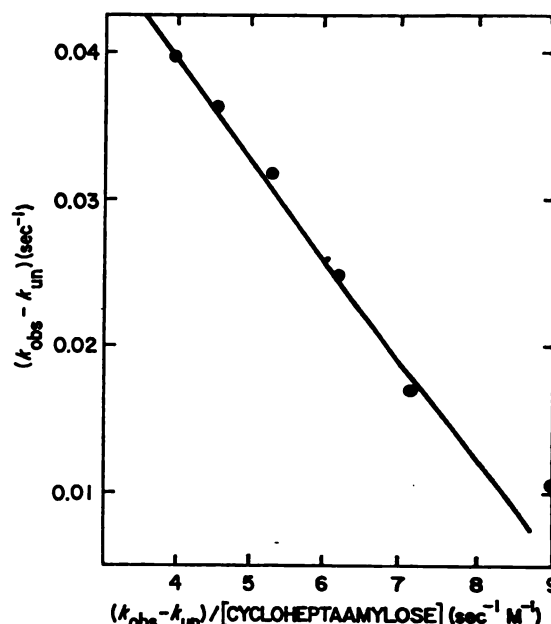


Figure 4. $(k_{\text{obs}} - k_{\text{un}})$ for *p*-nitrophenyl acetate decomposition is plotted as a function of $(k_{\text{obs}} - k_{\text{un}})/[\text{cycloheptaamylose}]$ (data from Figure 2).

maximum saturation value similar to the behavior observed in enzyme kinetics. The data were treated by a variant of Michaelis-Menten kinetics previously employed for investigation of reactions involving complex formation. By plotting the *p*-nitrophenyl acetate data in the form of $1/(k_{\text{obs}} - k_{\text{un}})$ vs. the reciprocal of the cycloamylose concentration a straight line is obtained (Figure 3) having a slope of K_{dis}/k_2 and a Y intercept equal to $1/k_2$, where K_{dis} is the dissociation constant of the complex and k_2 is the rate constant for reaction of the entirely complexed ester ($k_{\text{obs}} - k_{\text{un}}$ at infinite cycloamylose concentration).²⁸

In order to permit a more accurate evaluation of the various values of K_{dis} and k_2 , a statistically preferable form²⁴ of Michaelis-Menten kinetics due to Eadie²⁵ was employed. As shown in Figure 4 for the *p*-nitrophenyl acetate data, by plotting $k_{\text{obs}} - k_{\text{un}}$ against $(k_{\text{obs}} - k_{\text{un}})/[\text{cycloamylose}]$ a straight line is obtained with slope $-K_{\text{dis}}$ and a Y intercept of k_2 .

Dissociation constants and maximal rate accelerations obtained in this manner (by electronic computation; see Experimental Section) are presented in Table IV. It is of importance to compare the dissociation constants and the rate effects observed with some of the isomeric phenyl acetates. *p*-Nitrophenyl acetate forms a more stable complex with both cyclohexaamylose and cycloheptaamylose than does *m*-nitrophenyl acetate, but the maximal rate accelerations k_2/k_{un} are much greater for the *meta* isomer. Similarly, although the stability of the *m*-*t*-butylphenyl acetate-cyclohexaamylose complex differs by only a factor of 3 from that of the *para* isomer, the release of phenol from the *meta* isomer is accelerated some 230 times more than from the *para* isomer. Qualitatively similar observations may be made for the reaction of *o*-, *m*-, and *p*-tolyl acetates in the presence of cyclohexaamylose. Thus, the

(28) This method of data treatment is in effect the Lineweaver-Burk plot of $1/\text{velocity}$ vs. $1/\text{substrate concentration}$ which is frequently employed in studies of the kinetics of enzyme-catalyzed reactions: H. Lineweaver and D. Burk, *J. Am. Chem. Soc.*, **56**, 658 (1934).

Table IV. Maximal Rate Accelerations and Dissociation Constants of Cycloamylose-Phenyl Acetate Complexes^a

Acetate	Hydroxide ion rate, k_{un} , 10^{-4} sec^{-1}	Cyclohexaamylose			Cycloheptaamylose		
		k_2 , 10^{-3} sec^{-1}	k_2/k_{un}	K_{dis} , $10^{-3} M$	k_2 , 10^{-3} sec^{-1}	k_2/k_{un}	K_{dis} , $10^{-3} M$
Phenyl	8.04	2.19	27	2.2 ± 0.7			
<i>o</i> -Tolyl	3.84	0.72	19	1.9 ± 0.5			
<i>m</i> -Tolyl	6.96	6.58	95	1.7 ± 0.5			
<i>p</i> -Tolyl	6.64	0.22	3.3	1.1 ± 0.7			
3,5-Dimethylphenyl	5.80	11.5	200	1.5 ± 0.4	4.86	84	8.8 ± 1.4
3,4,5-Trimethylphenyl	1.04 ^b				1.29 ^b	124 ^b	5.0 ± 1.1^b
<i>m</i> -Ethylphenyl	5.49 (1.42) ^b	13.3	242	1.07 ± 0.14	1.26 ^b	89 ^b	2.2 ± 0.4^b
<i>m</i> - <i>t</i> -Butylphenyl	4.90	12.9	260	0.20 ± 0.08	12.2	250	0.13 ± 0.03^c
<i>p</i> - <i>t</i> -Butylphenyl	6.07	0.067	1.1	0.65 ± 0.39			
<i>m</i> -Chlorophenyl	19.1 (5.05) ^b	7.89 ^b	156 ^b	0.56 ± 0.03^b	4.50	24	3.5 ± 0.9
<i>m</i> -Chlorophenyl	4.99 ^d	6.88 ^d	138 ^d	0.42 ± 0.05^d			
<i>m</i> -Chlorophenyl	9.08 ^e	14.9 ^e	164 ^e	4.2 ± 1.0^e			
<i>m</i> -Nitrophenyl	46.4 (14.0) ^b	42.5 ^b	300 ^b	1.9 ± 0.4^b	44.4	96	8.0 ± 1.8
<i>p</i> -Nitrophenyl	69.4	2.43	3.4	1.2 ± 0.4	6.34	9.1	6.1 ± 1.3
<i>m</i> -Carboxyphenyl	8.15	5.55	68	10.5 ± 3.1			
<i>p</i> -Carboxyphenyl	12.5	0.67	5.3	15.0 ± 9.0			

^a In pH 10.60 carbonate buffer, $I = 0.2$, 0.5% acetonitrile-water unless otherwise noted. All determinations at $25.0 \pm 0.1^\circ$. Error limits for K_{dis} were calculated from the experimental data by application of Student's t test at the 95% probability level. The error in k_2 may be expected to parallel the error in K_{dis} . ^b In pH 10.01 carbonate buffer, $I = 0.2$, 0.5% acetonitrile-water. ^c Determined by graphically estimating the cycloheptaamylose concentration necessary to result in the half-maximal velocity from a plot of k_{obsd} vs. [cycloheptaamylose]; [ester] $\approx 2 \times 10^{-3} M$. ^d In pH 10.01 carbonate buffer, $I = 2.0$ (by addition of potassium chloride), 0.5% acetonitrile-water. ^e In pH 10.58 carbonate buffer, $I = 0.2$, 10% (v/v) (1.9 M) acetonitrile-water.

tereospecific rate accelerations are unrelated to the strength of binding. The sensitivity of k_2 to the stereochemistry of the substrate is strikingly similar to enzyme-catalyzed reactions (see Discussion).

Competitive Inhibition of Cycloamylose Catalysis. In order to determine the stability of complexes of the cycloamyloses with a variety of unreactive molecules as well as to provide further information about the nature of the reactive complex, the competitive inhibition of the cyclohexaamylose-catalyzed decomposition reaction of *m*-nitrophenyl acetate was examined. As anticipated, the rate effects of the cycloamyloses were decreased upon addition of a variety of organic compounds to the reaction mixture. By determining the extent of inhibition as a function of added inhibitor concentration it was possible to obtain an inhibition constant K_i which is the dissociation constant of the cycloamylose-inhibitor complex (see Experimental Section). The treatment of the data is exemplified by Figure 5. Application of this method made possible the determination of the inhibition constants for the anions shown in Table V. From these data it is apparent that small anions such as acetate and propionate do not bind well to cyclohexaamylose. Anions derived from acids containing larger relatively hydrophobic groups such as adamantane or cyclohexane form relatively stable complexes (see Discussion).

Determination of Cycloamylose-Substrate Dissociation Constants by Spectrophotometric Methods. The formation of inclusion complexes with cycloamyloses is known to lead to perturbations of the ultraviolet spectra of a variety of organic molecules ranging from organic dyes²⁹ such as marine blue, methyl orange, and crystal violet to compounds such as *N*-acetyltyrosine ethyl ester.³⁰ Thus, it appeared possible to observe significant

Table V. Dissociation Constants of Cyclohexaamylose Complexes Determined by Competitive Inhibition of the *m*-Nitrophenyl Acetate Hydrolysis Reaction^a

Acid anion inhibitor ^b	K_i , M^c
Acetate	>1.0
Propionate	$5.7 \pm 2.0 \times 10^{-1}$
Isobutyrate	$2.2 \pm 0.3 \times 10^{-1}$
Pivalate	$2.0 \pm 0.6 \times 10^{-1}$
Benzoate	$8.1 \pm 1.0 \times 10^{-2}$
<i>p</i> -Toluenesulfonate	$6.0 \pm 2.0 \times 10^{-2}$
<i>p</i> -Benzoylbenzoate	$4.0 \pm 0.5 \times 10^{-2}$
Cyclohexanecarboxylate	$1.9 \pm 0.3 \times 10^{-2}$
<i>p</i> -Phenylbenzoate	$1.7 \pm 0.2 \times 10^{-2}$
<i>m</i> -Chlorobenzoate	$1.2 \pm 0.2 \times 10^{-2}$
Adamantanecarboxylate ^d	$7.0 \pm 2.0 \times 10^{-3}$
<i>m</i> -Chlorocinnamate	$7.0 \pm 1.0 \times 10^{-3}$
<i>p</i> -Chlorobenzoate	$6.0 \pm 2.0 \times 10^{-3}$
<i>p</i> -Chlorocinnamate	$5.1 \pm 1.0 \times 10^{-3}$

^a All determinations were made at $25.0 \pm 0.1^\circ$ using pH 10.0 sodium carbonate buffer, $I = 0.2$ (but when K_i was $>10^{-3} M$ then $I > 0.2$), 0.5% acetonitrile. ^b No unusual effects are observed with cationic inhibitors; for example, tetraethylammonium bromide gives $K_i = 3.3 \pm 0.6 \times 10^{-3} M$. ^c Calculated assuming a 1:1 stoichiometry in the complex; it is possible that molecules such as *p*-benzoylbenzoate form higher order complexes, as has been observed for methyl orange¹⁷ (where the dissociation constants differ by $\sim 10^5$). The error limits were obtained by drawing extreme lines through the experimental points. ^d K_i for inhibition of cycloheptaamylose catalysis is $7 \pm 4 \times 10^{-4} M$.

changes in the ultraviolet absorption spectra of aromatic molecules related to ester substrates occurring as the result of complex formation. This was indeed the case. An example of the type of observed spectral change is shown in Figure 6. Addition of $2.5 \times 10^{-3} M$ cyclohexaamylose to an aqueous solution of $1 \times 10^{-4} M$ *p*-*t*-butylphenol causes a spectral change almost identical with that observed when the phenol is dissolved in dioxane instead of water. This result is similar to observations made for cycloamylose complexes of iodine⁸ and *N*-acetyltyrosine ethyl ester.^{3,30} Glucose, at these concentration levels, has no significant effect on the ultraviolet spectrum. The similarity of the aqueous cyclohexaamylose solution spectrum to the

(29) W. Lautsch, W. Broser, W. Biedermann, and H. Gnichtel, *J. Polymer Sci.*, **17**, 479 (1955).

(30) T. L. Warrington and M. Laskowski, Jr., Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., 1963, p 76C; see also ref 8. For a study of the binding of benzoic acids to cyclohexaamylose, see B. Casu and L. Rava, *Ric. Sci. Rend.*, **36**, 733 (1966).

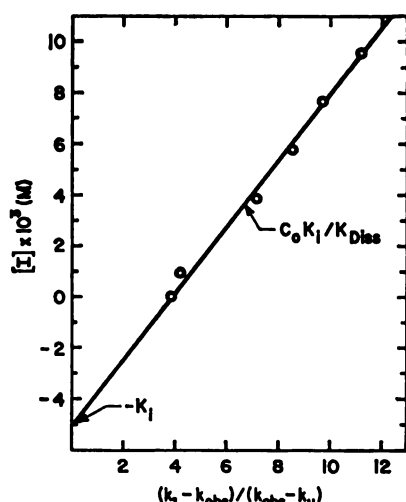


Figure 5. Added inhibitor concentration $[I]$ graphed as a function of $(k_2 - k_{\text{obs}})/(k_{\text{obs}} - k_u)$ for inhibition by *p*-chlorocinnamate ion of the acceleration of *m*-nitrophenyl acetate decomposition by cyclohexaamylose (experimental conditions given in Table V).

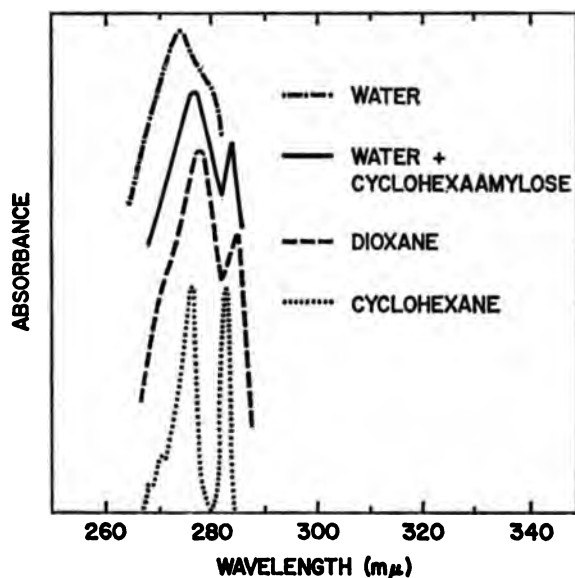


Figure 6. Ultraviolet absorption spectrum of *p*-*t*-butylphenol in various solvents (the absorbance values are arbitrarily shifted vertically for purposes of clarity); [cyclohexaamylose] = $2.5 \times 10^{-3} M$; [phenol] $\approx 1 \times 10^{-4} M$.

dioxane solution spectrum suggests that the aromatic chromophore is largely included in the cycloamylose cavity (see Discussion).

The absorbancy changes resulting from the addition of varying amounts of cycloamyloses to the aqueous solutions of the substrates were treated by plotting²⁵ $[A][B]/\Delta Abs$ against $[A] + [S]$, where $[A]$ and $[S]$ are the initial stoichiometric concentrations of cycloamylose and substrate and ΔAbs is the spectral perturbation observed as the difference spectrum. Under the experimental conditions employed the product $[A][S]$ was maintained much larger than $[C]^2$ where $[C]$ is the concentration of the complex. Examples of such determinations are shown in Figure 7. The dissociation constants of some cyclohexaamylose complexes determined in this manner are shown in Table VI. Of greatest interest is the agreement between dissociation constants obtained by spectrophotometric, kinetic, and inhibition methods. For *m*-chlorophenyl acetate the

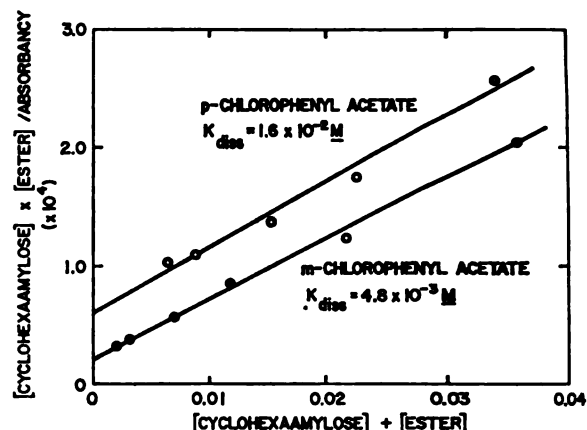


Figure 7. Determination of cyclohexaamylose-substrate dissociation constants by spectrophotometric methods by plotting $([\text{cyclohexaamylose}][\text{ester}])/\text{absorbance}$ as a function of $[\text{cyclohexaamylose}] + [\text{ester}]$; experimental conditions are given in Table VI.

Table VI. Dissociation Constants of Cyclohexaamylose Complexes Determined by Spectrophotometric Methods^a

Substrate	Wavelength, $m\mu^b$	K_{diss} , M
Phenol	273, 280	5.3×10^{-3}
3,5-Dimethylphenol	235, 280	1.6×10^{-3}
3,5-Dimethylphenyl acetate	235	1.3×10^{-3}
<i>m</i> -Chlorophenyl acetate	230, 235	4.7×10^{-3}
<i>p</i> -Chlorophenyl acetate	269, 276	1.6×10^{-3}
<i>m</i> - <i>t</i> -Butylphenol	230, 282	3.4×10^{-3}
<i>p</i> - <i>t</i> -Butylphenol	278, 285	1.2×10^{-3}
2-Naphthol	290, 335	3.1×10^{-3}
<i>p</i> -Chlorocinnamate ^c	290, 301	5.1×10^{-3}
Methyl orange ^{d,e}	510, 520	2.2×10^{-4}

^a Determined using pH 2.2 potassium chloride-hydrochloric acid buffer, $I = 0.06$ unless otherwise noted. All determinations were made at $25.0 \pm 0.1^\circ$. ^b Where more than one wavelength is listed the reported dissociation constant is the average of two determinations which agreed to within 10%. ^c Determined using pH 10.05 sodium carbonate buffer, $I = 0.2$. ^d Determined using pH 6.75, 0.1 *M* sodium and potassium phosphate buffer. At cyclohexaamylose concentrations $> 5 \times 10^{-3} M$, additional spectral perturbations began to appear suggesting the formation of higher order complexes having a much larger dissociation constant; see also ref 17. ^e Reported $1.12 \times 10^{-4} M$: W. Broser and W. Lautsch. *Z. Naturforsch.*, **8b**, 711 (1953).

comparable values are $5.6 \times 10^{-3} M$ (kinetic) and $4.7 \times 10^{-3} M$ (spectral), while for 3,5-dimethylphenyl acetate they are $1.5 \times 10^{-3} M$ and $1.3 \times 10^{-3} M$, respectively.¹¹ The spectrophotometric and competitive inhibition methods give the same value for the dissociation constant of the cyclohexaamylose complex of *p*-chlorocinnamate ion.

Temperature Dependence of Cyclohexaamylose-Substrate Dissociation Constants. The kinetic dissociation constants of some cyclohexaamylose-substrate complexes were determined at temperatures between 15 and 55° and the experimental results are shown in Table VII. In order to calculate the thermodynamic changes accompanying the dissociation process the least-squares slope was computed of the line formed by plotting $\ln K_{diss}$ against the reciprocal of the absolute temperature (Figure 8). From the relationship $d(\ln K_{eq})/d(1/T) = -\Delta H^\circ/R$ and the assumption that

(31) 2-Naphthol forms a relatively stable complex with cyclohexaamylose ($K_{diss} = 3.1 \times 10^{-3} M$) although an azo dye with a 2,8-disubstituted naphthol group apparently does not.¹⁷

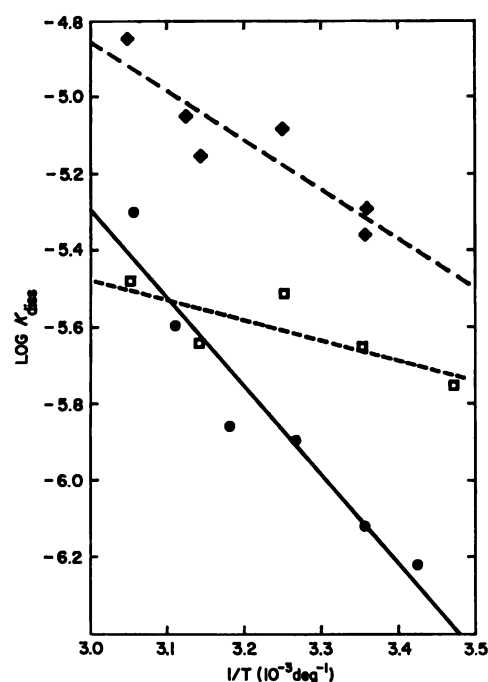


Figure 8. Plot of $\ln K_{diss}$ vs. the reciprocal of the absolute temperature. The data is that of Table VII for dissociation of cycloheptaamylose-substrate complexes: ●, *m*-ethylphenyl acetate; □, *m*-isopropylphenyl acetate; ◆, 3,4,5-trimethylphenyl acetate.

Table VII. Temperature Dependence of Some Cycloheptaamylose-Substrate Dissociation Constants^a

Ester	Temp, °C	K_{diss}^b $10^{-3} M$
<i>m</i> -Chlorophenyl acetate	15.3	3.2 ± 0.7
	25.0	3.5 ± 0.9^c
	34.8	4.0 ± 0.4
	45.1	3.5 ± 0.5
	55.0	4.3 ± 1.0
3,4,5-Trimethylphenyl acetate	25.0	5.0 ± 1.1
	25.1	4.7 ± 0.6
	34.8	6.2 ± 0.4
	45.3	5.8 ± 0.4
	47.1	6.4 ± 1.7
<i>m</i> -Ethylphenyl acetate	55.0	7.8 ± 0.3
	18.8	2.00 ± 0.44
	25.0	2.16 ± 0.36
	32.8	2.74 ± 0.56
	41.1	2.85 ± 0.37
	48.2	3.70 ± 0.53
	54.2	4.97 ± 0.68

^a At pH 10.01 (25°), $I = 0.2$ sodium carbonate buffer with 0.5% tonitrile-water unless otherwise noted. ^b Error limits computed from the experimental data by application of Student's *t* test at the 1% probability level. ^c At pH 10.60 (25°), other conditions as in *a*.

heat capacities of reactants and products are not significantly different (entirely justified here since the average error in K_{diss} is ~20%) one obtains the enthalpy change $\Delta H^\circ = -R(\text{slope})$ and $\Delta S^\circ = R(\text{intercept})$. The computed line was used to calculate an average value of ΔF°_{298} .

Discussion

The cycloamyloses cause a markedly stereoselective acceleration of the phenol release from substituted phenyl acetates in alkaline solution. Unlike methyl α-D-glucoside or glucose, which produces small, uniform rate

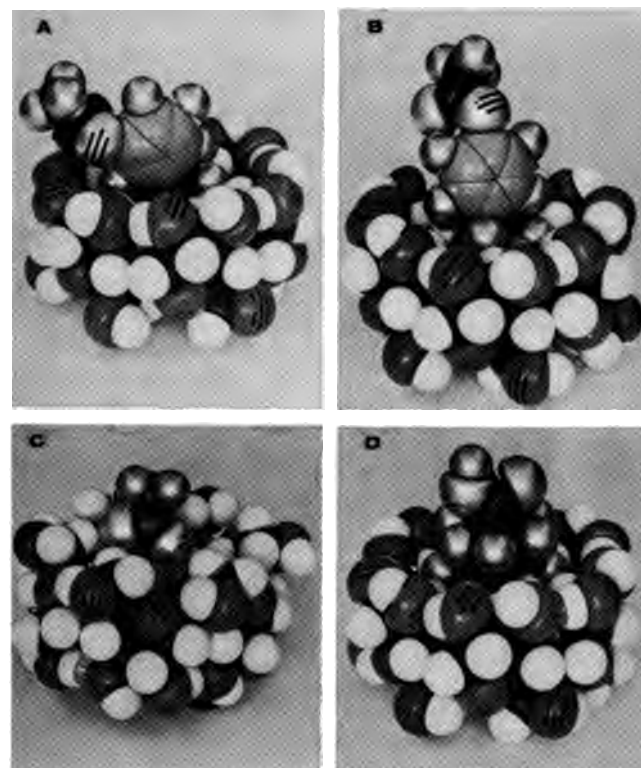
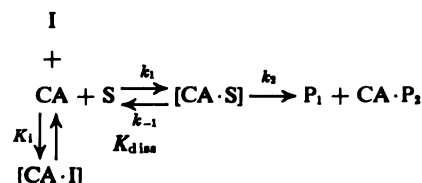


Figure 9. Scale molecular models of cyclohexaamylose complexes: (A) *m*-*t*-butylphenyl acetate complex with the *t*-butyl group inserted into the cavity from the secondary hydroxyl side; (B) *p*-*t*-butylphenyl acetate complex constructed as in A; (C) *p*-*t*-butylphenyl acetate complex constructed by inserting the acetyl group through the cavity until it protrudes from the primary hydroxyl side of the cyclohexaamylose; (D) adamantanecarboxylic acid complex. The oxygen and hydrogen atoms of the guest molecule are coated with metallic paint for greater contrast (the slots in the oxygen atoms are for hydrogen bonds).³²

effects, both cyclohexaamylose and cycloheptaamylose cause large, nonuniform effects, the rate of phenol release from *meta*-substituted phenyl acetates being greatly enhanced whereas phenol release from the corresponding *para* isomers is only slightly enhanced. The rate effects due to cyclooctaamylose are also large but are much less stereoselective. The stereoselectivity is exerted independently of the stability of the complex and is thus similar to observations made for enzyme-catalyzed reactions (see introductory section). The cycloamylose system also shows spectral changes on binding, competitive inhibition, nonproductive binding, and saturation of the substrate with cycloamylose.³² A minimal reaction scheme which accommodates these facts is shown below. Here, cycloamylose (CA) and



ester (S) undergo a reversible association to form a cycloamylose-substrate complex $[\text{CA} \cdot \text{S}]$ which may undergo a reaction with rate constant k_2 to form phenol P_1 and product(s) $\text{CA} \cdot \text{P}_2$. The cycloamylose

(32) For an example of the saturation of a substrate with an enzyme see F. J. Kézdy and M. L. Bender, *Biochemistry*, **1**, 1097 (1962).

(33) Accompanying article: R. L. VanEtten, G. A. Clowes, J. F. Sebastian, and M. L. Bender, *J. Am. Chem. Soc.*, **89**, 3253 (1967).

may also undergo a reversible association with an inhibitor I to form a cycloamylose-inhibitor complex [CA·I]. Except with sterically hindered or strongly solvated molecules the reversible association to form a 1:1 complex with cycloamyloses may be expected to be rapid compared¹⁷ to the rates of chemical reactions described here.

The catalytic activity of enzymes is localized in an area termed the active site which is responsible for the binding of substrates, coenzymes, and inhibitors, and is responsible for catalyzing the chemical transformations.³⁴ The cycloamylose system developed here is an interesting model for an enzyme active site in that its properties are completely explained by considering the region of the cycloamylose cavity and the secondary hydroxyl³⁵ groups to be the active site of the cycloamylose torus. Most importantly, such a model readily explains the stereoselective rate accelerations. A scale³⁶ molecular model of a complex of *m*-*t*-butylphenyl acetate with cyclohexaamylose is shown in Figure 9A. This model was constructed by inserting the hydrophobic *t*-butyl group into the cycloamylose cavity from the secondary hydroxyl side.³⁶ This results in fixing the position of the ester function in close proximity to the secondary hydroxyl groups. A striking difference is seen in models of cyclohexaamylose complexes of *p*-*t*-butylphenyl acetate. If the *t*-butyl group is inserted first into the secondary side, then the ester function is located at some distance from the hydroxyl groups (Figure 9B). However, if the acetyl portion is inserted into the cavity from the secondary side until it protrudes from the primary hydroxyl side (which cannot be done for the *meta* isomer), then the aromatic ring and most of the *t*-butyl group are included in the cycloamylose cavity (Figure 9C). The ester function may be partially shielded from nucleophilic attack by hydroxide ion in solution, which would be consistent with the fact that the basic hydrolysis of ethyl *p*-aminobenzoate is inhibited by complexation with cycloheptaamylose.¹⁶ In this model the ester function is located in close proximity to the primary hydroxyl groups. This model together with the unreactivity of the *para* isomer suggests that the interaction which leads to increases in the rate of phenol release involves the secondary hydroxyl groups; this has, in fact, been established.³³

These models of the cycloamylose-substrate complexes also explain why spectral changes may be observed when some organic substrates form cycloamylose complexes. In cyclohexaamylose complexes, the aromatic chromophore of *m*-*t*-butylphenyl acetate is not greatly removed from the aqueous environment (Figure 9A); the model is thus consistent with the fact that the spectrum of *m*-*t*-butylphenol plus cyclohexaamylose in

water shows only a small spectral perturbation compared to the spectrum of the phenol in water. However, *p*-*t*-butylphenol plus cyclohexaamylose shows a marked spectral change resembling the spectrum of the phenol in dioxane solution (Figure 6); this perturbation is consistent with the inclusion of the aromatic chromophore in the ether-like cycloamylose cavity. These arguments indicate that *p*-*t*-butylphenyl acetate is probably included in the cycloamylose active site with the ester function near the primary hydroxyl groups and the *t*-butyl group near the secondary hydroxyl groups, as shown in Figure 9C.

Differences are observed in the stereoselectivity of cyclooctaamylose and the two smaller amyloses (Table III). These differences are also seen in the values of K_{dis} and k_2 for cyclooctaamylose-accelerated reactions of *t*-butylphenyl acetate as seen in Table VIII. The selectivity ratio (*meta* rate acceleration/*para* rate acceleration) for *t*-butylphenyl acetate hydrolysis in the presence of cyclohexaamylose is 240 (Table IV) while with cyclooctaamylose it is only 1.7 (Table VIII). This is readily explained on consideration of the size of the respective active sites of the amyloses. In sharp contrast to cyclohexaamylose, the cyclooctaamylose cavity is so large that the *t*-butyl group of *para*-*t*-butylphenyl acetate may be placed in the cavity and the ester function may still be moved freely so as to orient it adjacent to the secondary hydroxyl groups. Since the cyclohexaamylose cavity is the smallest and most restrictive of the three it might be expected to be the most sensitive to the size of *para* substituents which prevent aromatic substrates from tipping in the cavity so as to orient the ester function in proximity to the secondary hydroxyl groups. This is in agreement with the observation that in the hydrolysis of *p*-nitrophenyl acetate, the maximal rate effect due to cyclohexaamylose is 3.4 while the effect due to cycloheptaamylose is 9.1 (Table IV). If there is no substituent on the phenyl ring then the acceleration due to cyclohexaamylose rises to 27 (Table IV). Thus the specificities exhibited by the *para*-substituted esters are negative specificities.

Table VIII. Maximal Rate Accelerations and Dissociation Constants for Cyclooctaamylose Complexes

Acetate substrate ^a	k_2 , sec ⁻¹	k_2/k_{un}	K_{dis} , M
<i>m</i> - <i>t</i> -Butylphenyl	4.7×10^{-3}	87	$9.9 \pm 3.6 \times 10^{-1}$
<i>p</i> - <i>t</i> -Butylphenyl	3.5×10^{-3}	55	$4.0 \pm 0.7 \times 10^{-1}$

^a For reaction conditions see footnote a, Table IV.

The differing rate effects which result from a change in the geometry of the active site have their parallel in enzyme chemistry. Chymotrypsin, trypsin, and subtilisin all catalyze hydrolysis reactions by similar mechanisms and yet they exhibit very different specificities.³⁷ Changes in the nature of the groups which control binding as well as in the stereochemistry of the active site readily account for differing specificities of enzymes despite seemingly identical mechanisms. Not surprisingly, enzyme-catalyzed reactions may also show

(34) A useful introductory discussion of enzyme chemistry including the active site may be found in H. R. Mahler and E. H. Cordes, "Biological Chemistry," Harper and Row, New York, N. Y., 1966, Chapter 7.

(35) The structure of cyclohexaamylose appears to be reasonably well represented by Corey-Pauling-Koltun scale molecular models [described in W. L. Koltun, *Biopolymers*, 3, 665 (1965)], since the diameter of the cavity as determined by crystallographic measurements¹² varies from 4.7 to 5.1 Å (measured between hydrogen atoms on C-3 of the glucose residues) while the scale model yields a distance of 5.3 Å.

(36) The secondary hydroxyl groups are on a relatively rigid carbon chain while the primary hydroxyl groups can rotate so as to partially block that part of the cavity. This further accentuates the "V" shaped nature of the cycloamylose cavity in which the open side is surrounded by the secondary hydroxyl groups.

(37) M. L. Bender and F. J. Kézdy, *Ann. Rev. Biochem.*, 34, 49 (1965); M. L. Bender and C. G. Miller, unpublished work.

ferences in reaction rates and stabilities of the enzyme-substrate complexes depending on the position of substituents on an aromatic substrate.^{38,39} The relative inhibitory properties toward cholinesterase of a series of alkyl-substituted phenyl N-methylcarbamates³⁹ exhibit an interesting parallel with data obtained for cyclohexaamylose-catalyzed decomposition of phenyl acetates. Table IX illustrates how the seemingly unusual behavior of the enzymic system is paralleled by the cycloamylose system (it is not intended to imply that there is necessarily any actual similarity of the active sites).

Table IX. Parallel Effects of the Inhibition of Cholinesterase^a on the Decomposition of Phenyl Esters in the Presence of Cyclohexaamylose

Alkyl group	Relative inhibition due to alkylphenyl N-methylcarbamates ^a	k_2/K_{dis} for accelerations by cyclohexaamylose ^b
H	(1)	(1)
<i>o</i> -Methyl	1.4	0.4
<i>p</i> -Methyl	2.0	0.2
<i>m</i> -Methyl	14	3.9
3,5-Dimethyl	33	7.7
<i>m</i> -Ethyl	42	12
<i>m</i> - <i>t</i> -Butyl	500	64

The mechanism of inhibition of cholinesterase by substituted carbamates probably involves acylation of the enzyme [R. D. O'Brien, *U.S. Med. Surg.*, 23, 117 (1965)] so that the "affinity" discussed by Metcalf and Fukuto³⁹ is probably k_2/K_a , where k_2 is the acylation and K_a is the dissociation constant of the cholinesterase-carbamate complex. ^a Taken from Table IV; see footnote a.

For catalysis involving prior inclusion it is reasonable to expect that the limited number of active sites (here all presumably to the number of cycloamylose molecules) could be saturated or entirely occupied by substrate molecules.²² This is in accord with the experimental data (cf. Figure 2). It is also strikingly illustrated by the fact that for the hydrolysis of *m*-*t*-phenyl acetate in the presence of cycloheptaamylose, the ester is almost completely complexed at cycloamylose concentrations greater than $\sim 6 \times 10^{-4}$ M, usually the same hydrolysis rate constant (as measured by phenol release) being obtained even as the cycloamylose concentration is increased to 10^{-2} M.

The presence of discrete catalytic sites such as in an inclusion complex also predicts that the addition of otherwise unreactive molecules to the reaction mixture should reduce the rate accelerations caused by cycloamyloses by acting as competitive inhibitors for the active site. This has been quantitatively demonstrated for the cycloamyloses, added organic molecules reducing the rate acceleration observed for release of phenol from *m*-nitrophenyl acetate (Table V).⁴⁰ Further support for the hypothesis that the active site of the cycloamylose is the region of the cavity

and the secondary hydroxyls as well as information about the nature of forces involved in the complex may be obtained from consideration of experiments carried out with carboxyl-substituted phenyl esters. Table IV gives the maximal rate accelerations and dissociation constants determined for the reactions of *m*- and *p*-carboxyphenyl acetates in the presence of cyclohexaamylose. As previously noted, the *meta* isomer shows a large rate acceleration (68-fold) compared to the *para* isomer (fivefold). If the ester function of the *para* isomer is made increasingly hydrophobic by alkyl substitution then it is possible to bring about an inhibition of the hydrolysis reaction (Table X). This must be the result of including the ester function in the cycloamylose cavity. It was anticipated that the hydrophilic carboxylate anion would not be readily included in the cavity as a consequence of its solvation requirements. This latter hypothesis is consistent with the fact that substitution of a *p*-nitro group for the structurally similar carboxylate anion results in a 12-fold increase in the stability of the cyclohexaamylose complex (Table IV). Thus, at least two factors contribute to the formation of nonproductive complexes: steric effects and electrostatic effects.

Table X. Rate Accelerations and Dissociation Constants of Cyclohexaamylose Complexes of Carboxyl-Substituted Phenyl Esters

<i>p</i> -Carboxyphenyl ester	k_2 , 10^{-3} sec ⁻¹	k_2/k_{un}	K_{dis} , 10^{-3} M
Acetate ^a	6.7	5.3	150 ± 90
2-Methylpropionate ^a	0.44	0.68	12 ± 4
3,3-Dimethylbutyrate ^b	0.089	0.19	1.1 ± 0.2

^a In pH 10.60 sodium carbonate buffer, $I = 0.2$, with 0.5% (v/v) added acetonitrile, $25.0 \pm 0.1^\circ$. ^b In pH 11.22 sodium phosphate, $I = 0.2$, with 0.5% (v/v) added acetonitrile, $25.0 \pm 0.1^\circ$.

Large hydrophobic substituents on guest molecules lead to the formation of relatively stable cycloamylose complexes. In an attempt to gain some understanding of the nature of the forces which lead to complex formation, the temperature dependencies of some cycloheptaamylose-substrate dissociation constants were examined using kinetic methods (Table VII). A

Table XI. Thermodynamic Changes for the Dissociation of Cycloheptaamylose Complexes^a

Substrate	ΔF°_{298} , kcal/mole	ΔH° , kcal/mole	ΔS° , gibbs/mole
<i>m</i> -Chlorophenyl acetate	3.4 ± 1	1 ± 1	-8 ± 3
3,4,5-Trimethylphenyl acetate	3.1 ± 1	2.5 ± 1	-2 ± 3
<i>m</i> -Ethylphenyl acetate	3.6 ± 0.7	4.6 ± 0.7	$+3 \pm 2$

^a The dissociation constants were determined kinetically (Experimental Section) using 7-10 points; for conditions see the footnotes to Table VII. The error limits given above were obtained by application of Student's *t* test to the experimental data of Table VII.

plot of $\ln K_{dis}$ vs. $1/\text{absolute temperature}$ is shown in Figure 8. From the slope and intercept of the least-squares line (see Experimental Section) the thermodynamic quantities associated with the dissociation process were calculated (Table XI). The dissociation constant of the *m*-chlorophenyl acetate-cyclohepta-

8) Cf. R. M. Epand and I. B. Wilson, *J. Biol. Chem.*, 240, 1104 (1965); H. F. Bundy and C. L. Moore, *Biochemistry*, 5, 808 (1966).

9) R. L. Metcalf and T. R. Fukuto, *J. Agr. Food. Chem.*, 13, 220 (1965).

10) This was qualitatively demonstrated by Hennrich and Cramer who showed that the presence of phenol in the reaction mixture reduced the rate acceleration of the alkaline decomposition of diphenyl pyrophosphate.¹⁰

amylose is not very temperature dependent: the binding is due primarily to a favorable entropy change. However, the binding of *m*-ethylphenyl acetate is due to a favorable enthalpy change.⁴¹ 3,4,5-Trimethylphenyl acetate exhibits intermediate behavior. Discussions and experimental data relating to hydrophobic binding indicate that a favorable entropy change is often involved.⁴²⁻⁴⁴ One reason⁴⁵ for the sizable enthalpy change observed in the binding of *m*-ethylphenyl acetate is probably that water molecules in the cavity cannot form their full complement of hydrogen bonds as a result of steric restrictions. The data for *m*-chlorophenyl acetate is difficult to interpret on this basis but may be related to the fact that the aromatic chloro substituent is capable of forming hydrogen bonds⁴⁶ with water molecules which would be freed on complexation, leaving only a net entropy effect. The hypothesis that exclusion of water from the region of the cavity is an important factor in binding to the cycloamyloses is consistent with the fact that complexes may be readily formed with guest molecules which are too large to be completely included. Thus, for example, adamantanecarboxylate which cannot enter the cavity of cyclohexaamylose (Figure 9D) still forms a relatively stable complex, K_{diss} being $7 \times 10^{-3} M$ (Table V). The inhibitor molecule is able to interact with a portion of the cyclohexaamylose cavity slightly past the region of the secondary hydroxyl groups. However, when the substrate is able to entirely exclude water from the region of the cavity, quite stable complexes may be formed. Cycloheptaamylose complexes of *m*-*t*-butylphenyl acetate and of adamantanecarboxylate, for example, have dissociation constants of $1 \times 10^{-4} M$ and $7 \times 10^{-4} M$, respectively. Substrates which fill the cavity completely or have large hydrophobic areas which can interact with the ether-like interior of the cavity form the most stable cycloamylose complexes, so that it would appear reasonable to expect a relationship between the free energy of complex formation and the molecular volume of the guest. In fact, there is an approximate linear relationship between the logarithm of the dissociation constant and the value of the parachor of the guest, the parachor being taken as a measure of molecular volume.⁴⁷ Thus, for the cyclohexaamylose dissociation constants reported here (excluding only the carboxyphenyl esters) a correlation coefficient of 0.79 is found for the least-squares-fitted line. As might be expected for the series of structurally similar substrates and inhibitors considered here, nearly identical correlations were obtained with molecular weight and with molar refraction.⁴⁸

(41) Similar observations have been made for the binding of aromatic amino acid derivatives to cycloheptaamylose: M. Laskowski, Jr., and T. L. Warrington, quoted in ref 8.

(42) F. M. Richards, *Ann. Rev., Biochem.*, **32**, 269 (1963).

(43) W. Kauzmann, *Advan. Protein Chem.*, **14**, 1 (1959).

(44) A. Wishnia and T. W. Pinder, *Biochemistry*, **5**, 1534 (1966).

(45) The observed enthalpy change is also consistent with interpretations based on hydrophobic bonding as opposed to hydrophobic bonding: I. M. Klotz, *Federation Proc., Suppl.* **15**, S24 (1965).

(46) C. M. Huggins, G. C. Pimentel, and J. N. Shoolery, *J. Phys. Chem.*, **60**, 1311 (1956); E. Krakower and L. W. Reeves, *Trans. Faraday Soc.*, **59**, 2528 (1963).

(47) O. R. Quayle, *Chem. Rev.*, **53**, 439 (1953). Electronic effects on the stabilities of cyclohexaamylose complexes of approximately isosteric *para*-substituted benzoic acids have been demonstrated: B. Casu and L. Rava, *Ric. Sci. Rend.*, [8] **36**, 733 (1966).

(48) S. S. Batsanov, "Refractometry and Chemical Structures," Consultants Bureau, New York, N. Y., 1961.

An alternative explanation contribution to the stability of plexes is, of course, that van der Waals dispersion force interactions untribution to the apolar binding completely satisfactory because of some substrate molecules can cycloamylose cavity at a time. important in the complexes ma crystallographic studies.⁴⁹

Conclusion

In connection with his pioneer chemistry Emil Fischer propose molecular configuration must and their substrates if reaction i configurational relationship co between a lock and key.^{50,51} H that simpler asymmetric system stereospecific effects like those sis.⁵⁰ The cycloamylose system sends an excellent model for enz; as it does complex formation, celerations, competitive inhib other effects. The model is rea of the lock and key theory of en:

Appendix

Determination of Dissociation photometric Methods.²⁵ Let A stoichiometric concentrations and substrate, having molar ϵ_a and ϵ_s , respectively. The per formation of a complex may term ΔAbs , which is related t sorbancy Abs by the relation $\epsilon_a A - \epsilon_s S$. The equilibrium complex C (assuming a 1:1 st

$$C = \Delta Abs,$$

where $\Delta \epsilon = \epsilon_c - \epsilon_a - \epsilon_s$. Th is given by $K_f = C/[A - C][S - C]$ sion becomes $C/K_f = AS - SC$ ing that $AS \gg C^2$ this becom AC , or

$$C = AS/(A +$$

On combining (1) and (2) and $K_{\text{diss}} = 1/K_f$ the following is obt

$$AS/(A + S + K_{\text{diss}})$$

$$AS/\Delta Abs = K_{\text{diss}}/\Delta \epsilon$$

Since $\Delta \epsilon$ and K_{diss} are constants a straight line when $[A][S]/\Delta Abs$ sum of the stoichiometric cor

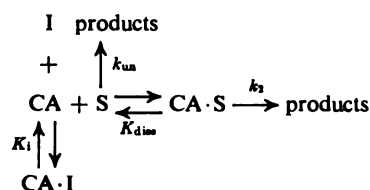
(49) An extensive investigation of the of a variety of 1:1 crystalline cycloamy J. A. Hamilton and R. L. VanEtten, unpubl.

(50) E. Fischer, *Ber.*, **27**, 2985 (1894).

(51) E. Fischer, *Z. Physiol. Chem.*, **26**,

Determination of Dissociation Constants by Inhibition Methods.

In the reaction scheme



K_i is the dissociation constant of the 1:1 cycloamylose-inhibitor complex $\text{CA} \cdot \text{I}$, k_{un} is the spontaneous reaction rate constant of the substrate S , K_{diss} is the dissociation constant of the 1:1 cycloamylose-substrate complex $\text{CA} \cdot \text{S}$ (determined by independent kinetic methods as already described), k_2 is the catalyzed reaction rate constant of the complexed substrate, and $[\text{S}]_0$ and $[\text{CA}]_0$ the initial stoichiometric concentrations of substrate and cycloamylose, respectively. The fraction F_c of complexed substrate will be $^{22} (k_{\text{obsd}} - k_{\text{un}})/(k_2 - k_{\text{un}})$. Then

$$\begin{aligned}
 K_{\text{diss}} &= [\text{S}][\text{CA}]/[\text{CA} \cdot \text{S}] = [\text{S}_0 - \text{CA} \cdot \text{S}][\text{CA}]/[\text{CA} \cdot \text{S}] \\
 &= [(1 - F_c)/F_c][\text{CA}] \\
 &= [(1 - F_c)/F_c][\text{CA}_0 - \text{CA} \cdot \text{I} - \text{CA} \cdot \text{S}]
 \end{aligned}$$

but since $[\text{A}_0 + \text{CA} \cdot \text{I}] \gg [\text{CA} \cdot \text{S}]$ this becomes

$$\begin{aligned}
 &= [(1 - F_c)/F_c][\text{CA}_0 - [\text{CA}][\text{I}]/K_i] \\
 &= [(1 - F_c)/F_c] \left(\text{CA}_0 - \frac{[\text{I}][\text{CA} \cdot \text{S}]K_{\text{diss}}}{[\text{S}]} \right) \\
 &= [(1/F_c) - 1] \left[\frac{[\text{CA}_0 - [\text{I}]K_{\text{diss}}]}{K_i} \left(\frac{F_c}{1 - F_c} \right) \right] \\
 &= [(1/F_c) - 1]\text{CA}_0 - ([\text{I}]K_{\text{diss}}/K_i)
 \end{aligned}$$

so that on rearranging

$$\begin{aligned}
 [\text{I}] &= [(1/F_c) - 1][\text{CA}_0]K_i/K_{\text{diss}} - K_i \\
 &= \left(\frac{1/(k_{\text{obsd}} - k_{\text{un}})}{(k_2 - k_{\text{un}})} - 1 \right) \frac{[\text{CA}_0]K_i}{K_{\text{diss}}} - K_i \\
 &= \left(\frac{k_2 - k_{\text{obsd}}}{k_{\text{obsd}} - k_{\text{un}}} \right) \frac{[\text{CA}_0]K_i}{K_{\text{diss}}} - K_i
 \end{aligned}$$

Thus, by plotting the inhibitor concentration *vs.* $(k_2 - k_{\text{obsd}})/(k_{\text{obsd}} - k_{\text{un}})$ an approximate straight line is obtained with intercept $-K_i$ and slope $([\text{CA}_0] \cdot K_i)/K_{\text{diss}}$.

The Mechanism of the Cycloamylose-Accelerated Cleavage of Phenyl Esters¹⁻³

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Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. Received January 6, 1967

Abstract: The release of phenols from a number of *meta*-substituted phenyl benzoates is accelerated in alkaline solution by cyclohexaamylose and cycloheptaamylose. The acyl portion is transferred to a hydroxyl group of the amylose, forming a cycloamylose benzoate which undergoes hydrolysis *via* a subsequent reaction at a rate independent of the nature of the phenolic group. Cyclohexaamylose benzoate was separated from phenol and unreacted *m*-nitrophenyl benzoate by gel filtration chromatography and was found to undergo hydrolysis at the same rate as the intermediate formed *in situ* during the acceleration of phenol release from a variety of *meta*-substituted phenyl benzoates (substituents on the phenyl group). The hydrolysis of cycloamylose benzoates (deacylation) conforms to a Hammett relationship with $\rho = 1.6$. The pH dependence of the initial rate acceleration (acylation) and of the deacylation reaction agrees with a dependence on a group of $\text{p}K_a = 12.1$. Heptamesylcycloheptaamylose (primary hydroxyl groups blocked) causes as large an acceleration of phenyl ester cleavage as native cycloheptaamylose, but dodecamethylcyclohexaamylose (primary hydroxyl and half of secondary hydroxyl groups blocked) causes a small inhibition of the hydrolysis. This is consistent with a proposed mechanism involving nucleophilic participation by an alkoxide ion derived from the secondary hydroxyl groups of the cycloamylose. The hydrolysis of cycloamylose benzoates occurs ~ 20 times more rapidly than would be predicted on the basis of simple steric and electronic considerations so that the deacylation step may be subject to general acid or general base catalysis by vicinal hydroxyl groups of the cycloamylose. The cycloamylose pathway of binding, acylation, and deacylation is formally similar to the pathway of chymotrypsin-catalyzed hydrolysis of esters. Comparisons of chymotrypsin catalyses and cycloamylose reactions are made, including a comparison of the second-order rate constants of these substances with substrates.

The cycloamyloses cause a markedly stereoselective acceleration of the release of phenols from substituted phenyl acetates, the rate accelerations with

meta-substituted esters being larger than with the corresponding *para*-substituted esters.³ For example, 0.01 *M* cycloheptaamylose causes a 250-fold increase

(1) This research was supported by a grant from the National Science Foundation.

(2) A preliminary account of this work has been published: M. L. Bender, R. L. VanEtten, and G. A. Clowes, *J. Am. Chem. Soc.*, **88**, 2319 (1966).

(3) Accompanying article: R. L. VanEtten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *ibid.*, **89**, 3242 (1967).

(4) National Institutes of Health Postdoctoral Research Fellow.

(5) Department of Chemistry, Purdue University, Lafayette, Ind. 47907.

in the rate of phenol release from *m*-*t*-butylphenyl acetate but only a 2.2-fold increase for the *para* analog. The rate effects are mediated by a cycloamylose-ester complex in solution, and the reaction system exhibits many characteristics of enzyme-catalyzed reactions.³ Because the rate effects are independent of the stabilities of the respective complexes it appeared unlikely that the rate effects were due to an unusual medium effect such as has been observed⁶ for the hydrolysis of alkyl hydrogen sulfate esters. Moreover, the stereospecificity of the rate accelerations can be readily interpreted only on the basis of an interaction of the secondary hydroxyl groups of the cycloamylose (derived from carbon atoms 2 and 3 of the individual glucose residues) with the carbonyl carbon of the ester. The carbonyl carbon of *para*-substituted phenyl esters can readily be placed in proximity to the primary hydroxyl groups (derived from carbon atom 6 of the glucose residues) of cyclooctaamylose whereas it cannot be placed in proximity to the secondary hydroxyl groups of cyclohexa- and -heptaamylose. Cyclooctaamylose causes a large acceleration of phenol release from both *m*- and *p*-*t*-butylphenyl acetate consistent with the fact that the cavity is so large that the carbonyl group of either ester may be placed in proximity to the secondary hydroxyl groups of the cycloamylose when the aromatic ring and the *t*-butyl group are included in the cavity.

The specific mechanism by which the cycloamylose hydroxyl groups accelerate the release of phenols from phenyl esters is not obvious since participation may occur by nucleophilic, general acid, or general base mechanisms.⁷ Thus it is important to attempt to distinguish between these possible mechanisms. The isolation of cyclohexaamylose phosphate from heterogeneous alkaline reaction mixtures (where the cycloamyloses cause an acceleration of phenol release from diphenyl pyrophosphate) has been reported.⁸ This observation suggested that the rate accelerations observed in the course of the present work might be the result of nucleophilic catalysis. The present investigation of the hydrolysis of substituted phenyl benzoates and of the pH dependence of the rate accelerations was therefore undertaken in order to determine the mechanisms by which the cycloamyloses exert their effects on phenyl ester hydrolysis reactions.

Experimental Section

All melting points and boiling points are uncorrected. Aqueous solutions were made up with distilled or double-distilled water and reagent grade chemicals. Eastman Spectro grade acetonitrile was employed for stock solutions of esters and for reaction solvents. Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. A Radiometer 4c pH meter was used for the determination of pH values.

Cyclohexaamylose and cycloheptaamylose were obtained and purified as already described.³ Dodecamethylcyclohexaamylose was very kindly provided by Dr. Hermann Schlenk.⁹ The preparation of hexamethylcyclohexaamylose and heptamethylcycloheptaamylose has been described.¹⁰ The hexa(6-O-mesyl)cyclohexa-

amylose¹¹ was purified by recrystallization from methanol. The ultraviolet absorption spectrum of this compound revealed an absorption band (λ_{\max} 259 m μ) which was attributed to residual pyridine. Efforts to completely remove the impurity by dilute acid wash (pH 2.2) and vacuum drying were unsuccessful. The amount of pyridine was calculated to be less than 5% (by weight) based on the optical extinction coefficient of pyridine (*ca.* 3600 in water). The infrared spectrum (potassium bromide disk) indicated the presence of covalent sulfonate (bands at 1345 and 1180 cm⁻¹) consistent with the literature value.¹²

Anal. Calcd for (C₇H₁₂O₇S)₆: C, 35.01; H, 5.04; S, 13.33. Found: C, 35.09; H, 4.95; S, 13.52.

Hepta(6-O-mesyl)cycloheptaamylose also showed a small absorption band attributed to residual pyridine (less than 2% by weight). The infrared spectrum showed bands at 1340 and 1165 cm⁻¹ which were attributed to covalent sulfonate.

Anal. Calcd for (C₇H₁₂O₇S)₇: C, 35.01; H, 5.04; S, 13.33. Found: C, 34.92; H, 5.19; S, 13.61, 14.02.

The mesyl compounds were relatively insoluble in water so that reactions in the presence of these compounds were carried out in 20.5% acetonitrile solution (v/v). The reported values of the pH are the observed values obtained for the aqueous acetonitrile solutions.

Benzoate esters were prepared by the Schotten-Baumann procedure using the appropriate benzoyl chloride (25 mmoles) and sodium phenolate (25 mmoles) in 40 ml of water. Solid esters were recrystallized from 95% ethanol and dried under vacuum.

m-*t*-Butylphenyl benzoate was obtained as a liquid; vacuum distillation through a 1 × 10 cm vacuum jacketed column gave the ester, bp 186–188° (11 mm).

Anal. Calcd for C₁₇H₁₈O₂: C, 80.30; H, 7.12. Found: C, 80.12; H, 7.27.

m-Chlorophenyl benzoate after recrystallization was obtained as colorless crystals, mp 69–70° (lit.¹⁴ mp 71–72°).

m-Nitrophenyl benzoate was obtained as colorless needles, mp 91–92° (lit.¹⁴ mp 95°).

m-Chlorophenyl *p*-chlorobenzoate was obtained as colorless needles, mp 99–99.5° (lit.¹⁶ 101.5°).

Anal. Calcd for C₁₃H₈Cl₂O₂: C, 58.42; H, 3.00; Cl, 26.59. Found: C, 58.52; H, 3.30; Cl, 26.06.

m-Chlorophenyl *m*-chlorobenzoate was obtained as colorless needles, mp 65–66°.

Anal. Calcd for C₁₃H₈Cl₂O₂: C, 58.42; H, 3.00; Cl, 26.59. Found: C, 58.67; H, 3.04; Cl, 26.40.

m-Chlorophenyl *p*-nitrobenzoate was obtained by reaction of *m*-chlorophenol (1.3 g, 10 mmoles) with *p*-nitrobenzoyl chloride (1.9 g, 10 mmoles) in dry pyridine (10 ml). The reaction mixture was heated to boiling for 5 min and then diluted with 200 ml of 5% hydrochloric acid. The resulting solid was separated, washed successively with several portions of dilute acid, dilute alkali, and water, and then dried under vacuum. The solid was then recrystallized twice from ethanol, being obtained as colorless needles, mp 96–97° (lit.¹⁶ mp 101°).

Anal. Calcd for C₁₃H₈ClNO₄: Cl, 12.79. Found: Cl, 13.03.

Reaction Kinetics of Phenyl Benzoates. The reactions of substituted phenyl benzoates in alkaline solution were studied spectrophotometrically using a Cary Model 14 recording spectrophotometer equipped with a thermostated cell holder and cell compartment, and 0–1.0 and 0–0.1 absorbance unit slide wires. The general experimental techniques have been described.³ The final concentrations of benzoate esters were 1.6–2.0 × 10⁻³ M while that of added acetonitrile was 0.5% (v/v) unless otherwise stated. The reactions of the phenyl benzoates shown in Table I occurred in two steps in the presence of 0.01 M cycloamyloses (see Results).

(11) The location of the mesyl groups on the primary hydroxyl groups of the cycloamylose (that is, the C-6 hydroxyl groups of the individual glucose residues) following this method¹⁰ of preparation has been established by Drs. F. Parrish and L. Long, Jr. (private communication). For a contrasting example of the reactivity of mesyl chloride with both primary and secondary hydroxyl groups see R. C. Chalk, D. H. Ball, and L. Long, Jr., *J. Org. Chem.*, **31**, 1509 (1966).

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 364.

(13) W. J. Wohlleben, *Ber.*, **42**, 4371 (1909).

(14) F. M. Beringer, A. Brierley, M. Drexler, E. M. Grundler, and C. C. Lumpkin, *J. Am. Chem. Soc.*, **74**, 2708 (1952).

(15) M. Neeman, A. Modiano, and Y. Shor, *J. Org. Chem.*, **21**, 671 (1956).

(16) R. S. Tadkod, P. B. Sattur, N. S. Kulkarni, and K. S. Nargund, *J. Karnatak Univ.*, **2**, 29 (1957); *Chem. Abstr.*, **53**, 8063a (1957).

(6) B. D. Batts, *J. Chem. Soc., Phys. Org.*, 547 (1966).

(7) For examples, see B. Capon, *Quart. Rev.* (London), **18**, 45 (1965), especially pp 58–62.

(8) N. Hennrich and F. Cramer, *J. Am. Chem. Soc.*, **87**, 1121 (1965).

(9) J. Staerk and H. Schlenk, Jr., Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., 1965, p 11C; see also R. Kuhn and H. Trischmann, *Chem. Ber.*, **96**, 284 (1963).

(10) W. Lautsch, R. Wiechert, and H. Lehmann, *Kolloid-Z.*, **135**, 134 (1954).

l release of phenol (or phenoxide ion) followed by a slower disappearance of benzoate ester. The appearance of phenol was followed to completion by observing the increase in absorbance at 390 $m\mu$. After the absorbance reached a constant value the spectrophotometer was adjusted to permit the observation of benzoate ester disappearance at 245 $m\mu$ (or 260 $m\mu$ for *p*-nitrophenyl disappearance). Because carbonate buffer absorbs very little at this wavelength, the slit width of the spectrophotometer was set at 1 mm. The infinite absorbance values were more sensitive to experimental errors and variations in instrumental operation than the small over-all absorbance change and slowness of the reaction. The estimated error for the phenol appearance reaction is $\pm 3\%$, while that for benzoate disappearance reactions is $\pm 5\%$.

The hydrolysis rate of *m*-*t*-butylphenyl benzoate in the absence of cyclohexaamylose was determined by extrapolation of data obtained in 10% (v/v) acetonitrile solution (apparent pH 12.75) on the basis of the known pH dependence of *m*-tolyl acetate hydrolysis and the hydrolysis rate in the acetonitrile solution. The estimated error of this rate constant is $\pm 15\%$ while that of the spontaneous hydrolysis rate constants is $\pm 5\%$.

A quantitative estimate of the amount of cycloamylose benzoate released during the course of the acylation of cycloamyloses by reaction with phenyl benzoates was made as follows. The observed change in absorbance during the alkaline hydrolysis of 2.5×10^{-4} *m*-methyl benzoate was 0.09 absorbance unit at 245 $m\mu$; the cycloheptaamylose-accelerated hydrolysis of *m*-nitrobenzoate the average change in absorbance at 245 $m\mu$ (observed after completion of the initial phenol release reaction) was 0.084 absorbance unit, while in the presence of cyclohexaamylose the change in absorbance in the second step of the reaction was 0.084 absorbance unit. Assuming that the extinction coefficients of these esters are not greatly perturbed in the presence of cycloamyloses (spectral perturbations of these compounds are relatively small) then the minimum amount of cycloheptaamylose benzoate released is $\sim 70\%$, while the minimum amount of cyclohexaamylose benzoate is $>90\%$. Since the disappearance of benzoate was not followed until completion of the phenol appearance reaction it appears reasonable to conclude that the acylcycloamylose intermediate is produced in stoichiometric amounts during the course of the initial (phenol release) rate acceleration.

Filtration Chromatography. In order to effect a separation of cycloamylose benzoate and reaction products the following experiment was carried out. Cyclohexaamylose (0.10 g, 1.0×10^{-4} mole) was dissolved in 3 ml of pH 11 carbonate buffer. Fine particles of *m*-nitrophenyl benzoate (0.026 g, 1.0×10^{-4} mole) were added with 0.2 ml of acetonitrile. The reaction mixture was stirred vigorously for 5 min, brought to pH 3 with a few drops of hydrochloric acid, and filtered through a small glass wool plug to remove undissolved ester. The resulting solution was chromatographed using a 1×23 cm column of Sephadex G-10 gel. The column was developed by eluting with distilled water. Consecutive 3-ml fractions were tested for the presence of cyclohexaamylose by consecutively spotting and drying four drops on filter paper and then spraying with 2% methanolic iodine solution. Cyclohexaamylose was found to be present in the first four fractions after passage of the void volume, consistent with the molecular exclusion limits of Sephadex G-10. Only traces of cyclohexaamylose were found in the subsequent fractions. After 15 fractions were collected, a 5-ml portion of pH 10.6 10% acetonitrile in carbonate buffer was passed through the column causing a distinct yellow band to appear *ca.* one-quarter of the way down the column. No *m*-nitrophenol or unreacted ester was present in the earlier fractions, as judged by spectral examination of neutral and the strongly basic solutions (made basic with sodium hydroxide).

The ultraviolet absorption spectra of fractions 2-4 showed peaks at 233, 274, and 280 $m\mu$ (shoulder) and were practically superimposable on the spectrum of ethyl benzoate or methyl benzoate.

ts

Hydrolyses of Phenyl Benzoates. The alkaline hydrolysis of substituted phenyl benzoates in buffered aqueous solution follow first-order kinetics, the rate constants varying in the manner expected on the basis of electronic effects of the substituents. As anticipated from data obtained for phenyl acetates⁸ the release

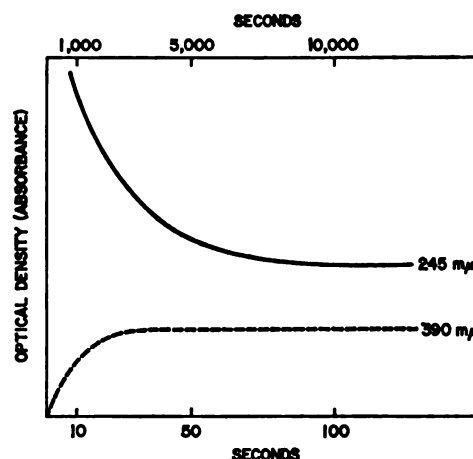


Figure 1. Hydrolysis of *m*-nitrophenyl benzoate at pH 10.6 in the presence of 0.01 *M* cyclohexaamylose; lower curve, change in optical density at 390 $m\mu$ due to *m*-nitrophenoxide ion appearance as a function of time (lower time scale); upper curve, subsequent reaction followed at 245 $m\mu$ (benzoate ester disappearance) as a function of time (upper time scale). For reaction conditions see Table I and the Experimental Section.

of the *meta*-substituted phenolic portion of the ester is considerably accelerated in the presence of 0.01 *M* cycloamyloses relative to the rate of alkaline hydrolysis at the same hydroxide ion concentration (Table I).

Table I. Rate Constants of the Cycloamylose-Catalyzed Reactions of Some Aryl Benzoates^a

Ester	Alkaline hydrolysis	Rate constants, 10^{-4} sec^{-1} 0.01 <i>M</i> cycloheptaamylose				
		290 or 390 $m\mu$	245 or 260 $m\mu$	290 or 390 $m\mu$	245 or 390 $m\mu$	290 or 390 $m\mu$
<i>m</i> -Nitrophenyl benzoate	15.4	1400	4.6	250	3.3	
<i>m</i> -Chlorophenyl benzoate	5.5	390	4.6	22	2.7	
<i>m</i> - <i>t</i> -Butylphenyl benzoate	1.2 ^b	140	4.4			
<i>m</i> -Chlorophenyl <i>p</i> -chlorobenzoate		810	10.6	75	5.3	
<i>m</i> -Chlorophenyl <i>m</i> -chlorobenzoate		1140	16.6	107	6.5	
<i>m</i> -Chlorophenyl <i>p</i> -nitrobenzoate	163	>1500	75 ^c			

^a pH 10.6, 25°, 0.5% (v/v) acetonitrile-water solution, $I = 0.2$, carbonate buffer, [ester] $\approx 1.6\text{--}2.0 \times 10^{-4} M$. ^b Obtained by extrapolation of data obtained for reaction in 10% (v/v) acetonitrile-water, pH 12.75, and comparison with similar data obtained for hydrolysis of *m*-tolyl acetate. ^c Determined at 260 $m\mu$.

Most importantly, there is a significant change in the over-all reaction pathway in the presence of cycloamyloses. Figure 1 shows the time course of the reaction of $2 \times 10^{-5} M$ *m*-nitrophenyl benzoate in the presence of 0.01 *M* cyclohexaamylose at constant pH (10.6). The release of phenol (as measured by phenoxide ion appearance at 390 $m\mu$ where there is no significant absorption by the ester or by benzoate ion) occurs very rapidly, reaching completion in 30 sec (bottom curve, Figure 1). Upon completion of this reaction the spectrophotometer wavelength can be changed to 245 $m\mu$, permitting the observation of a second rate process which occurs much more slowly (top curve, Figure 1) than does the liberation of the phenol.

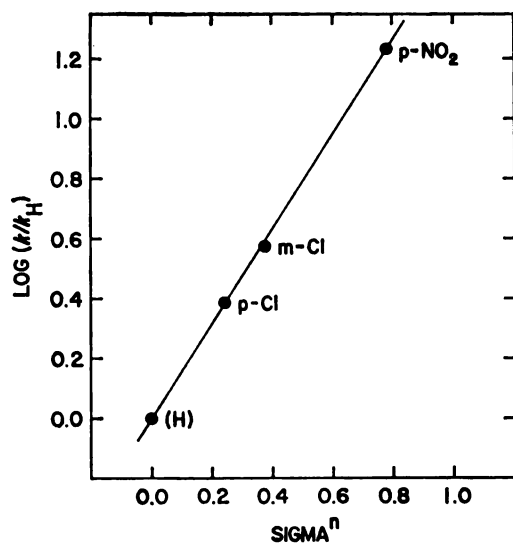


Figure 2. Hammett plot for deacylation of cyclohexaamylose benzoates at pH 10.6. The log of the relative hydrolysis rate of cyclohexaamylose benzoates (Table I) is graphed as a function of the Hammett substituent constant σ^n .

The appearance of phenols during reactions of a number of *m*-phenyl-substituted benzoate esters occurs some 8–300 times more rapidly than does the subsequent rate process observed at 245 $m\mu$ (Table I). Significantly, although the rates of phenol release from *m*-*t*-butyl-, *m*-chloro-, and *m*-nitrophenyl benzoates in the presence of cyclohexaamylose differ by an order of magnitude, the rates of the subsequent reactions followed at 245 $m\mu$ are the same within experimental error. Similarly, although the rate of appearance of the phenol from *m*-nitrophenyl benzoate in the presence of cycloheptaamylose is more than an order of magnitude greater than that from *m*-chlorophenyl benzoate, the rates of the subsequent reactions are essentially the same. These results indicate that the same intermediate is formed during the course of the phenol release reaction and that this common intermediate then undergoes hydrolysis at a rate which is independent of the nature of the phenolic portion of the original ester. The observed identical rates of reaction for the subsequent rate process demand the interpretation that a common intermediate is formed whose decomposition is the rate-determining step. This interpretation together with the results of gel filtration chromatography (below) is consistent only with the interpretation that the intermediate is a cycloamylose benzoate.

In order to provide further support for this interpretation the effect of substitution of the benzoate portion of the ester was examined. The *m*-chlorophenyl esters of *p*-chloro-, *m*-chloro-, and *p*-nitrobenzoic acids were hydrolyzed in the presence of excess cycloamyloses. After completion of the rapid phenol release reaction the subsequent benzoate ester disappearance was followed at 245–260 $m\mu$. The rate of the benzoate ester disappearance was increased by an amount consistent with the electronic effects of the substituent group on the benzoate ester (Table I, Figure 2). In fact the hydrolysis of cyclohexaamylose benzoates conforms to a Hammett relationship with $\rho = 1.6$, suggesting the absence of significant steric effects. The hydrolysis of cycloamylose benzoates was not dependent on cycloamylose concentrations up to 10^{-2} *M*. Cyclohexaamylose ben-

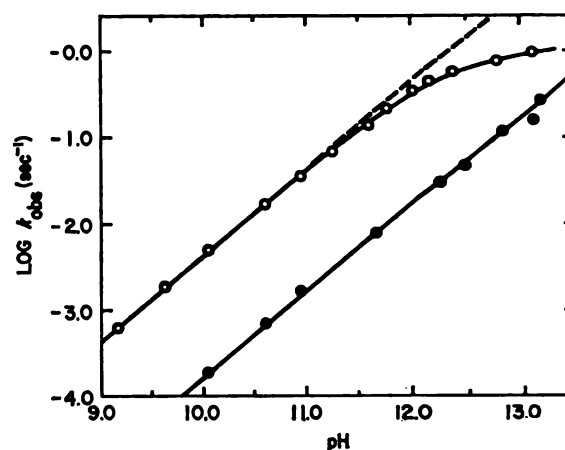


Figure 3. Pseudo-first-order rate constant for release of the phenol from *m*-tolyl acetate as a function of pH; lower curve, spontaneous hydrolysis; upper curve, rate constant in the presence of 5×10^{-1} *M* cyclohexaamylose (data of Table II).

zoate undergoes hydrolysis somewhat more rapidly than does cycloheptaamylose benzoate; this may be a consequence of the greater steric hindrance by the amylose residue derived from seven glucose molecules.

In an attempt to obtain a sample of cyclohexaamylose benzoate from a solution similar to a reaction mixture, equivalent amounts of *m*-nitrophenyl benzoate and cyclohexaamylose were mixed together in an alkaline aqueous acetonitrile solution, resulting in a rapid appearance of *m*-nitrophenoxide ion. After a few minutes this mixture was neutralized and chromatographed on Sephadex G-10 (see Experimental Section), which resulted in the complete separation of both the phenol and the unreacted ester from the fractions containing the cyclohexaamylose. The ultraviolet absorption spectrum of the recovered cycloamylose fraction showed the presence of a material having a spectrum identical with that of alkyl benzoate esters such as ethyl benzoate. The cycloamylose benzoate had λ_{\max} 233, 274, and 280 $m\mu$ (sh) in water. When the material was dissolved in pH 10.6 carbonate buffer it was found to undergo hydrolysis with a rate constant of 4.6×10^{-4} sec^{-1} , identical with that of the cyclohexaamylose benzoate formed *in situ* (Table I). On the basis of the observed differences in optical extinction coefficients between alkyl benzoate esters and benzoate ion it was calculated that the yield (calculated on the basis of the ester used) of cycloamylose benzoate formed *in situ* approached 100% for reactions of esters such as *m*-nitrophenyl benzoate where there is a large differential between the rate of the phenol release reaction and the subsequent deacylation (see Experimental Section).

pH Dependence of the Cycloamylose Rate Effects. If the intermediate cycloamylose benzoates are produced by a nucleophilic displacement reaction by an alkoxide ion derived from the secondary hydroxyl groups of the cycloamylose it would be reasonable to expect a first-order dependence on hydroxide ion of the rate of phenol release (k_2) and on the rate of the subsequent deacylation reaction (k_3). To this end the pH dependence of both the acylation and deacylation reactions was examined (Table II). In Figure 3 is shown the pH dependence of the rate of phenol release from *m*-tolyl acetate in the presence of 5×10^{-2} *M* cyclohexaamylose

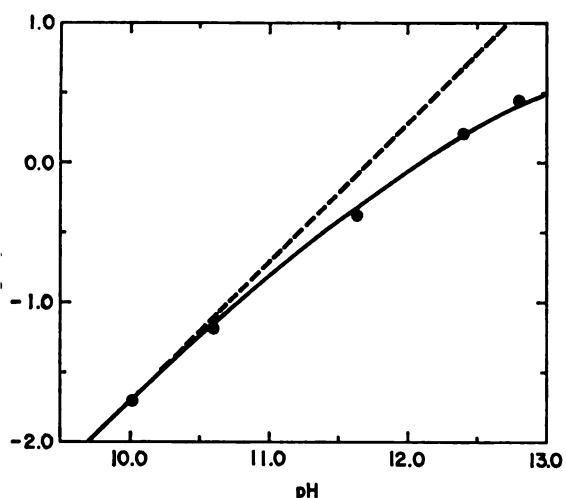


Figure 4. Maximal rates of acylation of cyclohexaamylose by *m*-acetate graphed as a function of pH (data of Table III).

curve) as well as the pH dependence of the hydrolysis reaction in the absence of cycloamylose (bottom curve). The basic hydrolysis reaction of the ester obeys the expected first-order dependence on hydroxide ion, as does the accelerated reaction below pH 11. The acylation of cyclohexaamylose by *m*-tolyl acetate occurs some 22 times more rapidly than the line hydrolysis reaction in the pH range 9–11.

II. Rate of Phenol Release from *m*-Tolyl Acetate in the Presence and Presence of Cyclohexaamylose as a Function of pH

I	Buffer ^a	k_{un} (spontaneous)	k_{obsd} (cyclohexaamylose added) ^b
17	Sodium carbonate	...	6.23×10^{-4}
62		...	1.86×10^{-3}
04		1.84×10^{-4}	4.97×10^{-3}
60		6.96×10^{-4}	1.51×10^{-3}
95	Sodium-potassium phosphate	1.60×10^{-3}	3.72×10^{-3}
26		...	7.00×10^{-3}
61		7.84×10^{-3}	...
67		...	1.39×10^{-1}
77	Potassium hydroxide	...	2.03×10^{-1}
03		...	3.48×10^{-1}
18		...	4.47×10^{-1}
27		3.00×10^{-3}	...
39		...	5.69×10^{-1}
49		4.50×10^{-3}	...
80		...	6.71×10^{-1}
84		1.16×10^{-1}	...
12		1.57×10^{-1}	9.39×10^{-1}
18		2.58×10^{-1}	...

^a Ionic strength = 0.2 throughout, with 0.5% (v/v) added acetonitrile, $25 \pm 0.2^\circ$. As many as possible specific effects observed when changing from one to the other buffer systems. ^b Cyclohexaamylose concentration $5.0 \times 10^{-3} M$. (The units of k are sec^{-1} .)

However, above pH 11 the rate acceleration begins to level off until at pH 13.1 there is observed only a sixfold acceleration. One interpretation of this result is that the cycloamylose molecule has become largely ionized so that further increases in hydroxide ion concentration will not result in a corresponding increase in cycloamylose alkoxide ion concentration; the hydroxide ion reaction will continue to increase in rate after there are no longer any of the catalytically

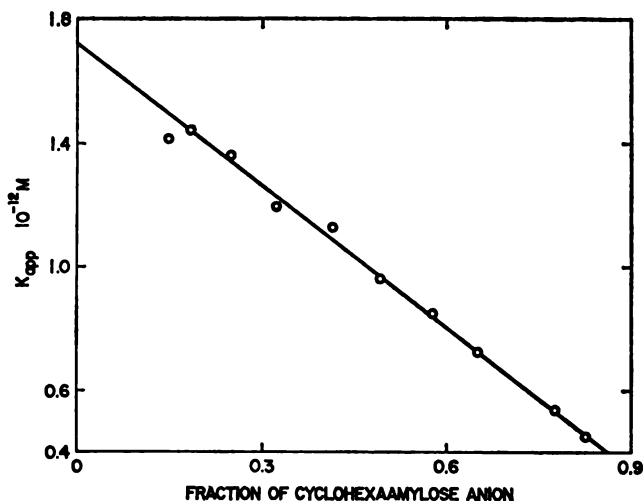


Figure 5. Calculation of the kinetic pK_a value for acylation of cyclohexaamylose with *m*-tolyl acetate. The apparent ionization constant K_{app} for cyclohexaamylose is plotted vs. the fraction of cyclohexaamylose ionized (data estimated from Figure 4; see Appendix).

active hydroxyl groups left to ionize. An alternative interpretation is that the dissociation constant of the cyclohexaamylose-*m*-tolyl acetate complex is pH dependent. Thus, the observed rate effect might decrease because less of the ester is complexed at higher pH. To eliminate this possibility the maximal rates of acylation (phenol release, k_2) were determined as a function of pH (Table III). These data for *m*-tolyl

Table III. Maximal Rates of Acylation of Cyclohexaamylose by *m*-Tolyl Acetate in the Presence of Cyclohexaamylose at Various pH Values^a

pH	k_2 , sec^{-1} ^b
10.01	$1.95 \pm 0.33 \times 10^{-3}$
10.60	$6.58 \pm 1.97 \times 10^{-3}$
11.63	$4.18 \pm 1.20 \times 10^{-1}$
12.40	1.6 ± 1.0
12.80	2.8 ± 0.6

^a Ionic strength = 0.2 with 0.5% (v/v) added acetonitrile, $25.0 \pm 0.1^\circ$; for buffers see Table II. ^b The maximal rate of acylation is determined by calculating the rate of phenol release in the presence of an infinite amount of cyclohexaamylose; for details see ref 3.

acetate are shown in Figure 4. Again the rate conforms to a first-order dependence on hydroxide ion below pH 11 but begins to fall off at higher pH. When the data of Figure 4 are transformed to a plot of K_{app} vs. fraction of hydrogen ions released (see Appendix), the pK of the catalytically active group is estimated to be 11.8 ± 0.4 (Figure 5). When the rate of deacylation of cyclohexaamylose benzoate (prepared *in situ* by reaction with *m*-nitrophenyl benzoate) is determined as a function of pH (Table IV), a curve is obtained (Figure 6) which is similar to that obtained for the pH dependence of acylation. The pH dependence of deacylation also exhibits a first-order dependence of hydroxide ion below pH 11 but the rate increases less rapidly above this point. The data shown in this figure were used to calculate the pK of the ionizing group as shown in Figure 7 (see Appendix); this was found to be 12.3 ± 0.2 . Thus, the rate effects caused by the cycloamyloses are dependent on an ionizable group with a $pK = 12.1$ which

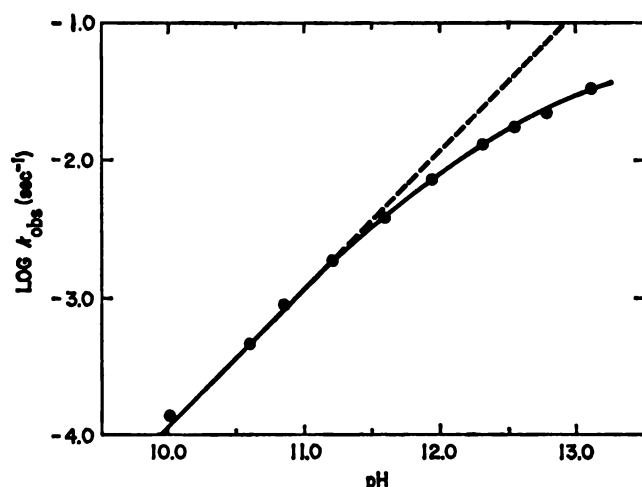


Figure 6. Pseudo-first-order rate constants for hydrolysis of cyclohexaamylose benzoate as a function of pH. The ester was formed *in situ* by acylation of the cyclohexaamylose with *m*-nitrophenyl benzoate (data of Table IV).

is assigned to one of the two kinds of secondary hydroxyl groups (see Discussion).

Table IV. Hydrolysis Rate of Cyclohexaamylose Benzoate as a Function of pH^a

pH	Buffer ^b	k_{obs} , sec ⁻¹	[Cyclohexaamylose], M
10.01	Sodium carbonate	1.36×10^{-4}	1.00×10^{-3}
10.60		4.58×10^{-4} ^c	1.00×10^{-3}
10.85		8.67×10^{-4}	1.00×10^{-3}
11.20	Sodium-potassium phosphate	1.84×10^{-3}	1.00×10^{-3}
11.22		1.99×10^{-3}	5.00×10^{-3}
11.56		3.52×10^{-3}	5.00×10^{-3}
11.58		3.80×10^{-3}	1.00×10^{-3}
11.93	Potassium hydroxide-chloride	7.33×10^{-3}	1.00×10^{-3}
12.31		1.34×10^{-2}	1.00×10^{-3}
12.55		1.75×10^{-2}	1.00×10^{-3}
12.57		1.88×10^{-2}	5.00×10^{-3}
12.63		2.02×10^{-2}	1.00×10^{-3}
12.63		2.08×10^{-2}	5.00×10^{-3}
12.63		1.98×10^{-2}	1.00×10^{-4}
12.78		2.26×10^{-2}	1.00×10^{-3}
13.11		3.33×10^{-2}	1.00×10^{-3}

^a The cyclohexaamylose benzoate was prepared *in situ* by acylation of the cycloamylose with 2.5×10^{-5} M *m*-nitrophenyl benzoate.

^b Ionic strength = 0.2 with 0.5% (v/v) added acetonitrile, $25.0 \pm 0.1^\circ$. ^c Data of Table I.

Effects of Blocking Cycloamylose Hydroxyl Groups. Since the hydroxyl groups of the cycloamyloses are almost certainly the catalytically active groups, the effect of substituting particular hydroxyl groups was examined in an attempt to identify which of the hydroxyl groups were required to produce large accelerations of the phenol release reaction. When both the 6 and 3 positions of the glucose residues of cyclohexaamylose are blocked by conversion to methoxyl groups⁹ the resulting dodecamethylcyclohexaamylose is catalytically inactive. Indeed, the alkaline hydrolysis of *m*-nitro- and *m*-*t*-butylphenyl acetates is slightly inhibited (Table V) although these compounds show a large acceleration of the phenol release reaction with cyclohexaamylose. The observed rate reductions must

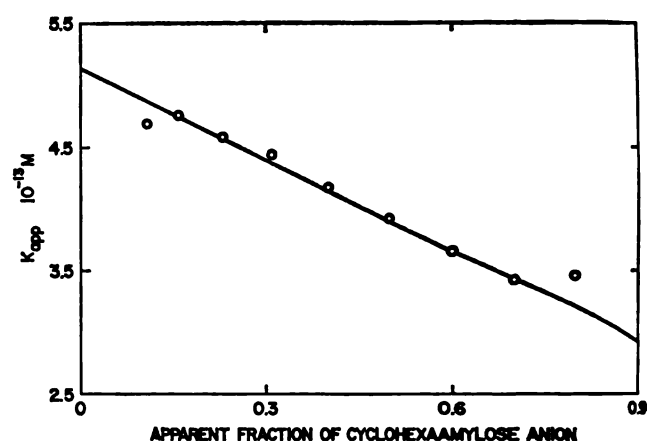


Figure 7. Calculation of the kinetic pK_a of cyclohexaamylose from data obtained for the hydrolysis of cyclohexaamylose benzoate. The apparent ionization constant K_{app} is plotted vs. the fraction of cyclohexaamylose ionized (data estimated from Figure 6; see Appendix).

be interpreted as the result of formation of a cycloamylose complex which protects the ester from reaction with hydroxide ion in solution.³ It is not the result of a medium effect since methyl glucoside produces a small rate acceleration.³

Table V. Rate Effects on Phenyl Acetate Hydrolysis of 1% Dodecamethylcyclohexaamylose^a

Phenyl acetate	Hydroxide ion rate constant k_{un} , sec ⁻¹	Rate with 1% dodecamethylcyclohexaamylose k_{obs} , sec ⁻¹	Rate effect $k_{\text{obs}}/k_{\text{un}}$
<i>m</i> -Nitro	7.01×10^{-3}	4.54×10^{-3}	0.64
<i>m</i> - <i>t</i> -Butyl	7.60×10^{-4}	4.61×10^{-4}	0.61

^a In pH 10.7 carbonate buffer with $I = 0.2$, 0.5% (v/v) added acetonitrile, 25° .

However, when only the primary (C-6) hydroxyl groups are blocked the rate accelerations observed for the cleavage of phenyl esters are at least as large as those produced by cyclohexa- and -heptaamylose. Hexamethylcyclohexaamylose and heptamethylcycloheptaamylose were prepared^{10,11} and their effects on the rate of reaction of *m*-*t*-butylphenyl acetate were determined in aqueous acetonitrile solutions (see Experimental Section). Since the extent of complex formation was expected to be less in the presence of large amounts of acetonitrile³ the dissociation constants of the cycloheptaamylose-*m*-*t*-butylphenyl acetate complex and the corresponding mesyl system were determined using methods previously described.³ The values of k_2 (the first-order rate constant of the fully complexed ester) as well as the values of K_{dis} (the dissociation constants of the complexes) are given in Table VI. As anticipated, the complex is less stable in the presence of large amounts of acetonitrile, the value of K_{dis} increasing from 1×10^{-4} M in 0.5% acetonitrile to 2×10^{-3} M in 20.5% solution. This is similar to results obtained for the effect of acetonitrile on the *m*-chlorophenyl acetate-cyclohexaamylose complex.³ Most importantly the maximal rate effects k_2/k_{un} for the mesyl compound and for unchanged cycloheptaamylose are nearly the same. Thus, block-

the primary hydroxyl groups by formation of the derivative results in no diminution of the rate whereas blocking the primary and one-half of the secondary hydroxyl groups by formation of the dimethyl derivative results in a complete loss of the accelerating effect.¹⁷

TABLE I. Maximal Rate Accelerations and Dissociation Constants of Cycloamylose-*m*-*t*-Butylphenyl Acetate Complexes^a

amylose	Ester hydrolysis rate constant, sec ⁻¹	k_2 , sec ⁻¹	k_2/k_{un}	K_{diss} , M
heptaamylose ^b	3.1×10^{-4}	0.286	940	$2.3 \pm 1.2 \times 10^{-3}$
6-O-methylcycloheptaamylose ^{c,d}	3.1×10^{-4}	0.475	1550	$3.1 \pm 0.9 \times 10^{-3}$

^a 20.5% acetonitrile, pH 10.6 carbonate buffer, $I = 0.2$. All measurements were made at $25.0 \pm 0.2^\circ$. Error limits were calculated from the experimental data by application of Student's *t* at the 95% probability level. The ester concentration was 10^{-4} M. ^b The cycloheptaamylose concentration was varied from 1.7×10^{-4} to 4.7×10^{-3} M. ^c The heptamethylcycloheptaamylose concentration was varied from 1.9×10^{-4} to 3.5×10^{-3} M. Since mesyl esters are reasonably reactive in the presence of alkoxide ion [S. Hartman and R. E. Robertson, *Can. J. Chem.*, **38**, 1960] the mesylcycloamylose solutions were used within 30 min after preparation.

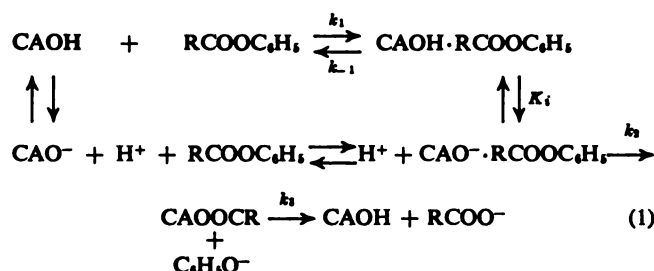
Discussion

Reaction Pathway. These kinetic and isolation studies prove that the large accelerations in the cleavage of *meta*-substituted phenyl esters in alkaline solution in the presence of cycloamyloses are the result of a nucleophilic reaction of an alkoxide ion derived from either C-2 or C-3 secondary hydroxyl groups of the cycloamyloses. The ester hydrolysis reaction shows the expected first-order dependence on hydroxide ion as observed in the reaction with the cycloamyloses in the pH range before an appreciable fraction of the cycloamylose has become ionized (cf. Figure 3). Since the cleavage reaction exhibits an apparent first-order dependence on ester concentration at a given pH, the hydrolysis reactions follow second-order kinetics overall. On the basis of minimal estimates of the percentage of acyl cycloamyloses produced during the course of some of the ester hydrolyses, it is clear that the nucleophilic pathway is by far the major pathway for the reaction; general acid or general base catalysis by a hydroxyl group may make only a small contribution, if any, to the hydrolytic process.

The following reaction scheme describes the reaction of phenyl esters in the presence of cycloamyloses. A phenyl ester undergoes a rapid reversible association¹⁸ with the cycloamylose, CAO, or with the

Large increases in the rate of phenol releases were seen with hexamethylcycloheptaamylose also, but this compound was too insoluble (relative to the amylose-ester dissociation constant) to permit an accurate determination of the maximal rate effect.

The rate of formation of the complex is expected to be very rapid for sterically unhindered and uncharged ester molecules [F. Cramer, W. R. S. and H.-C. Spatz, *J. Am. Chem. Soc.*, **89**, 14 (1967)]. No evidence was observed in the course of the present studies that the rate of complex formation was slow (i.e., within one or two orders of magnitude) relative to the rates of the cleavage reactions. Thus, even the reaction of *tert*-butylphenyl benzoate or *m*-*t*-butylphenyl acetate in the presence of cyclohexaamylose exhibited good first-order kinetics.



partially ionized form, CAO⁻. An alkoxide ion derived from the secondary hydroxyl groups of the cycloamylose may react with an included ester molecule to liberate the phenoxide ion in a reaction characterized by a rate constant k_2 which is equal to the observed rate constant³ of the phenol release reaction of the fully complexed ester. This reaction, which results in the acylation of the amylose, is markedly dependent on the stereochemistry of the phenyl group substituents. Since previous studies³ showed that *meta* substituents on the phenyl ring resulted in large rate effects the present study employed *meta*-substituted phenyl benzoates. As expected with these compounds, the cycloamyloses cause large increases in the rate of phenol release compared to the rate in buffered alkaline solution (Table I).

The rate effects of cycloamyloses on the hydrolysis of alkyl benzoate esters contrast sharply with their effects on reactions of phenyl esters. Complex formation with cycloheptaamylose apparently completely inhibits the alkaline hydrolysis of ethyl *p*-aminobenzoate.¹⁹ This effect can be explained in two ways. The unreactivity of the complexed ester can be explained on the basis of nonproductive binding³ in which the carbonyl carbon atom of the ester molecule is located in the cycloamylose cavity at some distance from the secondary hydroxyl groups. If, for example, the ester was complexed in such a way that the carbonyl group was positioned near the primary hydroxyl groups of the cycloamylose, it would be well protected from reaction in solution. Alternatively, the unreactivity of alkyl benzoate esters in the cycloamylose complexes may be due to an unfavorable partitioning of the tetrahedral intermediate.²⁰ For example, addition of an alkoxide ion of the cycloamylose to the carbonyl group of methyl benzoate would lead to the formation of a tetrahedral intermediate having either cycloamylose alkoxide ion or methoxide ion as potential leaving groups. Because of the greater acidity of the cycloamylose compared to methanol, it may be expected that the tetrahedral intermediate would preferentially revert to reactants.

It is interesting to find that the reactive hydroxyl group of cyclohexaamylose has a kinetic pK of 12.1. Although this pK at first appears low for an aliphatic alcohol there are related examples in the carbohydrate field. On the basis of changes in intrinsic viscosity and optical rotation of starch solutions, Rao and Foster postulated that modifications of the polymer chain configuration occur as the result of the ionization of

(19) J. L. Lach and T.-F. Chin, *J. Pharm. Sci.*, **53**, 924 (1964). We have made qualitatively similar observations for the alkaline hydrolysis of methyl benzoate, ethyl benzoate, ethyl cinnamate, and methyl *m*-chlorobenzoate.

(20) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1657 (1957).

the amylose hydroxyl groups at high pH.²¹ These authors concluded that the pH dependence of the optical rotation changes was consistent with a pK of 12 or slightly higher. Such a value is in agreement with the results of the present study. More recently, studies on the thermodynamics of ionization of carbohydrate derivatives²² showed that the pK of the (two adjacent) secondary hydroxyl groups of the ribose moiety of adenosine is 12.35. The relatively acidic hydroxyl groups of the cycloamylose are probably the result of a specific interaction involving the C-2 and C-3 secondary hydroxyl groups, just as in ribose. The existence of a hydrogen bond in the crystalline state between these hydroxyl groups has been noted.²³ The enhanced acidity of these hydroxyl groups may be due to the combined inductive effects of the relatively electronegative oxygen atoms and also to stabilization of the alkoxide ion by means of an intramolecular hydrogen bond to a neighboring hydroxyl group. Other workers are attempting to distinguish between these effects for ribose compounds.²²

Since the facile methylation of ribose derivatives by diazomethane in the presence of base has been reported²⁴ it is tempting to speculate that such a reaction could be exhibited by the cycloamyloses. Noting that only one of the two types of secondary hydroxyl groups of cyclohexaamyloses is methylated in certain methylation reactions,⁹ it is possible that this is the same group of $pK = 12.1$ determined in the present work. From the methylation data of Staerk and Schlenk,⁹ leading to dodecamethylcyclohexaamylose, the reactive secondary hydroxyl groups would appear to be the C-3 hydroxyl groups (numbering the carbons of the individual glucose units). This conclusion is consistent with the fact that the dodecamethyl derivative causes no rate enhancement of the phenyl ester cleavage reaction. While it is difficult to assess steric hindrance accurately from an examination of molecular models, it appears that the presence of a methyl group on either the C-2 or C-3 hydroxyl group would not completely hinder the approach of the remaining hydroxyl (oxygen atom) to the carbonyl carbon of an included ester molecule. Thus, either the introduction of the first methyl group radically changes the reactivity of the other secondary hydroxyl groups or, more likely, the C-2 and C-3 hydroxyl groups differ significantly in their reactivity and acidity.

The deacylation step, k_2 , in mechanism 1 depends on the electronic nature of the substituents on the benzoic acid portion of the ester but does not appear to be sensitive to differing steric patterns of *meta* and *para* substitution (Figure 2). The pseudo-first-order rate constant for the alkaline hydrolysis of cyclohexaamylose benzoate at pH 10.6 is $4.6 \times 10^{-4} \text{ sec}^{-1}$ (Table I), corresponding to a second-order rate constant of $1.2 \text{ M}^{-1} \text{ sec}^{-1}$. The secondary ester isopropyl benzoate is a reasonable model for cyclohexaamylose benzoate with respect to linkage and steric hindrance; the second-order rate constant for the alkaline hydrolysis of iso-

propyl benzoate is $0.6 \times 10^{-2} \text{ M}^{-1} \text{ sec}^{-1}$.²⁵ Thus, cyclohexaamylose benzoate hydrolyzes 200 times more rapidly than does isopropyl benzoate. The difference in pK between cyclohexaamylose and isopropyl alcohol may account for a factor of 10 in rate²⁶ but it still appears that cyclohexaamylose benzoate hydrolyzes some 20 times more rapidly than would be expected on the basis of steric and electronic effects. This rate difference is presumably the result of general acid or general base catalysis of the deacylation step by adjacent hydroxyl group(s). Both types of catalysis would exhibit the leveling off in the rate of the deacylation reaction at high pH when the alkoxide ion is ionized (Figure 6). If, however, isopropyl benzoate is not a proper model for the steric hindrance to be expected in cyclohexaamylose benzoate, then it is possible that the latter ester does not hydrolyze unusually rapidly. In this event the leveling off in the rate of deacylation at high pH could be explained by electrostatic repulsion of partly ionized cycloamylose and hydroxide ion.

Comparisons with Chymotrypsin. The cycloamylose system may be compared with chymotrypsin catalysis in a number of respects. Chymotrypsin reactions are typically true catalyses. However, although cycloamylose reactions often show large increases in the rate of phenol release (the acylation reaction), there is true catalysis of over-all hydrolysis for only some of the esters studied. Of the esters listed in Table I, the over-all hydrolysis of *m*-*t*-butylphenyl benzoate is catalyzed by cyclohexaamylose, since the rate constant for alkaline hydrolysis of the ester at pH 10.6 is approximately four times less than the rate constant for hydrolysis of cyclohexaamylose benzoate. For the other esters of Table I, however, the deacylation rate constant is less than the rate constant for direct alkaline hydrolysis of the ester. The failure of the cycloamylose to catalyze the over-all hydrolysis of these esters is due to the relatively slow deacylation reaction, which is catalyzed by no more than 20-fold by adjacent hydroxyl groups, although the acylation reaction can be accelerated by many times that figure. In principle, there is no reason why more catalytically active general base or nucleophilic catalysts could not be introduced into the cycloamylose molecule, and thus make the analogy between cycloamylose and chymotrypsin more nearly complete.²⁷

Both cycloamylose and chymotrypsin catalyze the hydrolysis of esters by the reaction scheme shown in eq 1. The reactant and catalyst form a complex in a rapid and reversible process described by a dissociation constant $K_{\text{diss}} = k_{-1}/k_1$. The similarity of the values of K_{diss} for chymotrypsin and for the cycloamyloses has been previously mentioned.³ Both catalysts produce large rate effects in the acylation step. The magnitude of the rate effect depends on the stereochemistry of the substrate whereas the value of the dissociation constant of the respective complex is independent of the stereochemistry of the substrate.¹ However, the value of K_{diss} in the two systems does de-

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(22) R. M. Izatt, J. H. Rytting, L. D. Hansen, and J. J. Christensen, *J. Am. Chem. Soc.*, **88**, 2641 (1966); J. J. Christensen, J. H. Rytting, and R. M. Izatt, *ibid.*, **88**, 5105 (1966).

(23) A. Hybl, R. E. Rundle, and D. E. Williams, *ibid.*, **87**, 2779 (1965).

(24) T. A. Khwaja and R. K. Robins, *ibid.*, **88**, 3640 (1966).

(25) M. L. Bender, *ibid.*, **73**, 1626 (1951).

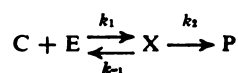
(26) J. F. Kirsch and W. P. Jencks, *ibid.*, **88**, 833, 837 (1964).

(27) The introduction of imidazole and amino groups onto the cycloamylose ring has recently been reported [F. Cramer and G. Mackensen, *Angew. Chem. Intern. Ed. Engl.*, **5**, 601 (1966)]. Rate effects of 3-4 were observed (relative to the effects produced by noncovalently bonded nitrogen bases and cycloamyloses) in the hydrolysis of *p*-nitrophenyl acetate at pH ~ 7 .

d on the type of substituent groups in the substrate, the cycloamyloses and chymotrypsin preferentially acting on apolar substrates. This is in contrast to the action of, for example, trypsin, which preferentially acts on cationic substrates.

Both chymotrypsin and the cycloamyloses have an aliphatic alcohol group at the active site which acts as an acyl group acceptor during the catalysis of ester hydrolysis.²⁸ Whereas the acylation step in reactions catalyzed by the cycloamyloses depends on a hydroxyl group with a pK of 12, the acylation step in chymotrypsin-catalyzed reactions depends on a group with a pK of presumably the imidazole group of a histidine residue.²⁹ The imidazole group is also active in the deacylation step. Mention has already been made of the apparent 20-fold intramolecular catalysis of the deacylation of cyclohexaamylose benzoate. Catalysis of the deacylation step is thus a feature of both the cycloamylose and chymotrypsin reaction systems but the much larger catalysis of chymotrypsin deacylations leads to a large over-all catalysis of hydrolysis. In addition, the deacylation step in chymotrypsin-catalyzed reactions is highly stereospecific, but this is not the case for the deacylation of the cycloamyloses.

In the acylation reactions the reaction rates of chymotrypsin and of the cycloamyloses are very similar. It is possible to calculate the second-order rate constants for reaction of substrates with the cycloamyloses in the following way. For the reaction scheme



on the assumption of a pre-equilibrium and the condition $C_0 \gg E_0$ leads to the Michaelis-Menten equation $1/r = k_2/[C]_0[E]_0/(K_{diss} + [C]_0)$. If the condition is imposed that $(C)_0 \ll K_{diss}$, then a second-order rate constant can be determined from $dP/dt = k_2(C)_0 \cdot [E]_0/K_{diss}$. The values of the second-order rate constants calculated in this manner using the values of k_2 (the maximal rate constant of acylation of the free ester in the pH region where the cycloamylose is completely ionized³⁰) and the dissociation constants of the respective complexes³ are shown in Table VII. Also shown in the table are corresponding values of $k_{cat}(\text{lim})/K_m(\text{app}) (= k_2(\text{lim})/K_s)$ ²⁸ for chymotrypsin reactions.

The second-order rate constants of Table VII show the method of comparing cycloamylose or chymotrypsin reactions with hydroxide ion reactions. The values in Table VII state the relative rates when equal amounts of cycloamylose or hydroxide ion catalysts are used, or when equal amounts of chymotrypsin or hydroxide ion

Table VII. Second-Order Rate Constants for Reactions of Phenyl Esters with Cycloamyloses and of Substrates with Chymotrypsin

Reactants	Rate constant, $M^{-1} \text{ sec}^{-1}$	Catalyzed rate/hydroxide ion rate
(1) Cyclohexaamylose + <i>m</i> - <i>t</i> -butylphenyl acetate ^a	2.1×10^3	
Hydroxide ion + <i>m</i> - <i>t</i> -butylphenyl acetate	1.2	1.8×10^3
(2) Cycloheptaamylose + <i>m</i> - <i>t</i> -butylphenyl acetate ^a	3.1×10^4	
Hydroxide ion + <i>m</i> - <i>t</i> -butylphenyl acetate	1.2	2.6×10^4
(3) Chymotrypsin + acetyl-tryptophanamide ^b	12.6	
Hydroxide ion + acetyl-tryptophanamide ^c	3×10^{-4}	4×10^4
(4) Chymotrypsin + acetyl-tryptophan ethyl ester ^b	4×10^6	
Hydroxide ion + acetyl-tryptophan ethyl ester ^d	0.6	10^6
(5) Chymotrypsin + acetyl-tyrosine ethyl ester ^e	1.2×10^4	
Hydroxide ion + acetyl-tyrosine ethyl ester ^e	0.45	3×10^4

^a Data for the cycloamylose reactions were obtained by division of the limiting value³⁰ of k_2 (see text) by K_{diss} (ref 5). ^b M. L. Bender, G. E. Clement, F. J. Kézdy, and H. d'A. Heck, *J. Am. Chem. Soc.*, **86**, 3680 (1964). ^c M. L. Bender, F. J. Kézdy, and C. R. Gunter, *ibid.*, **86**, 3714 (1964). ^d D. J. Whelan and M. L. Bender, unpublished work. ^e H. Gutfreund, "An Introduction to the Study of Enzymes," John Wiley and Sons, Inc., New York, N. Y., 1965, p 296.

catalysts are used. On this basis, the cycloamylose reactions are clearly superior to the hydroxide ion reactions, as are the chymotrypsin reactions. In fact, the rate enhancements of the cycloamyloses with respect to hydroxide ion are approximately as great as the rate enhancements of chymotrypsin with respect to hydroxide ion. Does this mean that cycloamyloses are identical kinetically with chymotrypsin? The answer to this question is no, because $k_2(\text{lim})$ is determined at *ca.* pH 13 for the cycloamylose while it is determined at *ca.* pH 8 for chymotrypsin. This comparison of Table VII is, however, a true indication of the effect of complexing on the rates of reaction. In that sense, cycloamyloses compare very well with chymotrypsin. If some method makes it possible to reduce the pH at which the cycloamylose acts without losing any of its other properties, it might be possible to come closer to chymotrypsin reactivity.

Cycloamylose-catalyzed and chymotrypsin-catalyzed hydrolyses of phenyl esters exhibit many similarities. Both catalyses occur by a similar pathway involving a rapid association to form complexes. The ester substrates then react with the catalyst to form an acylated intermediate, which subsequently undergoes hydrolysis in a slow step. The dissociation constants of binding of the two systems are similar, complex formation being best with apolar substrates. Increasing ionic strength of the solution tends to favor complex formation, while added apolar solvents decrease the stability of the complexes. Both systems are subject to competitive in-

¹ M. L. Bender and F. J. Kézdy, *J. Am. Chem. Soc.*, **86**, 3704 (1964), and references cited therein.

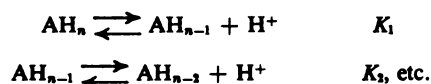
² For a recent study of the pH dependence of chymotrypsin-catalyzed reactions and references to previous work see M. L. Bender, M. J. Gunter, and D. J. Whelan, *Proc. Natl. Acad. Sci. U. S. A.*, **56**, 833 (1966).

³ At pH 10.6, assuming that both cyclohexaamylose and cycloheptaamylose have a pK of 12.1, the ratio of ionized to un-ionized cycloamyloses is 3.1×10^{-3} . The limiting rate of acylation of cyclohexaamylose by *m*-*t*-butylphenyl acetate assuming complete ionization will be $(12.9 \times 10^{-3} \text{ sec}^{-1})/(3.1 \times 10^{-3})$ where $12.9 \times 10^{-3} \text{ sec}^{-1}$ is the calculated value of k_2 at pH 10.6.³ The limiting values of k_2 calculated in this manner for the acylation of cyclohexaamylose and cycloheptaamylose by *m*-*t*-butylphenyl acetate are 4.2 and 4.0 sec^{-1} , respectively. No correction has been made for the fact that there are 6 or 7 equivalent hydroxyl groups in the cycloamylose; this correction would make the calculated values proportionately larger.

hibition by added organic molecules. The maximal rate effects produced in the two systems are unrelated to the *stabilities* of the complexes, but depend on their *stereochemistry*. The specific stereochemical relationships between the cycloamyloses and their substrates are well described on the basis of the three-dimensional structure of these materials. A similar description of enzyme-substrate interactions should be possible.

Appendix

Calculation of the Ionization Constant of Cyclohexaamylose from Kinetic Data. For the compound AH_n capable of successive ionizations



Because the successive ionizations and reactivities of the cycloamylose alkoxide ions are probably perturbed by preceding ionizations it is desired to determine the value of K_1 , the first ionization constant, as opposed to K_{app} , where

$$\begin{aligned} K_{app} &= \frac{[H^+][\text{no. of moles of charges on molecules}]}{[\text{no. of moles of undissociated molecules}]} = \\ &= \frac{[H^+](AH_{n-1}] + 2[AH_{n-2}] + \cdots + n[AH_{n-n}])}{[AH_n]} = \\ &= \frac{[H^+] \sum_{x=1}^n x[AH_{n-x}]}{[AH_n]} \end{aligned}$$

In the limit of single, kinetically productive ionizations then K_{app} will equal K_1 .

Figures 3 and 4 show, in addition to a plot of values observed in the presence of cycloamylose k_c , a second

line based on extrapolation from the observed data at low pH and low fraction of ionization; the extrapolated rate constant at any pH may be designated k_{ex} . At any pH the fraction k_c/k_{ex} is equal to the fraction of undissociated amylose AH_n . That is

$$\begin{aligned} k_c/k_{ex} &= [AH_n]/\sum_{x=1}^n x[AH_{n-x}] \\ 1 - k_c/k_{ex} &= \frac{\sum_{x=1}^n x[AH_{n-x}]}{[AH_n]} \end{aligned}$$

Since also

$$K_{app} = [H^+] \sum_{x=1}^n x[AH_{n-x}]/[AH_n]$$

it is possible to calculate K_1 by constructing a graph of K_{app} vs. fraction of ionized cycloamylose. Extrapolation to low fractions of ionization gives K_1 . The appropriate values of $1 - k_c/k_{ex}$ were taken from Figures 4 or 6, multiplied by the respective values of the pH to give K_{app} , and these values plotted in Figures 5 and 7, respectively. Extrapolation to low fractions of ionization gives the ionization constants. The kinetic pK_a value based on the acylation rate data is 11.8, while that for the deacylation rate data is 12.3. The uncertainty in these values is probably $\pm 10\%$ for the deacylation rate data and $\pm 30\%$ for the acylation rate data.

Acknowledgment. The authors thank Dr. Hermann Schlenk for kindly providing a sample of dodecamethylcyclohexaamylose and Dr. I. M. Klotz for helpful discussions regarding the calculation of ionization constants of polyprotic acids.

Kinetic Studies on the Alkaline Decomposition of Cystine Derivatives and Peptides¹

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Contribution from the Department of Chemistry, Duquesne University, Pittsburgh, Pennsylvania 15219. Received January 25, 1967

Abstract: Alkaline decomposition of endopeptides of cystine takes place *via* β elimination to give a persulfide moiety and a dehydroalanyl residue containing moiety. Rates of decomposition of N,N'-dicarbobenzyloxy-L-cystinyldiamide, N,N'-dicarbobenzyloxy-L-cystinyldiglycine, N,N'-dicarbobenzyloxy-L-cystinyldi-L-alanine, and oxidized glutathione are first order in substrate and hydroxyl ion concentrations with bimolecular rate constants at 90.5° of 2.0, 0.95, and 1.43 l. mole⁻¹ sec⁻¹, respectively, for the first three compounds and 0.11 l. mole⁻¹ sec⁻¹ for oxidized glutathione at 80.5°. Rates of decomposition at 90.5° of L-cystine bishydantoin are first order in substrate and show a pH dependency, interpretable in terms of a single ionization with a pK_a of 7.56. Initial elimination from oxidized glutathione is followed by addition of the amino group of glutamic acid residues to the dehydroalanyl residue. This secondary reaction observed with oxidized glutathione does not occur in the presence of morpholine. Similarly, in the presence of morpholine, alkaline decomposition of ribonuclease yields only one lysinoalanine residue, four normally being observed.

Recent work of Bohak³ on alkaline decomposition of cystinyl residues of proteins establishes β elimination as the route for such decompositions, the primary products being a dehydroalanyl residue⁴ and a cysteinyl residue.⁵ These decompositions of cystinyl peptides are similar, in principle, to the alkaline decomposition of L-cystine bisphenylhydantoin first reported by Bergmann and co-workers⁶ and attributed to an elimination reaction. A similar elimination was noted by Andrews and Andrews⁷ with L-cystine bishydantoin, pyruvic acid being found on treatment of the reaction mixture with acid. Tarbell and Harnish⁸ proposed a β -elimination mechanism for such decompositions of disulfides, suggesting that removal of a proton from carbon β to sulfur gives a carbanion which undergoes elimination to yield olefin and persulfide anion.

To further explore this mode of alkaline decomposition of cystine endopeptides and analogous cystine derivatives, a kinetic study of the alkaline decomposition of N,N'-dicarbobenzyloxy-L-cystinyldiamide, the corresponding bisglycine and bis-L-alanine, and L-cystine bishydantoin was undertaken and the results are reported herein.

Experimental Section

Compounds. N,N'-Dicarbobenzyloxy-L-cystine,⁹ mp 123°, after recrystallizations from chloroform, was used for synthesis of the following compounds: N,N'-dicarbobenzyloxy-L-cystinyldiamide, mp 181–182°, after two recrystallizations from methanol, prepared according to Boehringer, *et al.*,¹⁰ N,N'-dicarbo-

benzyloxy-L-cystinyldiglycine was prepared by the method of Du Vigneaud and Miller;¹¹ N,N'-dicarbobenzyloxy-L-cystinyl bis-L-alanine, mp 158–159°, after recrystallization from dioxane, was prepared by adaptation of the Du Vigneaud and Miller¹¹ procedure for the preparation of the corresponding glycine peptide.

Anal. Calcd for C₂₈H₃₄N₄O₁₀S₂: C, 51.70; H, 5.25; N, 9.85; S, 8.63. Found: C, 51.89; H, 5.38; N, 10.03; S, 8.34.

L-Cystine bishydantoin was synthesized from L-cystine hydantoin by oxidation with iodine.^{12,13}

Kinetic Runs. Substrate sufficient for 25.0 ml of approximately 3.00 × 10⁻³ M solution was placed in a 25.0-ml volumetric flask, and at zero time, 25.0 ml of buffer or sodium hydroxide solution at bath temperature was added. The flask was stoppered, inverted several times to dissolve the substrate, and returned to the constant temperature bath. Aliquots (1 ml) were removed at suitable intervals and analyzed for pyruvic acid by a modification of the enzymatic method.¹⁴ The aliquots were quenched with 2.0 ml of 3 N hydrochloric acid and then refluxed for 2.5 hr to liberate, by hydrolysis,^{15,16} pyruvic acid from the dehydroalanyl peptide formed by the decomposition. After cooling, the pH of the hydrolysis mixture was adjusted to 8.3–8.5 with 10 M sodium hydroxide and the volume was adjusted to 4.0 ml. An aliquot of this solution was then analyzed for pyruvic acid with reduced diphosphopyridine nucleotide and lactate dehydrogenase.

Persulfide Analysis. Kinetic runs were also monitored for alkyl persulfide, the analyses being carried out by modification of the procedure of Cavallini, *et al.*¹⁶ A 0.1-ml aliquot of the reaction mixture was added to a mixture of 1.0 ml of 0.2 M borate buffer, pH 9.0, and 0.5 ml of 0.1 M sodium cyanide (adjusted to pH 9.0 with acid), and cyanolysis of the persulfide was permitted to proceed for 10 min at room temperature. Under these conditions (pH 9.0–9.5 of the cyanolysis reaction mixture), thiocyanate was not obtained from starting disulfide. At the conclusion of the cyanolysis period thiocyanate was estimated with ferric ion.

Inorganic Sulfide, Sulfur, and Thiol Analyses. Persulfide formed during the course of a kinetic run was not stable, and after its disappearance, decomposition products at the -2 and 0 oxidation level were analyzed for, as follows. Inorganic sulfide was determined by the method of Fogo and Popowsky¹⁷ on a 0.2-ml aliquot of the reaction mixture for a kinetic run. Sulfur was

(1) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966; Abstracts, p 70C.

(2) Abstracted in part from the Ph.D. Thesis of G. Odstrchel, Sept 6, Duquesne University.

(3) Z. Bohak, *J. Biol. Chem.*, **239**, 2878 (1964).

(4) In the case of ribonuclease and other proteins, condensation of ϵ -amino groups of lysine with the newly formed dehydroalanine residues results to yield N-(DL-2-amino-2-carboxyethyl)-L-lysine residues.³

(5) Z. Bohak, personal communication.

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(17) J. K. Fogo and M. Popowsky, *Anal. Chem.*, **21**, 732 (1949).

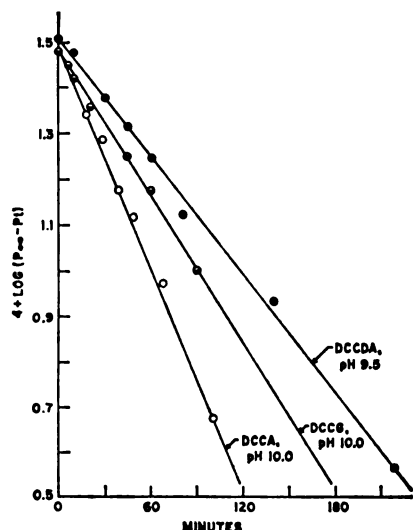
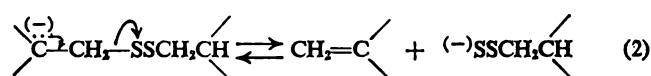
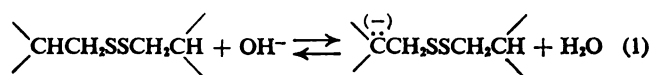


Figure 1. Typical first-order plots for the decomposition at 90.5° and several pH values, of DCCDA (N,N'-dicarbobenzyloxy-L-cystinyldiamide), DCCG (N,N'-dicarbobenzyloxy-L-cystinyldiglycine), and DCCA (N,N'-dicarbobenzyloxy-L-cystinyldi-L-alanine). Reactions followed by estimation of pyruvic acid after hydrolysis.

determined by the method of Meister, *et al.*,¹⁸ the sulfur in a suitable aliquot being reduced to hydrogen sulfide with cysteine and the hydrogen sulfide formed being removed with nitrogen and trapped in alkaline zinc acetate solution. The sulfide ion was then estimated by the procedure given above. Inorganic sulfur was calculated as the difference between hydrogen sulfide before and after the reduction treatment. Thiol was determined by Ellman's method¹⁹ on a 0.2-ml aliquot of the reaction mixture by addition of 3.0 ml of a 1 M phosphate buffer, sufficiently acid to give a final pH of 8, followed by 0.05 ml of the Ellman reagent [5,5'-dithiobis-(2'-nitrobenzoic acid)].

Results and Discussion

The base-catalyzed β elimination observed with symmetrical disulfides derived from cystine may be written as



with the rate-controlling step either reaction 1 or reaction 2. With reaction 1 rate controlling, a first-order rate dependence on hydroxide ion concentration is expected and with reaction 2 rate controlling, a sigmoid curve is the expected relationship between rates and hydroxide ion concentrations. In both cases the reaction is expected to be first order in disulfide concentration.

The compounds studied showed the expected first-order dependency on disulfide concentration. With respect to hydroxide ion concentration, both possible dependencies were observed, rates of the three dicarbobenzyloxycystinylbisamides showing first-order dependency while rates of cystine bishydantoin decompositions showed a sigmoid curve relationship.

Figure 1 presents several typical first-order plots at a given pH (0.2 M borate buffers) for the decomposition at 90.5° of N,N'-dicarbobenzyloxy-L-cystinyldiamide (DCCDA), N,N'-dicarbobenzyloxy-L-cystinyldiglycine (DCCG), and N,N'-dicarbobenzyloxy-L-cystinyldi-L-

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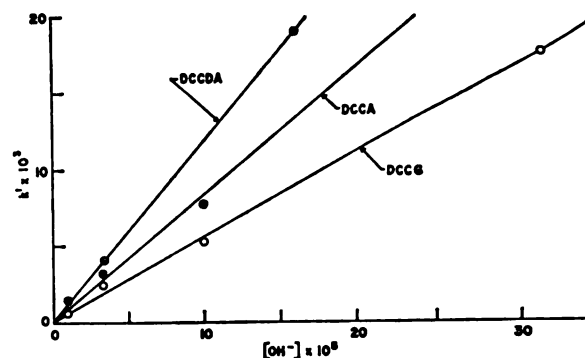


Figure 2. Plots of k' , apparent first-order rate constants, at 90.5° vs. hydroxide ion concentration for the several indicated compounds.

alanine (DCCA). Initial concentrations were 3×10^{-1} M and first-order kinetics were obeyed for some 70% of the reaction. The slope of each of the first-order plots yielded k' , the apparent first-order rate constants for the reaction, at a given pH where

$$v = k(\text{OH}^-)(\text{RSSR}) \quad (3)$$

and

$$k' = k(\text{OH}^-) \quad (4)$$

Plots of k' vs. hydroxide ion concentration (Figure 2) for the individual compounds gave straight lines passing through the origin, in agreement with eq 4, and k , the bimolecular rate constant, was calculated from the slopes of these lines. The values of k are 2.0, 0.95, and 1.43 l. mole⁻¹ sec⁻¹ for N,N'-dicarbobenzyloxy-L-cystinyldiamide, N,N'-dicarbobenzyloxy-L-cystinyldiglycine, and N,N'-dicarbobenzyloxy-L-cystinyldi-L-alanine, respectively.

As might be expected on the basis of structural similarities of the three N,N'-dicarbobenzyloxy-L-cystinylbisamides, and without regard to charge differences, k values are of the same order of magnitude. With regard to charge differences between the three compounds, it is apparent the negatively charged carboxylate groups are sufficiently removed from the reaction site so as not to interfere with approach of hydroxide ion. In this connection it may be noted that N,N'-dicarbobenzyloxy-L-cystine with its adjacent α -carboxylate group is unreactive to hydroxide under the reaction conditions employed. It would seem that in this case electrostatic repulsion would be mainly responsible for lack of attack by hydroxide.

Although not encountered in the limited series investigated, it is possible that substitution of the glycine of carbobenzyloxycystinyglycine by other amino acids would lead to relatively larger rate effects. Such effects from amino acid residues with sufficiently large side chains could conceivably arise from steric hindrance and/or alteration in the solvent environment around the site of the reaction and, assuming a *trans* conformation as would be expected for the elimination, from hindrances to attainment of this conformation. These effects would be expected to be greater at lower temperatures. Preliminary investigation of temperature effects yielded bimolecular rate constants of 2.83×10^{-1} and 0.31×10^{-3} l. mole⁻¹ sec⁻¹ for N,N'-dicarbobenzyloxy-L-cystinyldiglycine and N,N'-dicarbobenzyloxy-L-cystinyldi-L-alanine, respectively, at 31° in sodium hydroxide solution. At this temperature $k_{\text{glycine}}/k_{\text{L-alanine}}$

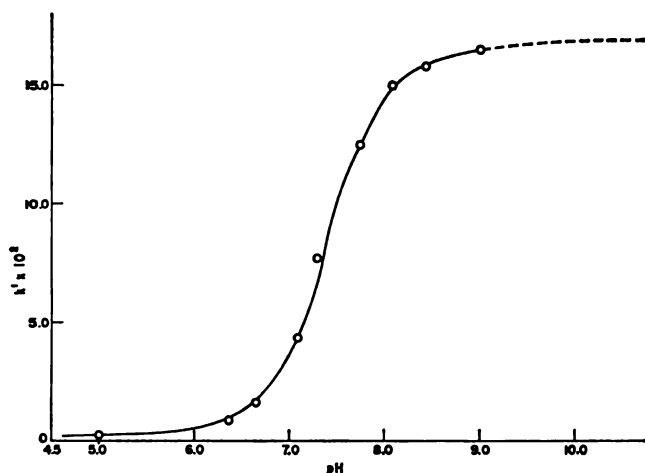


Figure 3. Plot of k' at 90.5° vs. pH for L-cystine bishydantoin. Reaction followed by estimation of pyruvic acid after hydrolysis.

is 9.1 while at 90.5° the corresponding ratio is 0.67 and it is clear that the rate effect of substitution of alanine for glycine is greater at the lower temperature.

Figure 3 presents a plot of k' vs. pH for the bishydantoin of L-cystine. The shape of the curve is that of an ionization curve with a pK in the vicinity of 7.5. A Henderson-Hasselbach plot of pH vs. $\log k'/(k'_{\max} - k')$ gives a straight line with a slope of 0.82 rather than 1.00 as expected for a single ionization. However, inclusion of a correction term²⁰ for activity of the anionic species, the ionic strength of the buffer varying with the pH, gives the modified Henderson-Hasselbach equation, and a plot (Figure 4) of $pH - \log \gamma_{A-}$ vs. $\log k'/(k'_{\max} - k')$ gives a straight line with a least-squares slope of 1.02 and intercept (pK_A) of 7.56. Buffer effects were not noted, variation at pH 9.02 of total buffer concentration from 0.1 to 0.2 M not affecting rates. Accordingly the reaction rate may be viewed as dependent on a single ionization albeit secondary ionizations are possible and racemization may also be occurring.²⁴ A possible reaction mechanism is given in Figure 5, hydrogen attached to imide nitrogen being considered the most acidic. Tautomerization to a form such as that given in the figure would then provide an intermediate for the elimination. The pK_A value, 7.56 at 90° found for L-cystine bishydantoin, is considerably less than that, 9.12 at 25° , for hydantoin itself,²⁶ the imide group of the latter ionizing.²⁷ The lower value for the cystine hydantoin may be due in part to a temperature effect and in part to an acid-strengthening effect in the L-cystine hydantoin.

(20) $-\log \gamma_{A-}$ was evaluated as $0.589/u$,²¹ the numerical value at 90° being that given by Manov, *et al.*²² The ionic strength at a given pH was calculated from the buffer anion concentration; total buffer concentration 0.2 M , $pK_A = 8.88$ for the first ionization of boric acid. The K_A value was obtained by extrapolation to 90° of a $\log K_A$ vs. $1/T$ plot, K_A values at several temperatures being obtained from the literature.²³

(21) E. S. Amis, "Kinetics of Chemical Change in Solution," The Macmillan Co., New York, N. Y., 1949, p 25.

(22) G. C. Manov, R. G. Bates, W. J. Hamer, and J. F. Acree, *J. Am. Chem. Soc.*, **65**, 1765 (1943).

(23) "Handbook of Chemistry and Physics," 47th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1966, p D88.

(24) The hydantoin of S-benzyl-L-cysteine racemizes rapidly in alkali.²⁵

(25) O. Gawron and A. J. Glaid, III, *J. Am. Chem. Soc.*, **71**, 3232 (1949).

(26) M. Zief and J. T. Edsall, *ibid.*, **59**, 2245 (1937).

(27) L. W. Pickett and M. McLean, *ibid.*, **61**, 423 (1939).

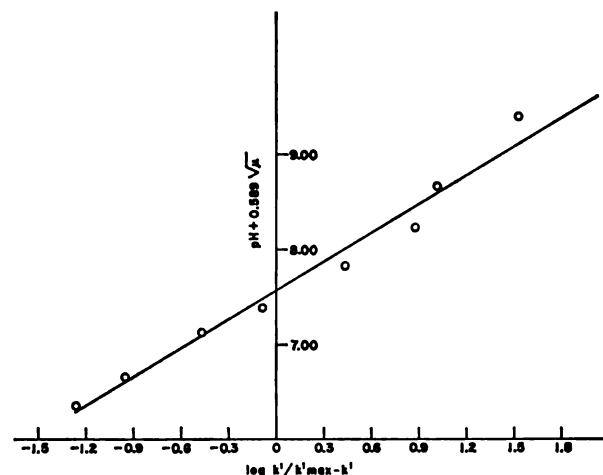


Figure 4. Plot of $(pH - 0.589/u)$ vs. $\log k'/(k'_{\max} - k')$ for the data of Figure 3. Slope, 1.02, and intercept, 7.56, for the solid line were calculated by the least-squares method from the experimental points.

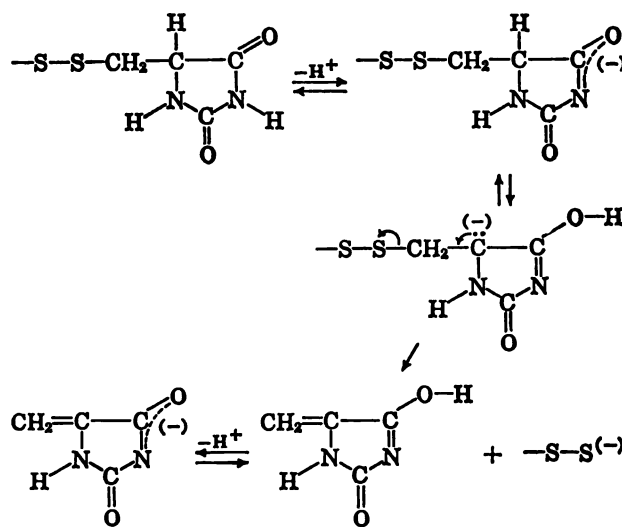
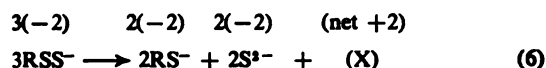


Figure 5. Possible mechanism for β elimination from L-cystine bishydantoin. Ionization from imide nitrogen followed by tautomerization and elimination.

Figure 6 presents plots at several pH values of the time course of decomposition of dicarbonyloxy-L-cystinyldiglycine at 100° , the reactions being followed by pyruvic acid and alkyl persulfide analyses. Comparison of the kinetic curves for persulfide and pyruvic acid indicates a similar pH dependence for initial rates of appearance of the two products and alkyl persulfide instability under the reaction conditions. The mode of decomposition of the particular alkyl persulfides encountered is not known. Investigation of persulfide decomposition products after disappearance of persulfide from reaction mixtures gave results demonstrating the presence of alkyl mercaptan and sulfide ion but not sulfur. At 100° , pH 10.0 (0.2 M borate), the stoichiometric ratios of products per mole of dicarbonyloxy-L-cystinyldiglycine are 0.67 mercaptan, 0.67 sulfide ion, and 1.0 pyruvate, while at 30° in 0.1 M sodium hydroxide, the corresponding ratios are 0.73, 0.1, and 0.97. The data obtained at 100° , assuming completeness of transformations subsequent to persulfide de-



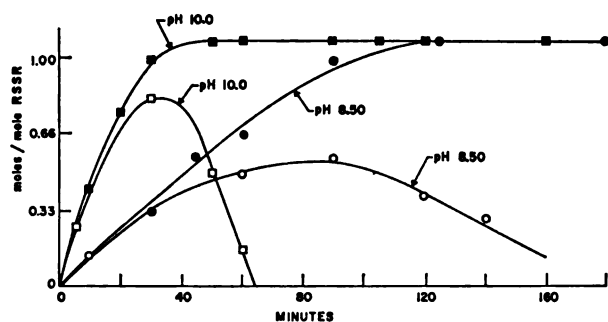


Figure 6. Rate curves for formation of pyruvic acid and persulfide by the decomposition of dicarbonyloxy-L-cystinyldiglycine at 100° at several pH values in 0.2 M borate buffers: ●, pyruvate; ○, persulfide.

composition, suggest the decomposition stoichiometry shown in eq 6, where (X) would contain one R and two sulfur atoms with a net oxidation number of +2. On this basis the decomposition reaction might be written as



Since a search for a decomposition product containing sulfur at a higher oxidation level than zero was not attempted, further discussion is inappropriate albeit it may be stated that RSSO_2^- fits the requirements for such a product and a mechanism may be written similar to that proposed by Danehy²⁸ and by Danehy and Hunter²⁹ for the alkaline decomposition of certain symmetrical alkyl disulfides. On the above basis, the low yield of sulfide ion in 0.1 M sodium hydroxide at 30° may signify a different pathway or destruction of sulfide ion.

To further explore the scope of β elimination from cystine peptides, oxidized glutathione was investigated, the decompositions being carried out at 80.5° in 0.2 M phosphate buffers. Both products, the dehydroalanyl residue and alkyl persulfide, were unstable (Figure 7) and could not be used to follow the reaction. The reaction was followed by analysis for residual oxidized glutathione with reduced triphosphopyridine nucleotide in the presence of glutathione reductase.³⁰ Disappearance of oxidized glutathione followed first-order kinetics and a plot (Figure 8) of k' , the first-order rate constants for individual runs, vs. hydroxyl ion concentration gives a straight line passing through the origin. Decomposition of oxidized glutathione is, therefore, similar to the other cystine peptides, the reaction being bimolecular with a bimolecular rate constant at 80.5° of 0.11 l. mole⁻¹ sec⁻¹. Disappearance of dehydroalanyl residue (pyruvic acid) was accompanied by loss of glutamic acid and appearance of a new amino acid as evidenced by amino acid analysis³¹ following acid hydrolysis. While the structure of the new amino acid was not determined, its mode of formation is analogous to that of lysinoalanine and, presumably in this case, the amino group of the glutamic acid adds across the double bond of the dehydroalanine residue to give N-(DL-2-amino-2-carboxyethyl)-L-glutamic acid. Oxi-

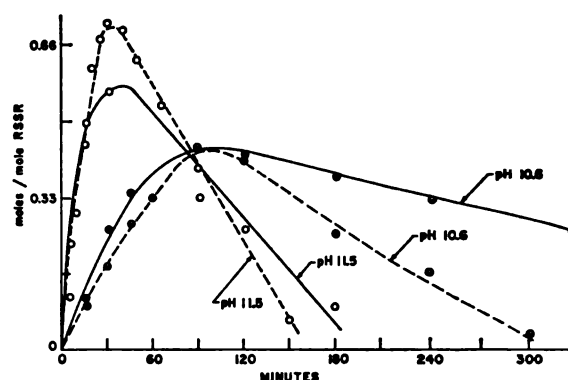


Figure 7. Product-time curves for decomposition of oxidized glutathione at 80.5° at several pH values in 0.2 M phosphate: —, pyruvate; ---, persulfide.

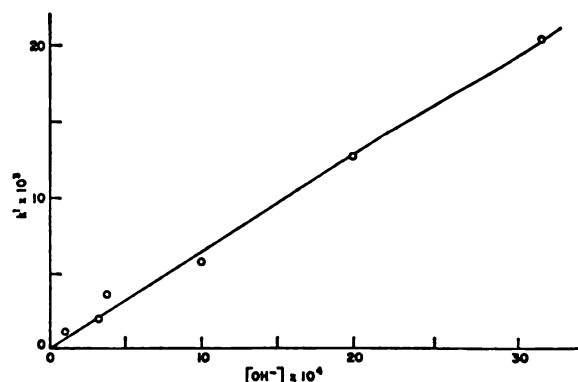


Figure 8. Apparent first-order rate constants, k' , for oxidized glutathione vs. hydroxyl ion concentration; 80.5°, 0.2 M phosphate buffers.

dized glutathione in its behavior toward alkali is, thus, entirely similar to the several cystine-containing proteins that undergo alkaline decomposition³ and can be used as a model for such protein studies.

In connection with alkaline decomposition of the four cystine residues of ribonuclease, it has been noted¹ that one of the four dehydroalanyl residues produced by the elimination reaction is rapidly converted by a consecutive reaction to a lysinoalanine residue while the other three are converted to lysinoalanine residues at a slower rate. In this laboratory we have noted¹¹ the appearance of only one lysinoalanine residue per mole of ribonuclease when the alkaline decomposition is allowed to proceed in the presence of 0.1 M morpholine, the other three being replaced by the corresponding morpholine adduct. This remaining lysinoalanine residue is most likely the one formed at the fastest rate and its formation indicates an intrachain proximity of the dehydroalanyl residue and ϵ -amino group involved, such that competition from morpholine is precluded. On this basis location in the amino acid sequence of the particular lysine and particular cystine residue involved is of interest with regard to their spatial relation. While a lysine-adjacent cystine pair is a likely lysinoalanine precursor,³ it is also possible that the single polypeptide chain is so looped as to bring together a lysine residue and a cystine residue that are removed one from the other in the sequence. Lysozyme with its four cystine residues, three of which, at least,

acid analyzer.

(32) O. Gawron and G. Odstrchel, unpublished observations.

(28) J. P. Danehy in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1966, p 337.

(29) J. P. Danehy and W. E. Hunter, Abstracts, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, p 42K.

(30) E. Racker and B. Vennesland, *Methods Enzymol.*, 2, 719 (1955).

(31) Analyses were performed on the Technicon automatic amino

being subject to alkaline decomposition,³ and its known sequence and three-dimensional structure³³ is a particularly good single polypeptide chain for investigating lysine-cystine proximity in this manner. It is also

(33) C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Nature*, 206, 756 (1965).

possible that a lysine ϵ -amino group close to a cystine residue acts as a base catalyst for the elimination.

Acknowledgments. Support of this investigation by Grant GB-2512 from the National Science Foundation and the assistance of David Ford and Mary Gallagher are gratefully acknowledged.

Novel Analgesics and Molecular Rearrangements in the Morphine-Thebaine Group. I. Ketones Derived from 6,14-*endo*-Ethenotetrahydrothebaine¹

K. W. Bentley and D. G. Hardy

Contribution from the Research Laboratories, Reckitt and Sons Ltd., Kingston-upon-Hull, England. Received September 26, 1966

Abstract: Several ketones II derived from 6,14-*endo*-ethenotetrahydrothebaine have been prepared by the Diels-Alder addition of certain α,β -unsaturated ketones to thebaine, by the action of cadmium alkyls on the corresponding acid chloride II (R = Cl), and, in some cases, by the action of Grignard reagents on the corresponding ester II (R = OEt) which is the adduct of thebaine and ethyl acrylate. Both 7 α and 7 β forms of the ketone II (R = Me), the ester II (R = OEt), and the nitrile III have been isolated. Attempts to convert the 7 α ketone II (R = Me) into the 7 β isomer have resulted only in the formation of a ketol X (R = H). Many of the bases prepared in this work are potent analgesics. The reaction product obtained from thebaine methiodide and *p*-benzoquinone has been shown to be a charge-transfer complex and not a true Diels-Alder adduct.

For many years determined efforts have been made to produce an analgesic markedly superior to morphine by minor and major modifications of the molecule of the alkaloid. The major modifications have all been in the direction of making simpler structures, representing what are believed to be the features of the molecule responsible for its analgesic action.² Structural simplifications of this type, however, have not so far resulted in any marked separation of the desirable and undesirable effects. It has been postulated that the action of such compounds is due to the fit of their molecules onto receptor surfaces, which triggers off their physiological effects.³ Compounds of structure more simple than that of morphine, however, being more flexible, would be expected to fit at least as easily as the alkaloid to each of the similar receptor surfaces associated with the different effects, thus reproducing all of the physiological effects of the alkaloid. These considerations led us to examine bases more complex and, in particular, more rigid than morphine in the hope that the reduced flexibility and the differences in peripheral shape between such compounds and other known analgesics would result in the new bases being unac-

ceptable at some of the receptor surfaces, and thus to a separation of the various effects.

Several series of such complex derivatives of codeine and thebaine, which are themselves derivatives of morphine, are accessible by the Diels-Alder addition of dienophiles to thebaine⁴ and by chemical transformations of the resulting adducts,⁵ and in these compounds the new two-carbon bridge across ring C renders the molecule rigid. Many of the compounds derived from thebaine in this way contain also a new reactive center, derived from the dienophile, at which further chemical reactions may be effected to yield bases of still greater peripheral complexity. Some of our early work along these lines has already been reported,⁶ but the work was suspended owing to the difficulty experienced in securing adequate pharmacological appraisal of the compounds prepared. During the course of this work, however, it was found that the ketonic base I, obtained by the catalytic reduction of the adduct of thebaine and *p*-benzoquinone, is an analgesic with about one-seventh the potency of morphine, when tested in rats by the conventional techniques.

In further pursuit of this idea, the other known Diels-Alder adducts of thebaine, namely the aldehyde II (R = H), the ketones II (R = Me and Ph), the nitrile III, and the diester IV were prepared, together with a number of new analogous bases, and these were tested in animals for analgesic properties.

(4) W. Sandermann, *Ber.*, 71, 648 (1938); C. Schopf, K. von Gottberg, and W. Petri, *Ann.*, 536, 216 (1938); S. I. Kanewskaya and S. F. Mitryagina, *J. Gen. Chem. USSR*, 17, 1203 (1947).

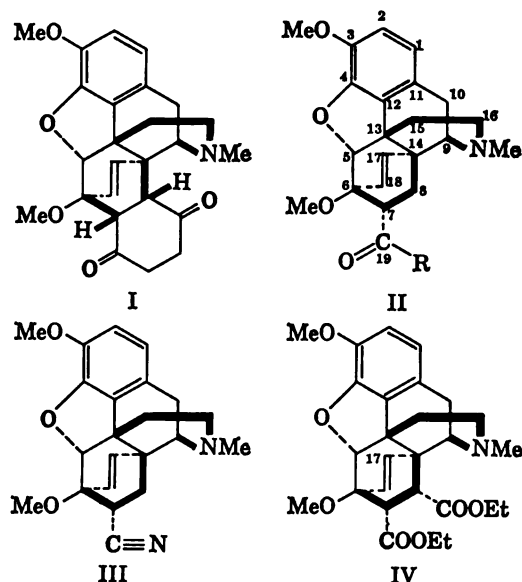
(5) (a) K. W. Bentley and J. Dominguez, *J. Org. Chem.*, 21, 1348 (1956); (b) K. W. Bentley, J. Dominguez, and J. P. Ringe, *ibid.*, 22, 409, 418, 422 (1957); (c) K. W. Bentley and J. P. Ringe, *ibid.*, 22, 425, 599 (1957); (d) K. W. Bentley and J. C. Ball, *ibid.*, 23, 1720, 1725 (1958); (e) K. W. Bentley, J. C. Ball, and H. M. E. Cardwell, *ibid.*, 23, 941 (1958).

(6) K. W. Bentley and A. F. Thomas, *J. Chem. Soc.*, 1863 (1956).

(1) (a) A preliminary report of part of this work has been made by K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1960). (b) Parts of this work are covered by British Patents 905,659 and 925,723.

(2) F. Bergel and A. L. Morrison, *Quart. Rev. (London)*, 2, 349 (1948); E. S. Stern, *ibid.*, 5, 405 (1951); A. H. Beckett, *J. Pharm. Pharmacol.*, 4, 425 (1952); O. Braenden, N. B. Eddy, H. Halbach, and P. O. Wolff, *Bull. World Health Organ.*, 2, 193 (1949); 10, 1003 (1954); 13, 937 (1955); 14, 353, (1956); N. B. Eddy, *Chem. Ind. (London)*, 1462 (1959); P. A. J. Janssen, "Synthetic Analgesics-Part I," Pergamon Press Ltd., London, 1960; P. A. J. Janssen, *Brit. J. Anaesthesia*, 34, 260 (1962); P. A. J. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, 2, 31 (1960); K. W. Bentley, *Endeavour*, 23, 97 (1964); "Analgesics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 123 (1965); E. L. May and L. J. Sargent, p 123, and R. A. Hardy and G. M. Howell, p 179.

(3) A. H. Beckett, *Progr. Drug Res.*, 1, 527 (1959).

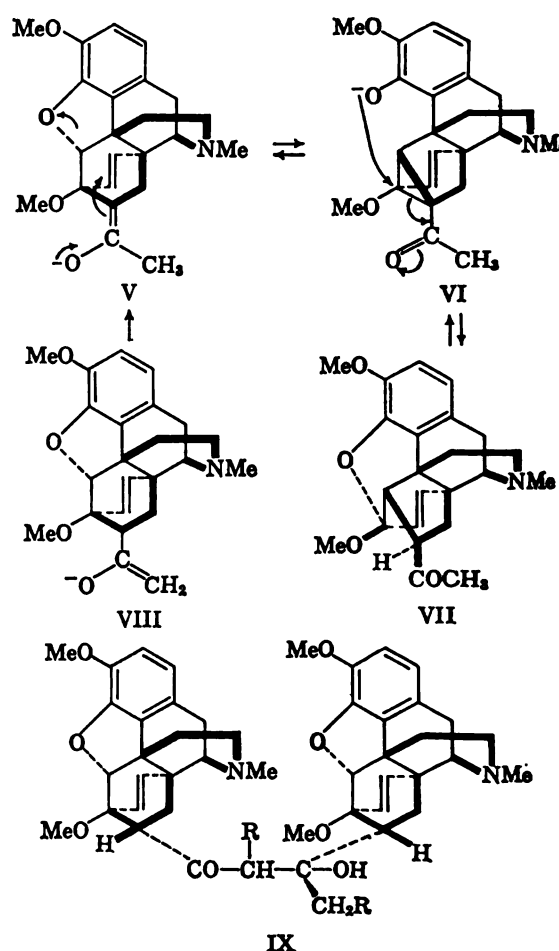


The addition of dienophiles to thebaine can occur readily only on the exposed face of the diene system, and gives rise to derivatives of 6,14-*endo*-ethenotetrahydrothebaine, the atom numbering of which is shown in formula II. The prefix *endo* implies disposition of the 6,14-etheno bridge "inside" the tetrahydrothebaine skeleton, that is, on the opposite side of the molecule to that occupied by the hydrogen atoms at positions 6 and 14 in tetrahydrothebaine itself. Addition of the dienophile to the exposed face of the diene system in two ways, leading to isomeric adducts differing in stereochemistry at C-7, can also be envisaged, and the isomers obtained in this way can be differentiated by the symbols α and β , which have the same implications as when used in the steroid field. A careful examination of models of the 7α and 7β forms of the ketone II ($R = \text{Me}$), the aldehyde II ($R = \text{H}$), the ester II ($R = \text{OEt}$), and the nitrile III reveals that there is little difference in steric hindrance in the two forms, which might be expected, therefore, to be of comparable stability. The stereochemical factors generally governing the mode of addition in the Diels-Alder reaction would, however, be expected to give in this case mainly adducts having the 7α configuration, II and III. The addition of unsymmetrical dienophiles such as alkyl and aryl vinyl ketones, acrylic esters, and acrylonitrile to thebaine appears to take place under electronic control, giving rise exclusively to C-7-substituted tetrahydrothebaine derivatives, very careful examination of the products of addition of methyl vinyl ketone and ethyl acrylate to the alkaloid producing no evidence of the production of C-8-substituted compounds.

The primary adduct of thebaine and methyl vinyl ketone consists almost entirely of the 7α ketone II ($R = \text{Me}$), mp 122° , but from the mother liquors of the crystallization of this base the 7β ketone, mp $200\text{--}201^\circ$, has been isolated in 0.5% yield. That these two bases are indeed epimers at C-7, and not C-7 and C-8 ketones, was conclusively demonstrated by the base-catalyzed rearrangement of both isomers to the same product, which is the ketone VII ($R = \text{Me}$). This base-catalyzed rearrangement, which will be discussed in detail in a later paper in this series,⁷ is analogous to the con-

version of nepenthone (II, $R = \text{Ph}$) into isonepenthone (VII, $R = \text{Ph}$), and involves loss of the asymmetry at C-7 in the intermediate enolate ion V. A rational mechanism for this rearrangement, $V \rightarrow VI \rightarrow VII$,⁸ can only be devised if the COCH_3 group is situated at C-7. The assignment of the 7α configuration to the base, mp 122° , and the 7β configuration to the minor product, mp $200\text{--}201^\circ$, of the Diels-Alder reaction has been confirmed by detailed nmr spectroscopic studies.⁸

Attempts were made to convert the 7α ketone II ($R = \text{Me}$) into an equilibrium mixture with the 7β isomer by reversible enolization to the enolate ion V. The primary enolization of the ketone is, however, kinetically controlled, and leads to the enolate ion VIII, and this can react with unenolized ketone to give a ketol IX ($R = \text{H}$) (see below). The ketolization is reversible, however, and under reversible enolizing conditions the thermodynamically more stable ion V will eventually be formed and reversible discharge of this ion should give an equilibrium mixture of 7α and 7β ketones. In practice, however, the process is complicated by the ease with which the enolate ion V suffers rearrangement through the phenate ion VI to the ketone VII ($R = \text{Me}$), which appears to be more stable than either of the C-7 epimers of the adduct II ($R = \text{Me}$).



Although these equilibration experiments provide no evidence as to which of the two C-7 epimers of the ketone II ($R = \text{Me}$) is the more stable, the formation of derivatives of the 7α -tertiary alcohol X ($R = R'$)

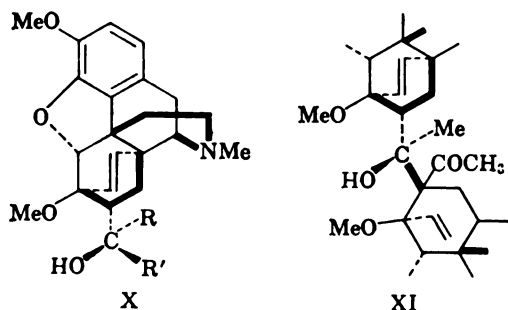
(7) K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey, and P. A. Mayor, *J. Am. Chem. Soc.*, **89**, 3312 (1967).

(8) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. R. Howell, C. T. Nora, and R. A. Hardy, Jr., *ibid.*, **89**, 3322 (1967).

= Me) from bases in which the bicyclooctene system has been opened, described in part IV of this series,⁹ suggests that in the alcohols the 7 α form is the more stable.

Treatment of the adduct II (R = Me) with 1 equiv of methylmagnesium iodide or other Grignard reagent gives little or no tertiary alcohol, the product being a viscous gum very similar in infrared absorption to the original ketone. The same product is obtained by the action of anhydrous magnesium iodide on the adduct, and it is shown by thin layer chromatography to consist of a mixture of the ketone II (R = Me) (20%), a new base (75%), and the product VII (R = Me) of base-catalyzed rearrangement (5%). This mixture on treatment with 0.1 equiv of potassium amide in liquid ammonia rapidly affords a good yield of the ketone II (R = Me), which is sparingly soluble in ammonia, and, when treated with an excess of methylmagnesium iodide, it gives an excellent yield of the tertiary carbinol X (R = R' = Me), which is obtained directly from the ketone II (R = Me) and an excess of this Grignard reagent (see following paper).

Separation of the main component of the mixture was achieved on alumina plates, and it was obtained as prisms, mp 151–152°, and found to be isomeric with the original ketone II (R = Me). Its infrared spectrum shows carbonyl absorption at 1715 cm⁻¹, and hydrogen-bonded hydroxyl absorption at 3490 cm⁻¹. The intensities of these absorption bands relative to the adjacent C–H bands, at 1450 and 2950 cm⁻¹, respectively, was 0.52 and 0.19, whereas the intensities of the carbonyl and hydroxyl absorption bands relative to the same C–H bands in the ketone II (R = Me) and the tertiary alcohol X (R = Me, R' = *i*-Am) are 1.07 and 0.42, respectively. The new base must, therefore, be a double molecule containing one hydroxyl and one carbonyl group between two ethenotetrahydrothebaine units, and, since it is convertible back into the ketone II (R = Me), can only be a ketol resulting from attack of the ketone by its own enolate ion. Enolization by Grignard reagents or anhydrous magnesium iodide would be irreversible and, hence, kinetically controlled and lead to the ion VIII, attack of which on the ketone would afford the ketol X (R = H). That this does correctly represent the structure of the ketol was confirmed by dehydration of the ketol to an α,β -unsaturated ketone by heating with 98–100% formic acid. Ketol formation from the ketone and the enolate ion V would lead to a product containing the part structure XI, dehydration of which to an α,β -unsaturated ketone would be impossible.



The nmr spectrum of the ketol fully supports the assigned structure X (R = H). The spectrum, ob-

(9) K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3293 (1967).

tained on a 40-Mc/sec instrument, shows no signal attributable to COCH₃, but does show signals (in δ units) at 6.58 (four aromatic H), a complex signal pattern from 6.2 to 5.4 attributed to two *cis* CH=CH systems in slightly different environments, and signals at 4.95 (OH), 4.61 (2OCH<), 3.86 (two aromatic OCH₃), 3.80 (three protons in the hydrogen-bonded C-6 OCH₃ group in the alcoholic part of molecule), 3.67 (three protons in the unbonded C-6 OCH₃ group in the ketonic part), 2.41 (2NCH₃), and 1.17 (CCH₃). It may be noted that the C-6 methoxyl group in the alcohol X (R = R' = Me) gives a signal at δ 3.75 and that in the ketone II (R = Me) gives a signal at δ 3.61.

Stereochemically, since enolization in this case does not involve C-7, both units in the ketol IX (R = H) belong to the 7 α series, and the formation of the 7 α ketone in good yield on deketalization of the base with potassium amide in liquid ammonia is in agreement with this representation.

The addition of ethyl acrylate to thebaine is also highly stereospecific, giving about 94% of the 7 α ester II (R = OEt) and 6% of the isomeric 7 β compound. That the major product has the same stereochemistry at C-7 as the adduct of thebaine and methyl vinyl ketone II (R = Me) was demonstrated by the conversion of both adducts into the tertiary carbinol XI (R = R' = Me) by methylmagnesium iodide. The nmr spectra of the esters show signals (in δ units) for the C-5 proton at 4.60 (7 α) and 5.17 (7 β) compared with 4.55 and 4.98 in the spectra of the 7 α - and 7 β -methyl ketones. The other features of the spectra are entirely in accord with the assigned structures.

The primary adduct of thebaine and acrylonitrile is a mixture of 7 α and 7 β isomers from which, after treatment with charcoal, approximately equal amounts of the two pure isomers can be obtained by chromatography. The 7 α nitrile III is identical with the product of dehydration of the oxime of the aldehyde II (R = H) previously reported.^{6d} The assignment of configuration at C-7 in these nitriles was made on the basis of detailed nmr studies.⁸

Although aryl vinyl ketones are readily prepared in the laboratory from aryl methyl ketones, alkyl vinyl ketones, other than the methyl and ethyl compounds which are commercially available, are not readily accessible, and attempts were made to prepare 7-acyl-6,14-*endo*-ethenotetrahydrothebaines from the ester II (R = OEt) and the nitrile III. Some ketones were obtained in poor yield as minor products from the reaction of the ester II (R = OEt) with Grignard reagents. With methylmagnesium iodide the sole product of this reaction is the tertiary carbinol XI (R = R' = Me), but with other alkylmagnesium halides the product consisted of a mixture of tertiary carbinol X (R = R' = Me), ketone II, and phenolic material resulting from rearrangement of the ester.⁹ The amount of tertiary carbinol produced decreased and the amount of phenolic material obtained increased very rapidly as the length and/or branching of the alkyl chain in the Grignard reagent increased; the amount of ketone produced remained low in all cases. Steric factors are presumably operative in this reaction, since the ease of accommodation of two identical alkyl groups around the carbon atom of the tertiary alcohol, in the presence of the large thebaine unit, would be

expected to decrease sharply as the complexity of the alkyl group increases. The ease of abstraction of a proton by the Grignard reagent from the α carbon would be expected to be almost independent of the size of the reagent, and hence rearrangement would be expected to be favored relative to carbinol formation by an increase in size or complexity of the reagent.

A better laboratory preparation of certain of the ketones of structure II was found to be the reaction between cadmium alkyls and the acid chloride II ($R = Cl$), prepared from the ester II ($R = OEt$) via the acid II ($R = OH$). The product of the reaction between the acid chloride and *n*-propylcadmium was resolved on alumina plates into the 7α -*n*-propyl ketone II ($R = n\text{-Pr}$) (80%), its 7β epimer (0.1%), the ketol X ($R = Et$) (20%), and a trace of phenolic base. The major product was identified as the 7α -*n*-propyl ketone II ($R = n\text{-Pr}$) by its infrared and its nmr spectra. The former showed carbonyl absorption at 1715 cm^{-1} and the latter showed a signal due to the C-5 proton as a finely split doublet at δ 4.55 (as in the spectrum of the 7α -methyl ketone) as well as signals (in δ units) at 6.6 (two aromatic H), 6.0 and 5.55 (doublets, $\text{CH}=\text{CH}$), 3.83 (C-3 OCH_3), 3.61 (C-6 OCH_3), 2.29 (NCH_3), and 0.95 (doublet, CHC_3). The 7β ketone was identified by its infrared spectrum, which was almost identical with that of the 7α isomer, and by its less polar behavior on thin layer chromatography.

The ketol IX ($R = Et$) showed carbonyl and hydrogen-bonded hydroxyl absorption in the infrared, and its nmr spectrum was similar to that of the ketol IX ($R = H$), showing signals (in δ units) at 6.59 (four aromatic H), 5.45–6.1 (complex, 2 $\text{CH}=\text{CH}$), 4.6 and 4.75 (two C-5 H), 3.82 (9 H, two C-3 OMe , C-3' OMe , and C-6' OMe), 3.64 (3 H, C-6 OMe), 2.31 and 2.36 (2 NMe), and complex signals due to CCH_3 in the region 1.38–0.98 attributed to the ethyl and propyl groups.

The ethyl and *n*-propyl ketones prepared in this way were converted by the action of methylmagnesium iodide into tertiary alcohols X ($R = Et$, $R' = \text{Me}$ and $R = n\text{-Pr}$, $R' = \text{Me}$) diastereoisomeric at C-19 with those ($R = \text{Me}$, $R' = Et$ and $R = \text{Me}$, $R' = n\text{-Pr}$) obtained by the reaction of the 7α ketone II ($R = \text{Me}$) with ethyl- and *n*-propylmagnesium halides, respectively (see following paper).

The adduct of thebaine and acrylonitrile (mixture of 7α and 7β isomers) reacts readily with methyl and other alkylmagnesium halides, but the reaction involves only base-catalyzed rearrangement, the same product being obtained in all cases. This reaction is discussed in detail in a later paper in this series.⁹ With phenylmagnesium bromide, however, the 7α ketone, nepenthone (II, $R = \text{Ph}$), was obtained in about 25% yield (about 50% based on the amount of 7α -nitrile present in the original adduct), and the *o*- and *p*-tolyl analogs were prepared in a similar manner. Differences in the behavior of nitriles with aliphatic and aromatic Grignard reagents have previously been reported.¹⁰

It was hoped that ketones II would be preparable by the oxidation of the related secondary alcohols X ($R = H$), many of which can be prepared by the action of Grignard reagents on the aldehyde II ($R = H$), but neither of the diastereoisomeric alcohols X (R

$= H$, $R' = \text{Me}$ and $R = \text{Me}$, $R' = H$) (see following paper) nor nepenthol (X, $R = \text{Ph}$, $R' = H$)¹¹ could be oxidized in this way.

Quaternization of the Diels–Alder adducts of thebaine is very difficult to accomplish, but good yields of the quaternary salts of the ketone II ($R = \text{Me}$) and the ester II ($R = \text{OEt}$) were obtained by heating the bases under reflux for 7 days with methyl iodide in acetone solution. Since the adducts of thebaine with acetylenic dienophiles can be quaternized with much greater ease, the sluggish reaction of the adducts II may be attributed to steric hindrance of attack of the nitrogen atom by the proximity of the C-8 β hydrogen. It may be mentioned that other workers have found that this proximity and anisotropy of the tertiary nitrogen also appear to affect the resonance of the 8 β hydrogen in the nmr spectra of bases in this series.⁸ Models of the quaternary salts can be constructed without difficulty, and in these there is no appreciable hindrance between this hydrogen atom and the N-methyl group. The slow quaternization of the adduct II ($R = \text{Me}$) contrasts markedly with the rapid reaction between thebaine methiodide and benzoquinone¹¹ and α -naphthaquinone⁶ previously reported. Since attempts to prepare quaternary salts of the adducts by the addition of acrolein, methyl vinyl ketone, phenyl vinyl ketone, ethyl acrylate, acrylonitrile, and maleic anhydride to thebaine methiodide were quite unsuccessful, the reaction between methiodide and *p*-benzoquinone has been reexamined.

The reaction in chloroform solution rapidly affords a very good yield of a red crystalline solid having the composition of a 1:1 adduct, which is recovered unchanged on rapid recrystallization from hot water.¹¹ The use of high-boiling solvents, such as cyclohexanol, for the recrystallization, however, results in the recovery of thebaine methiodide, which is also obtained when the solid is heated in open vessels at 140–150°. Reduction of a solution of the salt in aqueous ethanol with sodium borohydride or sulfurous acid proceeds with the production of a transient violet color, presumably due to quinhydrone, and the formation of hydroquinone and thebaine methiodide. The material is, therefore, clearly not a true adduct, but is a charge-transfer complex of thebaine methiodide with benzoquinone, representing the initial stage in the Diels–Alder reaction. The reaction is prevented from proceeding to completion by steric hindrance to a sufficiently close approach of the two molecules for bond formation, as a result of the presence of the additional methyl group on the nitrogen atom. The examination of models shows that such steric hindrance would be expected to be operative in preventing the addition of other dienophiles to thebaine methiodide, and in these cases the charge-transfer complexes are presumably insufficiently well stabilized for them to be isolated.

Neither methyl isopropenyl ketone nor crotonaldehyde gives adducts with thebaine at temperatures up to 140°, but the examination of models of the expected adducts shows that steric hindrance in the molecules is no greater than in the ketone II ($R = \text{Me}$), its 7β isomer, or its methiodide. The failure of the reaction in these cases must be attributed to steric hindrance to a sufficiently close approach of the reactants for the forma-

(10) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Constable and Co. Ltd., London, 1954, p 773.

(11) K. W. Bentley, R. Robinson, and A. E. Wain, *J. Chem. Soc.*, 958 (1952).

tion of the new bonds to C-6 and C-14, and the study of models of the reactants supports this view. With crotonaldehyde, which has the CH_3 and CHO groups in the *trans* relationship, close approach to thebaine in such a way as to ensure maximum overlap of the unsaturated centers is severely hindered by carbon atoms 15 and 16 of the nitrogen-containing ring of the alkaloid. With methyl isopropenyl ketone, the hindrance is largely between the methyl group and the hydrogen atoms at C-5 and C-15 in the base. Maleic anhydride and *p*-benzoquinone, which have *cis*-1,2-disubstituted double bonds, can easily be brought into close proximity to the diene system of thebaine and form adducts with great ease.

Of the ketones of general structure II prepared in this work and listed in the Experimental Section, several were found to be more potent as analgesics than morphine, when tested in rats by the tail pressure method and administration by the subcutaneous route. By contrast, the ester II ($\text{R} = \text{OEt}$) showed no analgesic activity at doses up to 200 mg/kg.¹²

Experimental Section

Addition of Methyl Vinyl Ketone to Thebaine. Thebaine (1000 g) was boiled under reflux with methyl vinyl ketone (3 l.) for 1 hr. The excess of unsaturated ketone was removed by distillation under reduced pressure, and the viscous residue was dissolved in boiling methanol (1200 ml). The resulting solution was cooled in ice with vigorous stirring. The crystalline solid that separated was collected, washed with ice-cold methanol, and air dried, when 7 α -acetyl-6,14-*endo*-ethenotetrahydrothebaine (II, $\text{R} = \text{Me}$) (1140 g, 93%) was obtained as white prisms, mp 119–121°, sufficiently pure for all chemical purposes, the melting point raised to 122° (lit.¹⁴ 122°) on recrystallization from methanol, ν_{max} 1715 cm^{-1} .

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4$: C, 72.4; H, 7.1. Found: C, 72.3; H, 7.1.

The hydrochloride formed white prisms, mp 262°, from ethanol.

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4 \cdot \text{HCl}$: C, 66.1; H, 6.7. Found: C, 66.4; H, 6.8.

The hydrobromide formed white prisms, mp 270°, from 90% ethanol.

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4 \cdot \text{HBr}$: C, 59.7; H, 6.1. Found: C, 59.9; H, 6.1.

The methiodide formed slowly when the base was heated under reflux with methyl iodide in acetone for 7 days. On recrystallization from aqueous ethanol it was obtained as prisms, mp 172°.

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4 \cdot \text{CH}_3\text{I} \cdot \text{H}_2\text{O}$: C, 53.3; H, 6.0. Found: C, 53.4; H, 6.2.

The mother liquors from the separation of the 7 β -acetyl compound were concentrated to 400 ml and kept at room temperature overnight, when crystalline material separated. This was collected, washed with ice-cold methanol, and dried (14 g). Thin layer chromatographic studies showed this base to comprise a mixture of about 40% of the 7 α ketone II ($\text{R} = \text{Me}$) and 60% of a less polar base. The solid was boiled under reflux with methanol (50 ml) when the more soluble 7 α ketone dissolved. The insoluble 7 β -acetyl-6,13-*endo*-ethenotetrahydrothebaine (6 g) was collected and recrystallized from ethanol, when it was obtained as white rectangular plates, mp 200–202°, subliming slowly above 180°, ν_{max} 1715 cm^{-1} .

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4$: C, 72.4; H, 7.1. Found: C, 72.4; H, 7.0.

The hydrochloride was obtained as white prisms, mp 266°, from ethanol-ether.

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4 \cdot \text{HCl}$: C, 66.1; H, 6.7. Found: C, 66.3; H, 6.8.

The hydrobromide was obtained as white prisms, mp 254°, from ethanol.

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4 \cdot \text{HBr}$: C, 59.7; H, 6.1. Found: C, 60.0; H, 6.3.

Concentration of the mother liquors from the separation of this base and from the isolation of the 7 α -7 β mixture gave a further

30 g of a mixture estimated by thin layer chromatography to contain about 70% of the 7 α ketone and 30% of the 7 β isomer, and this material was recovered unchanged in composition after boiling with, or recrystallization from, methanol. Allowing for material present in this mixture the Diels-Alder reaction affords a yield of at least 97.8% of adduct: 96.3% 7 α and 1.5% 7 β ketone.

Addition of Acrolein to Thebaine. On several occasions excellent yields (>85%) of the adduct were obtained by heating thebaine (25 g) with acrolein (75 ml) under reflux for 1 hr, removing the excess of acrolein by evaporation under reduced pressure, and crystallizing the residue from aqueous methanol. This process is, however, capricious and other reactions carried out under apparently identical conditions yielded only insoluble polymerized material from which neither adduct nor thebaine could be recovered. Neither careful purification of the reactants nor the addition of hydroquinone appeared to have any effect on the ease of polymerization. A more reliable process giving, however, a reduced yield of product was the following. A mixture of thebaine (25 g), benzene (250 ml), and acrolein (10 ml) was heated at 65–70° for 4 hr. The basic material was extracted from the benzene solution with aqueous 2 *N* acetic acid and then precipitated with ammonia. The crystalline material was collected, washed well with water, and recrystallized from aqueous methanol, when 6,14-*endo*-etheno-7 α -formyltetrahydrothebaine (II, $\text{R} = \text{H}$) (17 g) was obtained as white prisms, 106° (lit.¹⁴ 104°), ν_{max} 1730 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_4$: C, 72.0; H, 6.8. Found: C, 72.2; H, 6.9.

6,14-*endo*-Etheno-7 α -propionyltetrahydrothebaine (II, $\text{R} = \text{Et}$). Thebaine (25 g) was heated with ethyl vinyl ketone (25 g) in the presence of a small amount of hydroquinone at ~100° for 4 hr. The excess of ethyl vinyl ketone was removed under reduced pressure, and the dark viscous residue was dissolved in warm glacial acetic acid (25 ml). This solution was diluted with water (300 ml) and extracted with ether. The aqueous phase was freed from ether by boiling and basified (100 ml, 20% w/v aqueous sodium hydroxide), and the precipitate was collected, washed with water, and dried to give the adduct, mp ~40° (80%).

The base was converted into its hydrochloride with ethereal hydrogen chloride; the salt was recrystallized from ethanol (twice) and then converted into the base, mp 40–45°, with aqueous sodium hydroxide.

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_4$: C, 72.9; H, 7.4; N, 3.5. Found: C, 73.6; H, 7.6; N, 3.6.

Addition of Ethyl Acrylate to Thebaine. Thebaine (500 g) was boiled under reflux with ethyl acrylate (850 ml) for 6 hr. The excess of ethyl acrylate was removed by evaporation under reduced pressure until separation of the solid matter began. The mixture was centrifuged, the solid obtained was washed well with cold methanol, when 6,14-*endo*-etheno-7 α -ethoxycarbonyltetrahydrothebaine (500 g) was obtained as white prisms, mp 123–124°, raised to 124° by recrystallization from methanol, ν_{max} 1740 cm^{-1} .

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_6$: C, 70.0; H, 7.1. Found: C, 70.0; H, 7.3.

The hydrochloride, prepared in and recrystallized from ethanol, was obtained as white prisms, mp 258°.

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_6 \cdot \text{HCl}$: C, 64.4; H, 6.7. Found: C, 64.3; H, 6.7.

The methiodide formed slowly when the base was boiled under reflux in acetone with an excess of methyl iodide for 7 days and was obtained as white prisms, mp 240°, from ethanol.

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_6 \cdot \text{CH}_3\text{I}$: C, 54.3; H, 5.8. Found: C, 54.3; H, 5.8.

The mother liquors and methanol washings remaining after removal of the 7 α ester were evaporated under reduced pressure and the residual gum was dissolved in methanol (150 ml) and cooled in ice. The solid matter (60 g), consisting of an approximately 1:2:1 mixture of the 7 α and 7 β esters and thebaine, was crystallized twice from methanol, when 6,14-*endo*-etheno-7 β -ethoxycarbonyltetrahydrothebaine (9 g) was obtained as white prisms, mp 106–108°, ν_{max} 1740 cm^{-1} .

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_6$: C, 70.0; H, 7.1. Found: C, 69.6; H, 7.0.

The hydrochloride formed white prisms, mp 198–200°.

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_6 \cdot \text{HCl}$: Cl, 7.9. Found: Cl, 7.8.

6,14-*endo*-Ethenotetrahydrothebaine-7 α -carboxylic Acid (II, $\text{R} = \text{OH}$). 6,14-*endo*-Etheno-7 α -ethoxycarbonyltetrahydrothebaine (50 g) was heated on the water bath with concentrated hydrochloric acid (250 ml) for 3 hr. The filtered hot solution was cooled in ice and the crystalline solid that separated was collected and washed

(12) R. E. Lister, *J. Pharm. Pharmacol.*, 16, 364 (1964).

with ice-water, when the hydrochloride of the 7 α -carboxylic acid (47 g) was obtained as white prisms, mp 246–247°.

Anal. Calcd for $C_{22}H_{31}NO_4 \cdot HCl \cdot H_2O$: C, 61.6; H, 6.3. Found: C, 61.2; H, 6.7.

The free acid was obtained by continuous ether extraction of an aqueous solution of the hydrochloride adjusted to pH 6.1. Evaporation of the ether extract afforded a solid which was recovered on recrystallization from ethanol as white prisms, mp 230°.

Anal. Calcd for $C_{22}H_{31}NO_4 \cdot 1.5H_2O$: C, 64.4; H, 6.9. Found: C, 64.6; H, 6.9.

7 α -Chlorocarbonyl-6,14-endo-ethenotetrahydrothebaine Hydrochloride. 6,14-endo-Ethenotetrahydrothebaine-7-carboxylic acid hydrochloride (70 g), oxalyl chloride (25 ml), and dry benzene (250 ml) were heated together on the water bath for 2 hr. The volatile liquids were removed under reduced pressure, and the residue was heated again with oxalyl chloride (25 ml) and dry benzene (250 ml). Evaporation under reduced pressure afforded the acid chloride hydrochloride (70 g) as white prisms, mp 270° dec, sufficiently pure for further use.

Anal. Calcd for $C_{22}H_{31}NO_4Cl \cdot HCl$: Cl, 16.2. Found: Cl, 15.9, 16.5.

6,14-endo-Etheno-7 α -methoxycarbonyltetrahydrothebaine (II, R = OMe). Thebaine (5 g) and methyl acrylate (25 ml) were boiled together under reflux for 6 hr. The excess of methyl acrylate was removed under reduced pressure, and the residue was crystallized and recrystallized from methanol, when the methyl ester II (R = OMe) was obtained as white prisms, mp 148°, ν_{max} 1740 cm^{-1} .

Anal. Calcd for $C_{23}H_{37}NO_4$: C, 69.5; H, 6.9. Found: C, 69.8; H, 7.0.

Diels-Alder Addition of Acrylonitrile to Thebaine. Thebaine (100 g) was boiled under reflux with acrylonitrile (350 ml) for 3 hr. The excess of acrylonitrile was removed by evaporation under reduced pressure, and the residue was crystallized from methanol, when the adduct (95 g) was obtained as white prisms, mp 146°, raised to 148° on recrystallization. Thin layer chromatographic studies showed the adduct to consist of two components. The adduct was boiled under reflux for 5 min in methanol solution with activated charcoal (15 g); the solution was filtered and cooled in ice. The solid separating (45 g) had mp 182–188° and consisted mainly of one compound. On recrystallization of this material, 7 β -cyano-6,14-endo-ethenotetrahydrothebaine (35 g) was obtained as felted needles, mp 196–197°, ν_{max} 2230 cm^{-1} .

Anal. Calcd for $C_{22}H_{31}N_2O_2$: C, 72.4; H, 6.7; N, 7.5. Found: C, 72.4; H, 6.8; N, 7.4.

The filtrate remaining after removal of the 7 β nitrile following charcoal treatment of the adduct was evaporated and the residue found to contain principally the 7 α nitrile, which was obtained pure by partition chromatography on a Celite 545 column using heptane-methanol as the developing solvent.¹³ Two components were eluted while monitoring the eluate at 230 μ . The more polar compound was the second component to be eluted and was recovered from the eluate as plates, mp 183–184°, on recrystallization from ethanol, ν_{max} 2230 cm^{-1} . This 7 α nitrile was identical in mixture melting point and R_f value with the product of dehydration of the oxime of the 7 α aldehyde.¹⁴

Anal. Calcd for $C_{22}H_{31}N_2O_2$: C, 72.4; H, 6.7; N, 7.5. Found: C, 72.4; H, 6.9; N, 7.3.

Preparation of Ketones from the Acid Chloride II (R = Cl). **7 α -Butyryl-6,14-endo-ethenotetrahydrothebaine (II, R = *n*-Pr).** Anhydrous cadmium chloride (1.8 g) was added to a solution of *n*-propylmagnesium bromide (from 0.54 g of magnesium and 3.2 g of *n*-propyl bromide) in ether (20 ml), and the mixture was boiled under reflux for 30 min, after which the ether was removed by distillation and replaced by methylene chloride (30 ml). 7 α -Chlorocarbonyl-6,14-endo-ethenotetrahydrothebaine hydrochloride (5.0 g) in methylene chloride (20 ml) was added to the solution of dipropylcadmium, and the mixture was boiled under reflux for 1 hr, cooled, and then decomposed by the addition of cold 2 *N* hydrochloric acid (100 ml). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (50 ml). The combined methylene chloride solutions were dried and evaporated. The residue was suspended in dilute aqueous ammonia, and the suspension was extracted with ether and the extract evaporated. The residue was dissolved in benzene and the solution passed down an alumina column, with elution subsequently with benzene. The initial eluate containing the *n*-propyl ketone II

(R = *n*-Pr) was evaporated to give a glass (3.5 g), ν_{max} 1715 cm^{-1} . A portion (400 mg) of this was chromatographed in ether on thick alumina plates. The least polar band on extraction with chloroform yielded 7 β -butyryl-6,14-endo-ethenotetrahydrothebaine (4 mg), mp 128–130°, ν_{max} 1715 cm^{-1} . The immediately following band yielded 7 α -butyryl-6,14-endo-ethenotetrahydrothebaine (II, R = *n*-Pr) (320 mg), prisms, mp 84°, ν_{max} 1715 cm^{-1} .

Anal. Calcd for $C_{25}H_{35}NO_4 \cdot H_2O$: C, 70.3; H, 7.7. Found: C, 70.6; H, 7.4.

The most polar band afforded 7 α ,7'-bis[(2-ethyl-3-hydroxy-3-propyl-1-oxopropano)-6,14-endo-ethenotetrahydrothebaine] (IX, R = Et) (40 mg), ν_{max} 1715 and 3490 cm^{-1} , mp 130–133°.

Anal. Calcd for $C_{40}H_{62}N_2O_8$: C, 73.4; H, 7.6. Found: C, 73.1; H, 7.3.

By similar processes using the appropriate dialkylcadmium the following ketones were obtained: 6,14-endo-etheno-7 α -valeryl-tetrahydrothebaine (II, R = *n*-Bu, mp 87–90°, ν_{max} 1715 cm^{-1}). Anal. Calcd for $C_{25}H_{35}NO_4$: C, 73.6; H, 7.8. Found: C, 73.7; H, 8.0; 6,14-endo-etheno-7 α -isovaleryl-tetrahydrothebaine (II, R = *i*-Bu, mp 89–90°, ν_{max} 1715 cm^{-1}). Anal. Calcd for $C_{27}H_{39}NO_4$: C, 73.6; H, 7.8. Found: C, 73.4; H, 8.0; 6,14-endo-etheno-7 α -(4-methylpentanoyl)-tetrahydrothebaine (II, R = *i*-Am, mp 98–100°, ν_{max} 1715 cm^{-1}). Anal. Calcd for $C_{27}H_{39}NO_4$: C, 74.2; H, 8.0. Found: C, 74.2; H, 8.3).

Preparation of Ketones from the Ester II (R = OEt). **6,14-endo-Etheno-7 α -propionyl-tetrahydrothebaine (II, R = Et).** 6,14-endo-Etheno-7 α -ethoxycarbonyltetrahydrothebaine (10 g) was extracted from a Soxhlet extractor into a solution of ethylmagnesium bromide, prepared from magnesium (1.67 g), ethyl bromide (7.7 g), and ether (100 ml). The mixture was boiled under reflux for 2 hr and poured into aqueous ammonium chloride. The ether layer was separated, dried, and evaporated, when a viscous gum was obtained. This was triturated with cold methanol, and the solid so obtained was collected. (This was identified as a tertiary carbinol and is described in the following paper.) The methanol solution was acidified with dilute hydrochloric acid and poured into an excess of 2 *N* aqueous sodium hydroxide to give a yellow solution containing some insoluble matter. The insoluble matter (0.4 g) was collected and recrystallized from methanol, when the 7 α -propionyl compound II (R = Et) was obtained as prisms, mp 42–45°, identical with the material obtained by the addition of ethyl vinyl ketone to thebaine (see above).

By similar processes, using the appropriate alkyl halide, the following ketones were prepared from the ester: 7 α -butyryl-6,14-endo-ethenotetrahydrothebaine (mp 84°, identical with the base obtained from the acid chloride II (R = Cl) and propylcadmium); 6,14-endo-etheno-7 α -oentanlyl-tetrahydrothebaine (II, R = C_5H_{11} , prisms, mp 210°, yield 6%, ν_{max} 1713 cm^{-1}). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.4; H, 8.2. Found: C, 74.1; H, 8.4; 6,14-endo-etheno-7 α -vinylacetyl-tetrahydrothebaine (II, R = $CH_2CH=CH_2$, prisms, mp 99°, from aqueous methanol, yield 5%, ν_{max} 1710 cm^{-1}). Anal. Calcd for $C_{25}H_{35}NO_4 \cdot 1.5H_2O$: C, 69.2; H, 7.4. Found: C, 69.2; H, 7.7; 6,14-endo-etheno-7 α -tetrahydrofuryl-acetyl-tetrahydrothebaine (II, R = $CH_2C_4H_7O$, prisms, mp 125°, from aqueous ethanol, yield 6%, ν_{max} 1710 cm^{-1}). Anal. Calcd for $C_{27}H_{33}NO_5 \cdot H_2O$: C, 69.0; H, 7.4. Found: C, 68.7; H, 7.1; 6,14-endo-etheno-7 α -(3-tetrahydrofurylbutyryl)-tetrahydrothebaine (II, R = $CH_2CH_2CH_2C_4H_7O$, prisms, mp 98°, from aqueous methanol, yield 4%, ν_{max} 1710 cm^{-1}). Anal. Calcd for $C_{29}H_{37}NO_5 \cdot 2H_2O$: C, 67.6; H, 8.0. Found: C, 67.9; H, 8.2; 7 α -cyclohexylcarbonyl-6,14-endo-ethenotetrahydrothebaine (II, R = C_6H_{11} , prisms, mp 130°, from aqueous methanol, yield 7%, ν_{max} 1713 cm^{-1}). Anal. Calcd for $C_{28}H_{35}NO_4 \cdot 3H_2O$: C, 66.8; H, 8.1. Found: C, 66.9; H, 7.8).

Preparation of Ketones from the Nitrile III. **Nepenthone (II, R = Ph).** The Diels-Alder adduct of thebaine and acrylonitrile (mixture of 7 α and 7 β forms) (10 g) in dry ether (400 ml) was slowly added to a boiling stirred solution of phenylmagnesium bromide, prepared from magnesium (1.67 g) and bromobenzene (11 g) in ether (250 ml). The mixture was boiled under reflux with stirring for 5 hr, and then poured into aqueous ammonium chloride. The ether layer was separated, dried, and evaporated, leaving a solid residue, which was heated on the water bath for 30 min with 2 *N* hydrochloric acid (150 ml). The acid solution was poured into an excess of aqueous sodium hydroxide, and the precipitated base was isolated by ether extraction. Evaporation of the extract afforded a viscous residue, which crystallized in part on trituration with methanol. The solid was collected and recrystallized, when nepenthone (1.1 g) was obtained as prisms, mp 155°, alone or mixed with an authentic specimen.

(13) We are indebted to Dr. J. J. Brown, Miss C. T. Nora, and Mr. C. Piddacks for details of this separation of the pure 7 α and 7 β isomers.

Anal. Calcd for $C_{26}H_{29}NO_4$: C, 75.8; H, 6.6. Found: C, 75.6; H, 6.5.

In a similar manner, the following ketones were prepared in poor yield from *o*- and *p*-tolylmagnesium bromide: 6,14-*endo*-tetrahydrothebaine-7 α -(2-methylbenzoyl)tetrahydrothebaine (prisms, mp 223°, ν_{\max} 1690 cm^{-1} . *Anal.* Calcd for $C_{29}H_{31}NO_4$: C, 76.1; H, 6.8. Found: C, 75.7; H, 7.1); 6,14-*endo*-etheno-7 α -(4-methylbenzoyl)tetrahydrothebaine (prisms, mp 196°, ν_{\max} 1690 cm^{-1} . *Anal.* Calcd for $C_{29}H_{31}NO_4$: C, 76.1; H, 6.8. Found: C, 75.8; H, 6.7).

7 α ,7' α -Bis(1-hydroxy-1-methyl-3-oxopropano)-6,14-*endo*-etheno-tetrahydrothebaine (IX, R = H). 7 α -Acetyl-6,14-*endo*-etheno-tetrahydrothebaine (II, R = Me) (5 g) in anhydrous benzene (20 ml) was added with vigorous stirring to a solution of anhydrous magnesium iodide (3.6 g) in ether (50 ml) and benzene (20 ml) at room temperature. A white precipitate formed almost immediately. After 15 min the mixture was decomposed by the addition of aqueous ammonium chloride. The ether-benzene layer was separated, dried, and evaporated, when a viscous gum was obtained. Chromatographic separation of this product on silica plates using a system of a 7:4:1 mixture of ethyl acetate, 2-propanol, and water showed it to contain three components in the ratio of approximately 3:6:1. Preparative plate chromatography using the same system afforded specimens of the two major components. The component with greatest R_f value (30%) was identified as 7 α -acetyl-6,14-*endo*-ethenotetrahydrothebaine (II, R = Me). The 60% component (intermediate R_f value) was obtained as off-white prisms, mp 150–151°, from methanol, ν_{\max} 1715 and 3490 cm^{-1} , and was identified as 7 α ,7' α -bis(1-hydroxy-1-methyl-3-oxopropano)-6,14-*endo*-ethenotetrahydrothebaine (IX, R = H).

Anal. Calcd for $C_{40}H_{44}N_2O_8$: C, 72.4; H, 7.1. Found: C, 72.3; H, 7.0.

Separation of this ketol was also achieved on alumina plates using ether as solvent, and from these plates the minor component (10%) was also isolated. This has been identified as a product of rearrangement of the ketone II (R = Me) and is described in detail in another publication.⁷

7 α ,7' α -Bis(1-methyl-3-oxoprop-1-eno)-6,14-*endo*-ethenotetrahydrothebaine. Repeated chromatographic purification of the ketol XVI on alumina plates in ether solution led to the isolation also of a small quantity of a new base, mp 234°, ν_{\max} 1690 cm^{-1} . This was also obtained by heating the ketol (70 mg) with 98–100% formic acid (1 ml) at 100° for 10 min. The solution was diluted with water, basified with ammonia, and extracted with ether, when the unsaturated ketone (50 mg) was obtained as white prisms, mp 234°, from methanol.

Anal. Calcd for $C_{40}H_{42}N_2O_7$: C, 74.2; H, 7.0. Found: C, 74.0; H, 7.1.

Charge-Transfer Complex, Thebaine Methiodide–Benzoquinone. Thebaine methiodide (5 g) and benzoquinone (1.5 g) were heated on the water bath in chloroform (25 ml) until separation of an orange crystalline solid began. The mixture was cooled, and the orange complex was collected (5.0 g), mp 205–206°, on rapid heating (lit.¹¹ mp 205°).

Reduction of Complex. A solution of sodium borohydride (0.1 g) in water (2 ml) was added to a warm stirred solution of the complex (1 g) in ethanol (15 ml). A transient violet color developed, and the solution rapidly became almost colorless. On cooling the solution, thebaine methiodide (0.6 g), mp 224°, was recovered, and on filtration and dilution of the solution with dilute ammonium chloride hydroquinone (0.12 g), mp 170°, was obtained.

Similar results were obtained when the complex in aqueous ethanol was reduced with sulfur dioxide.

Acknowledgments. The authors wish to thank Dr. D. E. Webster of the University of Hull, England, for the determination of nmr spectra, Mr. A. C. Young for chromatographic studies on thin and thick layer plates, and the following for experimental assistance: Mr. J. Fulstow, Mr. J. F. Saville, Mr. N. M. Scollick, Mrs. E. W. Walker, Mr. G. R. Young, and the late Mr. S. R. Duff.

Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. II.¹ Alcohols Derived from 6,14-*endo*-Etheno- and 6,14-*endo*-Ethanotetrahydrothebaine

K. W. Bentley, D. G. Hardy, and B. Meek

Contribution from the Research Laboratories, Reckitt and Sons Ltd., Kingston-upon-Hull, England. Received September 26, 1966

Abstract: A series of secondary and tertiary alcohols have been prepared by the reduction and reaction with Grignard reagents of the aldehyde I (R = H), the ketones I (R = Me, Et, *n*-Pr, and Ph), and their 6,14-ethano analogs. The stereospecificity of the reactions is explained. In this way analgesics of very high potency, up to 500 times that of morphine, have been obtained.

The high analgesic activity of the ketone I (R = Me) and its C-7 epimer, reported in the preceding paper, contrasts with the inactivity of the related esters I (R = OMe or OEt). The effects on the activity of further modifications of the keto group, involving removal of the electron deficiency at the carbon atom, were accordingly studied. Reduction of the ketone I (R = Me) with aluminum isopropoxide affords a product consisting of 95% of one isomer of the secondary alcohol II (R = H, R' = Me), whereas reduction with

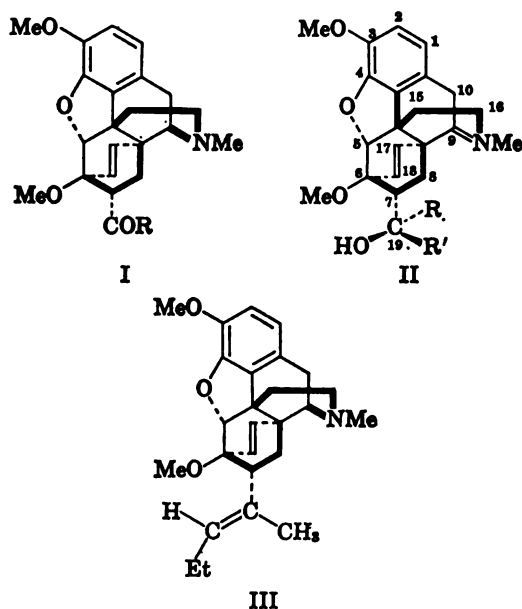
sodium borohydride yields an approximately 1:1 mixture of this and the diastereoisomeric alcohol II (R = Me, R' = H), which was resolved into its components by preparative thin layer chromatography. Since there is more or less free rotation about the bond linking the carbonyl group to C-7, both sides of this group are almost equally accessible to attack by a hydride ion, but in the Meerwein–Ponndorf reduction, which proceeds through hydrogen transfer in a cyclic transition state,² steric hindrance in the transition state results in the preferential transfer of hydrogen to one

(1) (a) Part I: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3267 (1967). (b) A preliminary report of part of this work has been made by K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1963). (c) This work is covered by British Patent 925,723.

(2) L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 2641 (1949).

side of the carbonyl group. The examination of models of such a six-membered transition state (see below) shows that steric hindrance is least in the arrangement that leads to the alcohol II ($R = H$, $R' = Me$).

An excess of methylmagnesium iodide converts the ketone I ($R = Me$) in high yield into the tertiary alcohol II ($R = R' = Me$), which is also readily prepared from the esters I ($R = OMe$ or OEt), and the nmr spectrum of this alcohol shows that the stereochemical disposition of groups at C-7 is the same as that in the parent ketone.^{3a} The tertiary alcohol epimeric at C-7 with II ($R = R' = Me$) was prepared in the same way from the 7 β isomer of the ketone I ($R = Me$). The carbinols prepared in this way were all found to be potent analgesics. Accordingly, the variation in analgesic activity within a series of alcohols of general structure II was studied, and during the course of this work many compounds were obtained with analgesic activities never previously approached in the morphine series, in which hitherto the most active members have been 14-acetoxymorphine⁴ and 5-methyldihydromorphine,⁵ both of which are about 12 times as active as morphine.



The alcohols of general structure II were prepared by the action of Grignard reagents or lithium alkyls on the aldehyde I ($R = H$), the ketones I ($R = Me$, Et , n -Pr, and Ph), and the ester I ($R = OEt$). The reactions of the ketones I with Grignard reagents $R'MgX$ are generally complex and lead to the formation of a number of products resulting from the following processes: (a) normal Grignard reaction with $R'MgX$ to give the tertiary carbinol II (major reaction); (b) normal Grignard reaction with $R'MgX$ to give the tertiary alcohol diastereoisomeric with II (minor reaction); (c) Grignard reduction where possible, *i.e.*, when R' contains a β -hydrogen atom, to give the secondary alcohol II ($R' = H$) (major reaction in many

cases);^{6a} (d) Grignard reduction to give the diastereoisomeric secondary alcohol II ($R = H$) (minor reaction); and (e) base-catalyzed rearrangement of the ketone followed by Grignard reaction at the carbonyl group (minor reaction). Of these processes the base-catalyzed rearrangement is of minor importance and will be discussed in detail together with other topics in a subsequent communication.^{6b}

The normal Grignard reaction in this series shows a remarkably high degree of stereoselectivity, and in those cases in which Grignard reduction does not compete with the normal reaction a high yield of an almost pure diastereoisomer of the tertiary carbinol is obtained. For example, the ketone I ($R = Me$) with phenylmagnesium bromide afforded almost entirely the alcohol II ($R = Me$, $R' = Ph$), whereas the diastereoisomeric alcohol II ($R = Ph$, $R' = Me$) was the almost sole product of the action of methylmagnesium iodide on the phenyl ketone I ($R = Ph$). The presence of a trace of the second isomer in the product in each case was demonstrated by thin layer chromatography. The stereochemical assignments of structures to these isomeric carbinols, at first tentatively made after a study of models, were rigorously confirmed by nmr spectroscopic studies.^{3a}

Similarly the tertiary carbinol II ($R = Me$, $R' = n$ -Pr), resulting from the normal Grignard reaction of *n*-propylmagnesium iodide with the methyl ketone I ($R = Me$), is diastereoisomeric with the principal product II ($R = n$ -Pr, $R' = Me$) of the interaction of methylmagnesium iodide and the *n*-propyl ketone I ($R = n$ -Pr). The seat of the isomerism was clearly shown in this case to be the alcoholic group since both carbinols were dehydrated to the same olefin III, which gave propionaldehyde on ozonolysis.⁷ The structure of the carbinol II ($R = Me$, $R' = n$ -Pr) has been confirmed by X-ray crystallographic analysis of the hydrobromide.^{3b}

Grignard reduction is, where possible, a process seriously competitive with the normal Grignard reaction, and in some cases accounts for up to 30% of the total product. Like the normal reaction, it shows a remarkably high degree of stereoselectivity, and the product consists almost entirely of the alcohol II ($R' = H$), though the presence of about 5% of the diastereoisomer II ($R = H$) can be detected on thin layer chromatographic plates. Both the Grignard and Meerwein-Ponndorf reduction processes are generally believed to proceed by hydrogen transfer in similarly constituted transition states,^{2,8} IV and V, and might thus in the case of the ketone I ($R = Me$) be expected to lead to the same product. This expectation is not borne out in practice.

Grignard reduction of the ketone with *n*-propyl- or isobutylmagnesium halides affords the secondary alcohol diastereoisomeric with that obtained in the Meerwein-Ponndorf reduction, and identical with the

(3) (a) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. H. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89**, 3322 (1967); (b) J. H. van den Hende and R. Nelson, private communication; *J. Am. Chem. Soc.*, **89**, 2901 (1967).

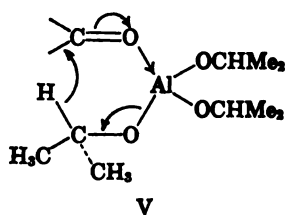
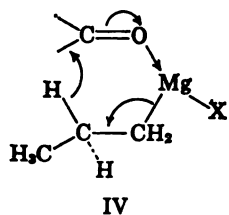
(4) R. E. Lutz and L. F. Small, *J. Org. Chem.*, **4**, 220 (1939).

(5) L. F. Small, H. M. Fitch, and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936); G. Stork and L. Bauer, *ibid.*, **75**, 4373 (1953).

(6) (a) This reaction was first reported to us by C. F. Howell, J. I. Brown, W. Fulmor, G. O. Morton, and R. A. Hardy, Jr., of Lederle Laboratories, Pearl River, N. Y., whom we thank also for much helpful discussion of the mechanisms of the reaction of the ketones I with Grignard reagents. (b) Part VI: K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddelsey, and P. A. Mayor, *J. Am. Chem. Soc.*, **89**, 3312 (1967).

(7) Part IV: K. W. Bentley, D. G. Hardy, and B. Meek, *ibid.*, **89**, 3293 (1967).

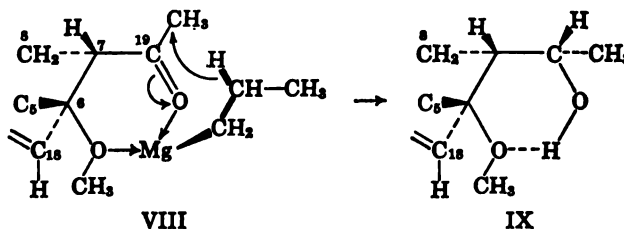
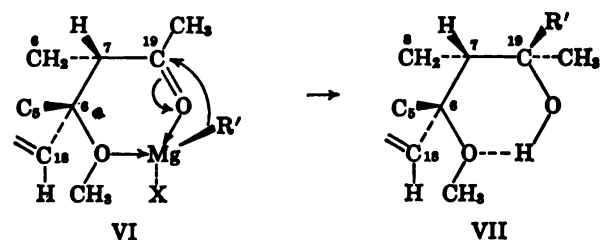
(8) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Constable and Co. Ltd., London, 1954, p 147.



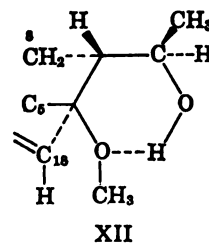
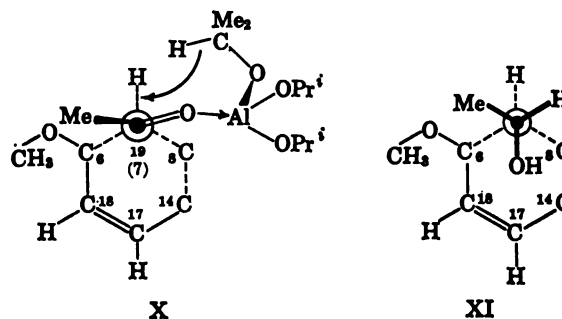
second component of the product of reduction of the ketone with sodium borohydride. If the Meerwein-Pondorff reduction leads, as postulated above, to the alcohol II ($R = H$, $R' = Me$), the product of Grignard reduction must have the structure II ($R = Me$, $R' = H$), and these structural assignments have been confirmed in the following way. The Meerwein-Pondorff reaction product in chloroform solution shows hydroxyl absorption at 3504 cm^{-1} , indicating strong hydrogen bonding between the hydroxyl and the spatially proximate C-6 methoxyl group, which results in an arrangement involving disposition of the hydrogen atom in the carbinol system of the alcohol II ($R = H$, $R' = Me$) "downward" toward the 6,14-etheno bridge. In agreement with such a representation, in which steric hindrance of the etheno bridge is minimal, this alcohol is very readily hydrogenated at room temperature and pressure. Hydrogen bonding of a similar kind in the isomeric alcohol II ($R = Me$, $R' = H$) would, however, involve disposition of the larger CH_3 group "downward" toward the etheno bridge, and this would be expected to result in some hindrance to hydrogenation of the bridge and also to a weakening of the hydrogen bond or even to the establishment of an alternative arrangement with a weak bond between the hydroxyl group and the π orbitals of the etheno bridge. In agreement with this, the Grignard reduction product of the ketone I ($R = Me$) is resistant to hydrogenation at room temperature, and shows hydroxyl absorption at 3540 cm^{-1} (weaker hydrogen bond than in the isomeric carbinol) and also at 3605 cm^{-1} (feeble bond to the etheno bridge).

Thus, both Grignard reaction with and Grignard reduction of the ketone I ($R = Me$) afford products belonging to the same stereochemical series II ($R = Me$). This asymmetric induction may be explained on the basis of a model similar to those outlined by Cram and his co-workers.⁹ If the Cram five-membered transition state is replaced in this series by a six-membered intermediate in which a complex is formed by coordination of the magnesium atom with oxygen atoms of both C-7 carbonyl and C-6 methoxyl groups (thus completing the outer electron shell of the magnesium), then an inspection of models shows that "top-side" approach of the group R' to the carbonyl carbon, as depicted in VI, leading to VII is much less hindered than approach from below (the vicinity of the 6,14-etheno bridge). In the same complex, if the group R' is one in which β -hydrogen transfer can occur then Grignard reduction (VIII) would lead to alcohol IX [identical with the complete structure II ($R = Me$, $R' = H$)] belonging to the same stereochemical series as the products of the normal reaction.

In the Meerwein-Pondorff reduction, however, the aluminum atom can complete its valency shell by co-



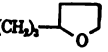

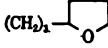
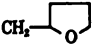
ordination with the carbonyl oxygen atom alone, and the establishment of a more rigid cyclic arrangement involving the C-6 methoxyl group is not necessary. In such a case, free rotation about the carbonyl-C-7 bond is still possible and hydrogen transfer in the complex would be expected to occur with the groups in the disposition involving least steric hindrance. This arrangement is that in which the coordinated carbonyl group is most remote from the group with the greatest effective size, namely the C-6 methoxyl group. This arrangement is shown in part structure X, which is a Newman projection of part of the ketone I ($R = Me$) looking along the line of the carbonyl-C-7 bond, and least hindered hydrogen transfer to the carbonyl group would occur as shown, from above, to give the secondary alcohol XI which is identical with XII. This alcohol is diastereoisomeric with that obtained by Grignard reduction, and is represented in full by structure II ($R = H$, $R' = Me$).



The reaction of the ketone I ($R = Me$) with lithium alkyls involves, in the cases studied, more base-catalyzed rearrangement than does the reaction with Grignard reagents, but this still remains a minor side reaction ($<10\%$), and the formation of tertiary carbinol is somewhat less stereoselective. Secondary alcohol formation is not observed, however, and in those cases in which Grignard reduction is troublesome the use of the corresponding lithium alkyl is to be preferred.

(9) D. J. Cram, F. Ahmed, and A. Elhatez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

Table I. Alcohols of Structure II

R	R'	Mp, °C	Composition	Calcd, % C	H	Found, % C	H	Mp, °C, HCl	Molar potency ^a
H	Me	82	C ₂₂ H ₂₉ NO ₄	72.1	7.6	72.0	7.5	210	1.0
Me	H	81	C ₂₃ H ₃₁ NO ₄	72.1	7.6	71.8	8.0	240	0.9
H	Et	...	C ₂₄ H ₃₃ NO ₄ ·HBr·3H ₂ O ^b	54.3	7.1	54.6	7.1	90 ^b	0.8
H	<i>n</i> -Pr	...	C ₂₅ H ₃₅ NO ₄ ·C ₄ H ₉ O ₆ ·3H ₂ O ^c	56.5	7.1	56.4	7.1	176 ^c	5.3
H	<i>n</i> -C ₈ H ₁₇	78	C ₃₀ H ₄₃ NO ₄	74.9	8.9	74.6	8.6	155 ^c	0.2
H	Ph	210	C ₂₈ H ₃₁ NO ₄	75.4	7.1	75.6	7.1		0.01
H	CH ₂ Ph	95	C ₂₉ H ₃₃ NO ₄	75.8	7.2	75.6	7.3	125 ^c	7.6
H	CH ₂ CH ₂ Ph	80	C ₃₀ H ₃₅ NO ₄	76.0	7.4	75.6	7.4	166	80
H	(CH ₂) ₃ OEt	...	C ₂₇ H ₃₇ NO·C ₄ H ₉ O ₆ ·3H ₂ O ^c	56.9	7.5	56.8	7.2	100 ^c	12
H		114	C ₂₅ H ₃₉ NO ₅	69.8	8.2	70.0	8.1		24
H		98	C ₂₉ H ₃₇ NO ₄	74.4	8.3	74.1	8.3		9.0
Me	Me	166	C ₂₄ H ₃₁ NO ₄	72.5	7.9	72.5	7.7	221	2.7
Me	Et	74 (132)	C ₂₅ H ₃₃ NO ₄	73.1	8.1	72.9	8.1	245	20
Et	Me	165	C ₂₅ H ₃₃ NO ₄	73.1	8.1	72.9	8.2		
Me	<i>n</i> -Pr	176	C ₂₆ H ₃₅ NO ₄	73.3	8.2	73.3	8.2	217	96
<i>n</i> -Pr	Me	148	C ₂₆ H ₃₅ NO ₄	73.3	8.2	73.2	8.4		
Me	<i>i</i> -Pr	165	C ₂₆ H ₃₅ NO ₄	73.3	8.2	73.0	8.3	218	10
Me	<i>n</i> -Bu	150	C ₂₇ H ₃₇ NO ₄	73.8	8.4	73.9	8.4		24
Me	<i>i</i> -Bu	150	C ₂₇ H ₃₇ NO ₄	73.8	8.4	73.8	8.6	188	2.5
Me	<i>t</i> -Bu	216	C ₂₇ H ₃₇ NO ₄	73.8	8.4	73.8	8.5		0.1
Me	<i>n</i> -Am	103	C ₂₈ H ₃₉ NO ₄	74.1	8.6	73.8	8.4	250	15
Me	<i>i</i> -Am	126	C ₂₈ H ₃₉ NO ₄	74.1	8.6	74.0	8.4	258	30
Me	<i>t</i> -Am	...	C ₂₈ H ₃₉ NO ₄ ·HCl·2H ₂ O	64.0	8.4	63.8	8.2	188	0.6
Me	<i>n</i> -C ₈ H ₁₃	...	C ₂₉ H ₄₁ NO ₄ ·HCl·3H ₂ O	63.0	8.7	62.7	8.7	270	2.0
Me	<i>n</i> -C ₇ H ₁₅	...	C ₃₀ H ₄₃ NO ₄ ·HCl·2H ₂ O	64.9	8.6	65.0	8.6	256	1.2
Me	<i>n</i> -C ₈ H ₁₇	...	C ₃₁ H ₄₅ NO ₄	75.5	9.1	75.3	8.9	262	0.3
Me	Ph	208	C ₂₉ H ₃₃ NO ₄	75.8	7.2	75.5	7.2	194	0.07
Ph	Me	152	C ₂₉ H ₃₃ NO ₄	75.8	7.2	75.6	7.2	230	0.09
Me	CH ₂ Ph	187	C ₃₀ H ₃₅ NO ₄	76.1	7.4	76.1	7.3		150
Me	(CH ₂) ₃ Ph	146	C ₃₁ H ₃₇ NO ₄	76.4	7.6	76.1	7.8	236	500
Me	(CH ₂) ₃ Ph	94	C ₂₇ H ₃₉ NO ₄ ·2H ₂ O	72.3	8.0	72.5	7.9	235	2.1
Me	<i>o</i> -Tolyl	239	C ₃₀ H ₃₅ NO ₄	76.1	7.4	76.1	7.3	190	0.15
Me	<i>p</i> -Tolyl	197	C ₃₀ H ₃₅ NO ₄	76.1	7.4	76.0	7.4	250	0.10
Me	CH ₂ C ₆ H ₄ F- <i>p</i>	148	C ₃₀ H ₃₅ FNO ₄	73.3	7.0	73.0	7.3		
Me	CH ₂ C ₆ H ₄ Cl- <i>p</i>	180	C ₃₀ H ₃₅ ClNO ₄	70.9	6.1	70.7	6.9		
Me	CH ₂ C ₆ H ₄ OMe- <i>p</i>	117	C ₃₁ H ₃₇ NO ₄ ·H ₂ O	71.6	7.5	71.8	7.3		1.5
Me	CH ₂ =CHPh	92	C ₃₁ H ₃₅ NO ₄ ·HCl	71.2	7.1	71.2	6.9	248	4.0
Me	CH=CH ₂	155	C ₂₅ H ₃₁ NO ₄	73.3	7.6	73.3	7.6		1.4
Me	C≡CH	186	C ₂₅ H ₂₉ NO ₄	73.7	7.1	73.6	7.2		0.2
Me	CH ₂ CH=CH ₂	160	C ₂₅ H ₃₁ NO ₄	73.6	7.8	73.6	7.8	260	0.41
Me	Cyclohexyl	201	C ₂₉ H ₃₉ NO ₄	74.8	8.4	74.8	8.3	202	59
Me	Cyclopentyl	86	C ₂₈ H ₃₇ NO ₄	74.6	8.2	74.3	8.0	240	1.0
Me	(CH ₂) ₃ OEt	107	C ₂₈ H ₃₉ NO ₄ ·2H ₂ O	66.5	8.5	66.3	8.3	248	6.0
Me	(CH ₂) ₃ OPh	221	C ₃₁ H ₄₁ NO ₄ ·5H ₂ O	73.3	7.8	73.1	7.5	260	0.05
Me		128	C ₃₀ H ₄₁ NO ₅	72.5	8.6	72.6	8.4	185	92
Me		140	C ₂₈ H ₃₇ NO ₅	71.1	8.1	71.0	8.0		
Et	Et	152	C ₂₆ H ₃₃ NO ₄	73.3	8.1	73.0	8.0	130	2.5
Et	Ph	166	C ₃₀ H ₃₅ NO ₄	76.1	7.4	76.2	7.4		
<i>n</i> -Pr	<i>n</i> -Pr	209	C ₂₈ H ₃₅ NO ₄	74.2	8.7	73.9	8.7	186	3.1
<i>n</i> -Bu	<i>n</i> -Bu	...	C ₃₀ H ₄₁ NO ₄ ·C ₄ H ₉ O ₆ ·2H ₂ O ^c	61.1	7.9	61.2	7.8	62 ^c	3.0
CH ₂ Ph	CH ₂ Ph	190	C ₃₀ H ₃₉ NO ₄	78.7	7.2	78.5	7.2	190	0
Ph	Ph	220	C ₃₄ H ₄₅ NO ₄	78.2	6.7	77.9	6.7	266	0
Ph	<i>n</i> -Pr	177	C ₃₁ H ₃₇ NO ₄	76.5	7.6	76.2	7.6	210	0.2
Ph	CH ₂ Ph	210	C ₃₂ H ₃₉ NO ₄	78.5	6.9	78.3	7.0	220	0
Ph	Cyclohexyl	232	C ₃₄ H ₄₁ NO ₄	77.6	7.8	77.3	7.9	239	0.04
Ph	CH ₂ CH=CH ₂	217	C ₃₁ H ₃₅ NO ₄	76.6	7.2	76.5	7.0		0.53

^a Morphine = 1. ^b Hydrobromide. ^c Bitartrate.

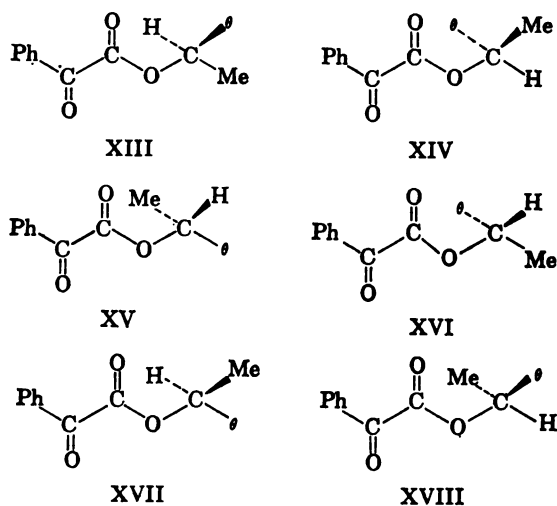
The alcohols of general structure II prepared in this way are listed, together with their analgesic potencies, in Table I. The analgesic activities were determined by the tail pressure method in rats, with administration of the compounds usually as their hydrochlorides in aqueous solution by the subcutaneous route, and this

work will be reported in detail elsewhere, together with the results of other pharmacological studies.¹⁰ The highest activities are observed in those alcohols in which there is a moderate disparity in size between R and R',

(10) Some details are briefly given by R. E. Lister, *J. Pharm. Pharmacol.*, 16, 364 (1964).

and in homologous series in which the group R remains constants as a hydrogen atom or a methyl group peak activity is reached when R' has a size equivalent to that of a three to five carbon chain, and further lengthening of the chain results in a steady decrease in activity. The preferred constant substituent R is a methyl group, and the most potent analgesic in this series is the alcohol II (R = Me, R' = CH₂CH₂Ph).

The alcoholic hydroxyl group of the secondary alcohols was readily esterified, but this modification has little effect on the analgesic potency. The tertiary alcohols, however, are very resistant to esterification. The two diastereoisomeric secondary alcohols II (R = H, R' = Me and R = Me, R' = H) were esterified with phenylglyoxalyl chloride and, following Prelog's method,¹¹ the resulting esters were treated with methylmagnesium iodide and the products hydrolyzed to atrolactic acid. With the alcohol II (R = H, R' = Me), the three conformations of the phenylglyoxalyl ester are XIII, XIV, and XV, in which θ represents the tetrahydrothebaine unit, and in these the size of groups is in the order $\theta > \text{Me} > \text{H}$ and, as in the cases studied by Prelog, attack by the Grignard reagent on XIII would be from below and on XIV and XV would be from above. However, the examination of models of

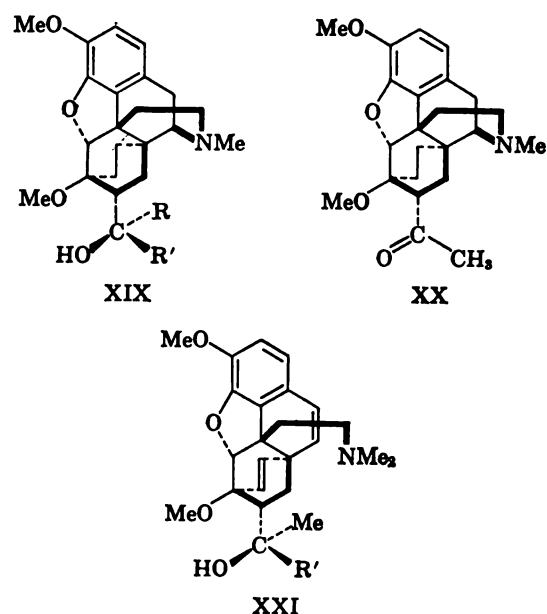


these three conformations reveals that nonbonded interactions are very much less in the form represented by XIII than in the other two, and the ester would be expected to adopt predominantly this form, attack of which by the Grignard reagent would lead, after hydrolysis, to an excess of (+)-atrolactic acid. With the ester from the diastereoisomeric alcohol II (R = Me, R' = H) the conformation XVI would be expected to be heavily favored over XVII and XVIII, and the same process with this ester would be expected to lead to an excess of (–)-atrolactic acid. In this event this sequence of reactions on the alcohol obtained by Meerwein-Ponndorf reduction of the ketone I (R = Me) gave atrolactic acid, $[\alpha]^{20D} +4.8^\circ$, whereas the product of Grignard reduction of the ketone in the same way afforded atrolactic acid, $[\alpha]^{20D} -5.4^\circ$, and these results support the structures assigned above to these bases.

O-Alkylation of the tertiary alcohols was also very difficult, but the base II (R = R' = Me) was methylated with potassium amide and methyl iodide in liquid ammonia to its methyl ether. Other attempted alkylations of this

base and the methylation of other tertiary alcohols in the series proved unsuccessful.


Catalytic reduction of the tertiary alcohols was in all cases achieved only at elevated temperature and pressure. Hydrogen bonding between the hydroxyl and C-6 methoxyl groups results in conformations in which one or the other of the alkyl groups R and R' in structure II is disposed in the direction of the 6,14-etheno bridge, with consequent hindrance of the approach of this bridge to the catalyst surface. Reduction is achieved over Raney nickel catalyst at 160–170° (200 atm) to give bases of general structure XIX. These 6,14-etheno alcohols are also preparable from the 6,14-ethano ketone XX which is obtained from the etheno ketone I (R = Me) by reduction under milder conditions. The effect of the COCH₃ group in the ketone I (R = Me) in shielding the etheno bridge is much less than the effect of the alcoholic group in the hydrogen-bonded alcohols II, and since the shielding effect on the etheno bridge of the smaller CHO group is even less than that of the COCH₃ group, the aldehyde I (R = H) can be reduced under even milder conditions. In the 7 β -acetyl compound, the COCH₃ group is disposed on the side of the molecule opposite to the etheno bridge, hydrogenation of which is accordingly unhindered, and this base can be rapidly reduced at room temperature. The Grignard reaction with the 6,14-ethano ketone XX in general follows the same pattern as that with the etheno analog II (R = Me), giving rise to tertiary carbinol XIX, secondary carbinol as a result of Grignard reduction, and base-catalyzed rearrangement. Base-catalyzed rearrangement is generally more important in this than in the etheno series, and on occasions accounts for up to 30% of the product.^{6b} The normal Grignard reaction displays the same stereospecificity as in the 6,14-etheno series. The 6,14-ethano alcohols XIX prepared by these methods are listed in Table II.



As in the parent Diels–Alder adducts I (R = Me and OEt), quaternary salt formation with the alcohols II proceeded only very slowly, good yields being obtained only after several days under reflux with methyl iodide in acetone. In the cases examined, Hofmann degra-

(11) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

Table II. Alcohols of Structure XIX

R	R'	Mp, °C	Composition	Calcd, %		Found, %		Molar potency*
				C	H	C	H	
H	H	124	C ₂₅ H ₂₉ NO ₄	71.1	7.9	71.0	8.0	
H	Me	51	C ₂₆ H ₃₁ NO ₄	71.6	8.1	71.5	8.2	
Me	Me	142	C ₂₇ H ₃₃ NO ₄	72.1	8.3	71.9	8.2	2.9
Me	Et	146	C ₂₈ H ₃₅ NO ₄	72.6	8.5	72.6	8.3	
Me	<i>n</i> -Pr	187	C ₂₉ H ₃₇ NO ₄	73.1	8.7	72.8	9.1	
Me	<i>i</i> -Pr	158	C ₂₈ H ₃₇ NO ₄	73.1	8.7	73.4	8.7	34
Me	<i>n</i> -Bu	147	C ₂₉ H ₃₉ NO ₄	73.4	8.9	73.5	8.9	240
Me	<i>sec</i> -Bu	164	C ₂₇ H ₃₉ NO ₄	73.4	8.9	73.1	8.8	
Me	<i>i</i> -Bu	170	C ₂₇ H ₃₉ NO ₄	73.4	8.9	73.3	8.9	20
Me	<i>t</i> -Bu	188	C ₂₇ H ₃₉ NO ₄	73.4	8.9	73.2	9.0	30
Me	<i>n</i> -Am	113	C ₂₈ H ₄₁ NO ₄	73.8	9.1	73.6	9.6	36
Me	<i>i</i> -Am	126	C ₂₈ H ₄₁ NO ₄	73.8	9.1	73.6	9.0	150
Me	CH ₂ Ph	146	C ₃₀ H ₃₇ NO ₄	75.8	7.8	75.6	8.0	110
Me	Ph	202	C ₂₉ H ₃₅ NO ₄	75.5	7.6	75.0	7.7	0
Me		195	C ₂₉ H ₄₁ NO ₄	74.5	8.8	74.4	9.1	15

* Morphine = 1.

dation of the quaternary salts proceeded very readily to give the expected methine bases XXI.

Nomenclature. The systematic nomenclature for the bases in this series, based on the 6,14-*endo*-ethenotetrahydrothebaine system, is cumbersome and, since many degradation and rearrangement products of thebaine, codeine, and morphine already have simple trivial names, a simpler system, based on a trivial name for a key intermediate, would be an advantage. The trivial name *nepenthone* was assigned to the phenyl ketone I (R = Ph) in order to facilitate the naming of derivatives. The intermediates that have been most widely used in this work are the aldehyde I (R = H) and the ketones I (R = Me and Ph) and of these the ketone I (R = Me) is much the most active as an analgesic and gives rise to a very wide series of alcohols of structure II (R = Me) of high activity. These alcohols are more easily prepared and of much greater pharmacological interest than the corresponding bases II (R ≠ Me). Accordingly, a trivial name has been assigned to the ketone I (R = Me). This ketone is the adduct of thebaine and methyl vinyl ketone and by a suitable selection of syllables from the names of these compounds the name *thevinone* emerges for the ketone I (R = Me). The related secondary alcohol II (R = Me, R' = H) then becomes *thevinol*, and the other bases in the series II (R = Me), being obviously homolog of II (R = Me, R' = H), may be named as alkylthevinols, e.g., the alcohol II (R = Me, R' = *n*-Pr) becomes *propylthevinol* and II (R = Me, R' = CH₂CH₂-Ph) becomes *phenethylthevinol*.

As will be seen in the following paper, most of the alcohols of the series II have been demethylated to phenolic 3-hydroxy analogs, and bases of this series corresponding to those of structure II (R = Me), being derivatives of tetrahydrooripavine rather than tetrahydrothebaine, can be termed alkylorvinols, e.g., the 3-hydroxy analog of the base II (R = Me, R' = cyclohexyl) would be *cyclohexylorvinol*.

The acid I (R = OH), being an oxidized form of thevinone, can be named *thevinic acid* and the ester I (R = OEt) then becomes *ethyl thevinoate* and the acid chloride I (R = Cl) *thevinoyl chloride*. (The term thevinic acid is avoided as this leads to the acid chloride being named thevinyl chloride, which should be reserved for the halide corresponding to thevinol.)

Since a series of 6,14-ethano alcohols XIX derived from the ketone XX is known, this last base can be termed *hydrothevinone* and the alcohols thus become *alkylhydrothevinols*, or *hydroorvinols* after O-demethylation. Relatively simple extensions of this nomenclature permit rational names to be assigned to other bases resulting from transformations of the ketone I (R = Me) and the alcohols II (R = Me), and these will be discussed where necessary in subsequent publications.

Experimental Section

Examples only of representative Grignard reactions and reductions are given in this section to show the general processes used.

7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrothebaine (19-Methylthevinol) (II, R = R' = Me). a. A solution of 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (thevinone) (I, R = Me) (10 g) in dry ether (500 ml) or in dry benzene (50 ml) was added slowly with vigorous stirring to a refluxing solution of methylmagnesium iodide, prepared from magnesium (1.67 g) and methyl iodide (9.9 g) in ether (100 ml), and the mixture was stirred and heated under reflux for 2 hr. The mixture was then shaken with aqueous ammonium chloride, and the organic layer was separated, dried, and evaporated, leaving a crystalline base (10 g), which was recrystallized from ethanol. The base was obtained in this way as plates, mp 166°.

Anal. Calcd for C₂₆H₃₁NO₄: C, 72.5; H, 7.9. Found: C, 72.5; H, 7.7.

b. 6,14-*endo*-Etheno-7α-ethoxycarbonyltetrahydrothebaine (ethyl thevinoate) (I, R = OEt) (10 g) was extracted from a Soxhlet extractor into a boiling stirred solution of methylmagnesium iodide (from 1.67 g of magnesium and 9.9 g of methyl iodide) in ether (100 ml). The mixture was boiled under reflux for 3 hr, and the product isolated as in a above, when it was obtained (9.8 g) as white prisms, mp 166°, alone or mixed with material prepared from the ketone.

7β-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydrothebaine (19-Methyl-β-thevinol) (C-7 Epimer of II, R = R' = Me). a. A solution of 7β-acetyl-6,14-*endo*-ethenotetrahydrothebaine (0.5 g) in ether (100 ml) was added to a stirred refluxing solution of methylmagnesium iodide (from 0.17 g of magnesium and 1 g of methyl iodide), and the mixture was boiled under reflux for 1 hr. Isolation of the product in the usual way afforded a mixture of two nonketonic products. These were separated on thick alumina plates, and the base, having the greater R_f value, was obtained as prisms, mp 190°, on recrystallization from ethanol. It was identified as the alcohol epimeric at C-7 with II (R = R' = Me) by its nmr and infrared spectra, which were very similar to but not identical with those of II (R = R' = Me).

Anal. Calcd for C₂₆H₃₁NO₄: C, 72.5; H, 7.9. Found: C, 72.5; H, 7.7.

The second product, of lower R_f value, was phenolic and has been identified as a product of base-catalyzed rearrangement of the

it ketone followed by Grignard reaction and is described in a later paper.^{6b}

duction of 7 α -Acetyl-6,14-endo-ethenotetrahydrothebaine (Thebe) (I, R = Me). a. The ketone I (R = Me) (10 g) was boiled aluminum isopropoxide (10 g) and 2-propanol (100 ml) with distillation of the solvent through a 36-plate fractionating column until the distillate no longer gave a precipitate with a solution of 4-dinitrophenylhydrazine in aqueous hydrochloric acid. On completion of the reaction, the mixture was evaporated to small bulk poured into dilute hydrochloric acid. The acid solution was treated with potassium sodium tartrate and basified with ammonia, and the precipitated base was isolated by ether extraction, the carbinol II (R = H, R' = Me) was obtained as a viscous gum that was crystallized from aqueous methanol, being then obtained as white prisms, mp 78–80°, raised to 82° by further recrystallization from aqueous methanol or ether at low temperatures.

anal. Calcd for C₂₃H₃₃NO₄: C, 72.1; H, 7.6. Found: C, 72.1; H, 7.5.

Thin layer chromatographic studies showed that the base, mp 70°, first obtained contained about 5% of the isomeric carbinol (R = Me, R' = H), which is the main product of Grignard reaction of the ketone.

The O-formyl ester was prepared by heating the alcohol with 100% formic acid at 100° for 1 hr and was obtained as plates, mp 10°, from aqueous methanol.

anal. Calcd for C₂₃H₃₃NO₅: C, 70.1; H, 7.1. Found: C, 70.1; H, 7.2.

The O-acetyl ester, prepared from the alcohol and acetic anhydride and pyridine, was obtained as plates, mp 170°, from aqueous ethanol.

anal. Calcd for C₂₅H₃₃NO₅: C, 70.7; H, 7.3. Found: C, 70.7; H, 7.5.

The ketone I (R = Me) (10 g) was boiled under reflux in ethanol (50 ml) with sodium borohydride (1 g) for 30 min. The solution was concentrated by evaporation and poured into water; the precipitated base was isolated by ether extraction, when it obtained as a viscous gum, shown by thin layer chromatography to consist of an approximately 1:1 mixture of the products of the Wein-Pondorff and Grignard reduction of the ketone.

7 α -(1-(R)-Hydroxy-1-methylbutyl)-6,14-endo-ethenotetrahydrothebaine (19-Propylthevinol) (II, R = Me, R' = *n*-Pr) and Grignard reaction of the Ketone I (R = CH₃). 7 α -Acetyl-6,14-endo-ethenotetrahydrothebaine (I, R = CH₃) (50 g) in dry benzene (250 ml) was added to a vigorously stirred refluxing solution of *n*-propylmagnesium iodide (from 8.35 g of magnesium and 58.5 g of 1-iodopropane) in ether (500 ml), and the mixture was boiled under reflux for 2 hr.

The product, isolated in the usual way, was a viscous gum which crystallized on trituration with methanol (100 ml). The solid collected and recrystallized from ethanol, when the alcohol (R = Me, R' = *n*-Pr) was obtained as white prisms, mp 176° (decolor). *anal.* Calcd for C₂₈H₃₉NO₄: C, 73.3; H, 8.2. Found: C, 73.3; H, 8.2.

The mother liquors were diluted with methanol (50 ml) and water added until precipitation of gummy material began. The solution was allowed to stand for 15 min, decanted from the gummy material, and then kept in the refrigerator, when the Grignard reaction product, 7 α -(1-(S)-hydroxyethyl)-6,14-endo-ethenotetrahydrothebaine (thevinol) (II, R = Me, R' = H) (12 g) was obtained as needles, mp 76–78°, raised to 81° on recrystallization from aqueous methanol.

anal. Calcd for C₂₃H₃₃NO₄: C, 72.1; H, 7.6. Found: C, 72.1; H, 8.0.

The O-formyl ester, prepared by heating the secondary alcohol 98–100% formic acid at 100° for 1 hr, was obtained as prisms, mp 48°, from aqueous methanol.

anal. Calcd for C₂₄H₃₃NO₅·0.5H₂O: C, 68.6; H, 7.2. Found: C, 68.6; H, 7.3.

The O-acetyl ester, prepared from the alcohol, acetic anhydride, and pyridine, was obtained as prisms, mp 120°, from aqueous ethanol.

anal. Calcd for C₂₅H₃₃NO₅: C, 70.7; H, 7.3. Found: C, 70.7; H, 7.5.

The third base has been isolated from the residues of separation of the Grignard reduction product. This was a phenol, mp 201–202°, and is a product of base-catalyzed rearrangement of the parent ketone followed by normal Grignard reaction with propylmagnesium iodide; it is described fully in a later paper.^{6b}

7 α -(1-(S)-Hydroxy-1-methylbutyl)-6,14-endo-ethenotetrahydrothebaine (II, R = *n*-Pr, R' = Me). 7 α -Butyryl-6,14-endo-ethenotetrahydrothebaine (I, R = *n*-Pr) (15 g) in ether (500 ml) was added

to a stirred solution of methylmagnesium iodide (from 2 g of magnesium and 6 ml of methyl iodide) in ether (150 ml), and the mixture was boiled under reflux for 1 hr. Isolation of the product in the usual way afforded 10.1 g of a base containing about 10% of the alcohol II (R = Me, R' = *n*-Pr). After several recrystallizations from methanol the alcohol II (R = *n*-Pr, R' = Me) was obtained almost pure, as prisms, mp 144–145°, and a pure specimen, mp 148–149°, for spectral studies was obtained by layer chromatographic separation on alumina.

Anal. Calcd for C₂₈H₃₉NO₄: C, 73.3; H, 8.2. Found: C, 73.2; H, 8.4.

7 α -(1-(R)-Hydroxy-1-methylpropyl)-6,14-endo-ethenotetrahydrothebaine (19-ethylthevinol) (II, R = Me, R' = Et) was obtained by the above general method from the ketone I (R = Me) and ethylmagnesium bromide as prisms, mp 74°, with resolidification and final melting at 135°.

Anal. Calcd for C₂₅H₃₃NO₄: C, 73.1; H, 8.1. Found: C, 72.9; H, 8.1.

It was also obtained by the reduction of the vinylcarbinol II (R = Me, R' = CH=CH₂); see below.

7 α -(1-(S)-Hydroxy-1-methylpropyl)-6,14-endo-ethenotetrahydrothebaine (II, R = Et, R' = Me) was prepared by the general method from the ketone I (R = Et) and methylmagnesium iodide, when it was obtained as prisms, mp 165°.

Anal. Calcd for C₂₅H₃₃NO₄: C, 73.1; H, 8.1. Found: C, 72.9; H, 8.2.

It was also obtained by the reduction of the acetylenic carbinol II (R = C \equiv CH, R' = Me); see below.

7 α -(1-(R)-Hydroxy-1-methylprop-2-enyl)-6,14-endo-ethenotetrahydrothebaine (19-Vinylthevinol) (II, R = Me, R' = CH=CH₂). A solution of 7 α -acetyl-6,14-endo-ethenotetrahydrothebaine (I, R = Me) (19 g) in dry tetrahydrofuran (30 ml) was added to a refluxing solution of vinylmagnesium bromide (from 3.0 g of magnesium and 13.4 g of vinyl bromide) in tetrahydrofuran, and the mixture was boiled under reflux for 2 hr. Saturated aqueous ammonium chloride was added, and the organic layer was separated, dried, and evaporated. The residual brown gum was crystallized from methanol when the alcohol was obtained as white prisms, mp 155°.

Anal. Calcd for C₂₅H₃₃NO₄: C, 73.3; H, 7.6. Found: C, 73.3; H, 7.6.

Reduction. The alcohol II (R = Me, R' = CH=CH₂) (5 g) in ethanol (100 ml) was shaken under hydrogen at 22° (750 mm) in the presence of platinum oxide (100 mg). Hydrogen (300 ml) was absorbed over 30 min, after which reduction ceased. Filtration and evaporation of the solution gave 5.0 g of material which on crystallization from ethanol gave prisms, mp 74 and 135°, unaltered on mixing with the alcohol II (R = Me, R' = Et), obtained from the action of ethylmagnesium bromide on the ketone I (R = Me). The infrared spectra and chromatographic behavior on alumina plates of the bases from the two sources were also identical.

7 α -(1-(S)-Hydroxy-1-methylprop-2-ynyl)-6,14-endo-ethenotetrahydrothebaine (19-Ethynylthevinol) (II, R = C \equiv CH, R' = Me). 7 α -Acetyl-6,14-endo-ethenotetrahydrothebaine (I, R = Me) (38 g) in dry tetrahydrofuran (200 ml) was added with stirring to a solution of lithium acetylide-ethylenediamine complex (10 g) under an atmosphere of argon. The mixture was stirred at 35° for 3 hr and poured into water (200 ml). The mixture was extracted three times with ether, and the combined extracts were dried and evaporated. The residue crystallized in part on trituration with methanol (20 ml), and the solid (10.5 g) was collected and recrystallized from methanol when the alcohol II (R = C \equiv CH, R' = Me) was obtained as prisms, mp 185–186°.

Anal. Calcd for C₂₅H₃₃NO₄: C, 73.7; H, 7.1. Found: C, 73.6; H, 7.2.

A further 4.1 g of material, mp 183–184°, was obtained on concentration of the mother liquors. Final evaporation of these liquors afforded a gum shown by thin layer chromatography to consist of an approximately 1:1 mixture of the above base and a second compound, presumably the diastereoisomeric alcohol II (R = Me, R' = C \equiv CH), since the infrared spectrum of the mixture was almost identical with that of the pure base, mp 185–186°.

Reduction. The acetylenic alcohol II (R = C \equiv CH, R' = Me) (4.0 g) was hydrogenated over platinum oxide (100 mg) in ethanol at 22° (760 mm). Hydrogen (449 ml, 2 moles) was absorbed over 20 min, and isolation of the product afforded the alcohol II (R = Et, R' = Me), mp 165°, identical in melting point, mixture melting point, infrared absorption, and *R_f* value with the product of the action of methylmagnesium iodide on the ketone I (R = Et).

Study of the Stereochemistry at C-19 of the Alcohols II (R = H, R' = Me and R = Me, R' = H). A solution of 7 α -(1-(R)-hydroxy-

ethyl)-6,14-*endo*-ethenotetrahydrothebaine (II, R = H, R' = Me) (5 g) and phenylglyoxalyl chloride (6 g) in pyridine (12 ml) was kept at room temperature overnight. Ice water was then added until separation of solid matter occurred. The solid was isolated by ether extraction, and the viscous gum so obtained was crystallized by trituration with methanol. The solid was collected (3.5 g) and recrystallized from methanol when the phenylglyoxalyl ester was obtained as off-white plates, mp 206°.

Anal. Calcd for $C_{21}H_{23}NO_4 \cdot H_2O$: C, 69.85; H, 6.7. Found: C, 70.0; H, 7.0.

A solution of methylmagnesium iodide (from 0.95 g of magnesium and 25 ml of methyl iodide) in ether (30 ml) was added to a solution of the phenylglyoxalyl ester (5 g) in dry benzene (100 ml), and the mixture was kept at room temperature for 3 hr and then boiled under reflux for 3 hr. The mixture was poured into aqueous ammonium chloride; the organic layer was separated and the aqueous layer extracted twice with chloroform. The combined ether-benzene and chloroform solutions were evaporated, and the residue was boiled under reflux with 5% methanolic potassium hydroxide (200 ml) for 5 hr. Most of the methanol was evaporated, and the mixture was diluted with water (200 ml) and extracted four times with ether to remove the organic base. The aqueous layer was acidified with hydrochloric acid and extracted continuously with ether for 3 days. The ether extract on evaporation afforded a gum from which atrolactic acid, mp 114–115°, $[\alpha]^{20}_D +4.8^\circ$, was obtained as white needles on extraction with light petroleum (bp 80–100°).

Repetition of the above reactions using 7 α -(1-*S*)-hydroxyethyl)-6,14-*endo*-ethenotetrahydrothebaine (II, R = Me, R' = H) as starting material afforded the phenylglyoxalyl ester as prisms, mp 96 and 170°, and atrolactic acid, mp 114–115°, $[\alpha]^{20}_D -5.4^\circ$.

Anal. Calcd for $C_{21}H_{23}NO_4 \cdot H_2O$: C, 69.85; H, 6.7. Found: C, 70.2; H, 7.0.

7 α -Acetyl-6,14-*endo*-ethanotetrahydrothebaine (Dihydrothevinone) (XX). 7 α -Acetyl-6,14-*endo*-ethenotetrahydrothebaine (I, R = Me) (5 g) in ethanol (200 ml) was shaken with 10% palladium on charcoal (0.5 g) under hydrogen at 58 psi at 50° for 10 hr. The mixture was filtered from the catalyst and evaporated. The residue was crystallized from ethanol when the 6,14-*endo*-ethano-7 α -ketone (3.8 g) was obtained as white prisms, mp 134–136°, ν_{max} 1710 cm^{-1} .

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 72.0; H, 7.6. Found: C, 71.6; H, 7.6.

7 β -Acetyl-6,14-*endo*-ethanotetrahydrothebaine (β -Dihydrothevinone) (C-7 Epimer of XX). 7 β -Acetyl-6,14-*endo*-ethenotetrahydrothebaine (0.38 g) was hydrogenated over 10% palladium on charcoal (0.20 g) in ethanol (100 ml) at 22° (755 mm). Hydrogen (22 ml) was absorbed over 7 min. The solution was filtered and evaporated, and the residue was crystallized from ethanol when the 6,14-ethano-7 β -ketone was obtained as prisms, mp 166°.

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 72.0; H, 7.6. Found: C, 71.8; H, 7.6.

6,14-*endo*-Ethano-7 α -formyltetrahydrothebaine (XX, CH₃ = H). 6,14-*endo*-Etheno-7 α -formyltetrahydrothebaine (I, R = H) (1.84 g) was hydrogenated over 10% palladium on charcoal (0.3 g) in ethanol (50 ml) at 22° (760 mm). Hydrogen (112 ml) was absorbed over 2.5 hr. The isolated product was crystallized from ethanol when the 6,14-*endo*-ethano-7 α -aldehyde was obtained as prisms, mp 98°, ν_{max} 1740 cm^{-1} .

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4. Found: C, 71.2; H, 7.2.

6,14-*endo*-Ethano-7 α -(1-*R*)-hydroxyethyltetrahydrothebaine (XIX, R = H, R' = Me). 6,14-*endo*-Etheno-7 α -(1-*R*)-hydroxy-

ethyltetrahydrothebaine (II, R = H, R' = Me) (25 g) (from the Meerwein-Ponndorf reduction of the ketone I, R = Me) was hydrogenated at 22° (760 mm) in ethanol (100 ml) over 10% palladium on charcoal (1 g). Hydrogen (1500 ml) was absorbed over 50 min. The product was isolated as prisms, mp 49–51°, from aqueous methanol.

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.6; H, 8.1. Found: C, 71.5; H, 8.2.

The *O*-*p*-toluenesulfonate was obtained as prisms, mp 157°, from benzene-methanol.

Anal. Calcd for $C_{26}H_{27}NO_6 \cdot 0.5H_2O$: C, 65.6; H, 7.0; S, 5.8. Found: C, 65.3; H, 7.0; S, 5.7.

The diastereoisomeric alcohol II (R = Me, R' = H), from the Grignard reduction of the ketone I (R = Me), was resistant to hydrogenation under the above conditions and at temperatures up to 60°.

6,14-*endo*-Ethano-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (Dihydro-19-methylthevinol) (XIX, R = R' = Me). 6,14-*endo*-Etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (II, R = R' = Me) (40 g) was hydrogenated in ethanol (300 ml) over W4 Raney nickel (10 g) at 160–165° (164–182 atm) for 4 hr. The solution was filtered and concentrated to yield the 6,14-ethano alcohol as white prisms, mp 142°, after recrystallization from ethanol.

Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.2; H, 8.3; N, 3.5. Found: C, 71.8; H, 8.2; N, 3.5.

b. The same base was obtained by the action of methylmagnesium iodide (from 0.83 g of magnesium and 5.2 g of methyl iodide) on 7 α -acetyl-6,14-*endo*-ethanotetrahydrothebaine (dihydrothevinone) (4.8 g) in ether solution.

Hofman Degradation of the Alcohols II (R = Me, R' = *n*-Pr and R = Me, R' = Ph). 19-Propylthevinol (II, R = Me, R' = *n*-Pr) and 19-phenylthevinol (II, R = Me, R' = Ph) (2 g) were separately boiled under reflux with methyl iodide (10 ml) and acetone (20 ml) for 7 days. The solvent was evaporated, and the residue was recrystallized from ethanol to give 19-propylthevinol methiodide (white prisms, mp 188–190°). *Anal.* Calcd for $C_{27}H_{35}NO_4 \cdot 0.5H_2O$: C, 56.3; H, 6.8. Found: C, 56.4; H, 5.8) and 19-phenylthevinol methiodide (white prisms, mp 194–196°). *Anal.* Calcd for $C_{30}H_{31}NO_4 \cdot 0.5H_2O$: C, 59.0; H, 6.1. Found: C, 58.7; H, 6.1).

The methiodides (1 g) were degraded by boiling under reflux with 20% aqueous potassium hydroxide for 15 min. The solution was diluted and the product collected at the pump and recrystallized from aqueous ethanol to give 19-propylthevinol methine (XXI, R' = *n*-Pr; white needles, mp 90–95°, λ_{max} 230, 279, 308, 318 $m\mu$ (ϵ_{max} 12,000, 7000, 3000, 2300). *Anal.* Calcd for $C_{28}H_{37}NO_4 \cdot H_2O$: C, 70.9; H, 8.5. Found: C, 71.2; H, 8.3) and 19-phenylthevinol methine (XXI, R' = Ph, white plates, mp 160°, λ_{max} 279 and 310 $m\mu$ (ϵ_{max} 8050 and 3500). *Anal.* Calcd for $C_{30}H_{33}NO_4 \cdot H_2O$: C, 73.4; H, 7.5. Found: C, 73.2; H, 7.6).

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Novel Analgesics and Molecular Rearrangements in the Morphine-Thebaine Group. III.¹ Alcohols of the 6,14-endo-Ethenotetrahydrooripavine Series and Derived Analogs of N-Allylnormorphine and -norcodeine

K. W. Bentley and D. G. Hardy

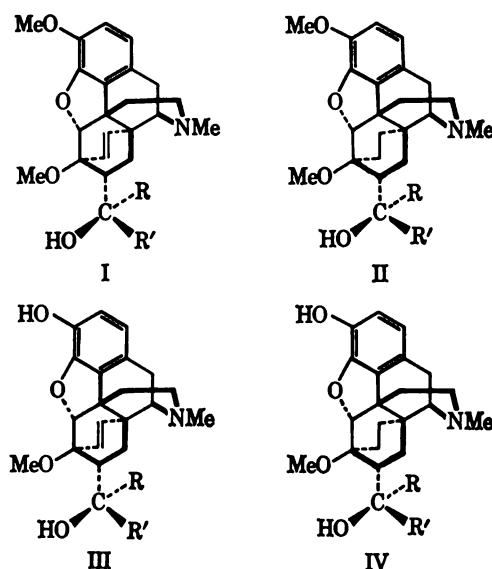
Contribution from the Research Laboratories, Reckitt and Sons Ltd., Kingston-upon-Hull, England. Received September 26, 1966

Abstract: Secondary and tertiary alcohols of general structures IV and V have been prepared by the demethylation of the corresponding bases I and II described in part II of this series. The phenols so obtained are analgesics of extremely high potency, up to an unprecedented 12,000 times that of morphine. The bases of this and earlier series have been converted into analogs of N-allylnormorphine and N-allylnorcodeine of general structures XI and XII via the N-cyanonor compounds and via novel N,N'-methylenebis compounds XIII resulting from the reaction of the bases I and II with methyl azodicarboxylate. Some bases of the series XII are morphine antagonists of unprecedented potency, up to 150 times that of N-allylnormorphine.

In the preceding paper the preparation of two series of codeine derivatives of general structures I and II is reported, many of the members of which were considerably more active as analgesics than any base previously prepared in the morphine-thebaine group. Since the demethylation of codeine derivatives to the corresponding derivatives of morphine almost always results in an appreciable increase in analgesic activity, most of the alcohols of structures I and II were converted into the related phenols. The O-demethylation could not be accomplished without decomposition by typical reagents owing to the extreme ease with which the alcohols undergo acid-catalyzed rearrangement,^{1c} which was effected in most cases by heating the bases with potassium hydroxide in diethylene glycol at 200–220°. Demethylation of the methyl ethers to the phenols to a very small extent was occasionally observed during the Grignard reactions leading to the alcohols of structure I. The demethylating action of Grignard reagents is well known,² but the method has little preparative value.

The alkaline demethylations affected only the methyl group attached to C-3, that at C-6 remaining unchanged. From the point of view of analgesic activity, however, the retention of the C-6 methoxyl group is advantageous, since methylation of the hydroxyl group at this position in morphine and codeine increases the activity. The demethylation of the C-3 methoxyl group in the codeine-thebaine group under alkaline conditions appears to have been first observed during the Huang-Minlon reduction of thebenone.³ The 4,5-oxygen bridge in these bases, which is unaffected under the conditions of the demethylation, also represents the ether of a phenolic hydroxyl group, but none of this bridge during simple demethylations in the morphine series has never been observed, though

fused potassium hydroxide converts methylmorphineol into 3,4,5-trihydroxyphenanthrene.⁴



The bases obtained in this way, having structures III and IV, are listed in Tables I and II, respectively. In all cases it is found that demethylation of the C-3 methoxyl group results in an increase in analgesic potency, but the increase is by no means uniform throughout the series. The most potent compounds in this series do not correspond to the most potent of the methyl ethers, but, in a simple screening procedure in which analgesia is determined at a fixed time after administration of the compounds, comparisons are not always meaningful, since no account is taken of speed of onset, time of peak action, or duration of analgesia. The most potent analgesics in the morphine series reported prior to this work are about 12 times as active as morphine, but in other groups higher activities than this have frequently been encountered. The highest well-documented activities are reported in a series of benzimidazoles, of which the most active is about 1000 times as potent as morphine.⁵ Of the oripavine

(a) Part II: K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3273 (1967). (b) A preliminary report of part of this work has been made by K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1963). (c) Part IV: K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3293 (1967).

(d) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-allic Substances," Constable and Co. Ltd., London, 1954, p 1029. (e) K. W. Bentley and R. Robinson, *Experientia*, **6**, 353 (1950); K. Bentley, R. Robinson, and A. E. Wain, *J. Chem. Soc.*, 958 (1952).

(4) E. von Gerichten and O. Dittmer, *Ber.*, **39**, 1718 (1906).

(5) A. Hunger, J. Kebele, A. Rossi, and K. Hofmann, *Helv. Chim. Acta*, **43**, 1032, 1046 (1960).

Table I. Alcohols of Structure III

R	R'	Mp, °C	Composition	Calcd, %		Found, %		Mp, °C HCl	Molar potency ^a
				C	H	C	H		
H	H	219	C ₂₁ H ₂₅ NO ₄	71.0	7.1	71.1	7.2	287	17
H	Me	298	C ₂₃ H ₂₇ NO ₄	71.4	7.3	71.2	7.5	272	37
Me	H	280	C ₂₃ H ₂₇ NO ₄	71.4	7.3	71.6	7.6	290	15
H	Ph	160	C ₂₇ H ₃₁ NO ₄ · H ₂ O	72.8	6.7	72.6	6.7	300	4.2
H	CH ₂ CH ₂ Ph	120	C ₂₉ H ₃₃ NO ₄	75.7	7.2	75.8	7.3	290	1100
Me	Me	266	C ₂₃ H ₂₉ NO ₄	72.1	7.6	72.4	7.5	290	63
Me	Et	268	C ₂₄ H ₃₁ NO ₄	72.6	7.8	72.5	8.1	282	330
Et	Et	157	C ₂₆ H ₃₃ NO ₄ · 0.5H ₂ O	71.4	8.1	71.5	8.1	310	55
Me	<i>n</i> -Pr	215	C ₂₅ H ₃₁ NO ₄ · H ₂ O	70.0	8.1	70.0	7.9	267	3200
Me	<i>n</i> -Bu	174	C ₂₆ H ₃₃ NO ₄ · H ₂ O	70.4	8.3	70.6	8.5	272	5200
Me	<i>i</i> -Bu	217	C ₂₆ H ₃₃ NO ₄ · H ₂ O	70.4	8.3	70.7	8.6	292	10
Me	<i>n</i> -Am	106	C ₂₇ H ₃₅ NO ₄ · 0.5H ₂ O	72.3	8.5	72.6	8.6	278	4500
Me	<i>i</i> -Am	132	C ₂₇ H ₃₇ NO ₄	73.6	8.2	73.4	8.1	258	9200
Me	<i>n</i> -C ₁₀ H ₁₃	288	C ₂₈ H ₃₉ NO ₄	74.1	8.6	74.6	8.6	265	58
Me	Ph	252	C ₂₉ H ₃₃ NO ₄ · H ₂ O	72.7	7.2	72.9	7.4	286	34
Me	CH ₂ CH ₂ Ph	226	C ₃₀ H ₃₅ NO ₄	76.1	7.5	75.9	7.6	255	2200
Me	Cyclopentyl	302	C ₂₇ H ₃₃ NO ₄	74.1	8.1	74.0	7.9	248	70
Me	Cyclohexyl	242	C ₂₈ H ₃₇ NO ₄	74.5	8.2	74.2	8.2	263	3400

^a Morphine = 1.0.

Table II. Alcohols of Structure IV

R	R'	Mp, °C	Composition	Calcd, %		Found, %		Molar potency ^a
				C	H	C	H	
Me	<i>n</i> -Pr	116 (205)	C ₂₃ H ₃₁ NO ₄	72.6	8.5	72.8	8.8	12,000
Me	<i>i</i> -Am	180	C ₂₇ H ₃₉ NO ₄	73.5	8.9	73.4	8.9	11,000

^a Morphine = 1.

Table III. 3-O-Acetyl Esters of Alcohols of Structure III

R	R'	Mp, °C	Composition	Calcd, %		Found, %		Mp, °C HCl	Molar potency ^a
				C	H	C	H		
Me	Me	191	C ₂₃ H ₃₁ NO ₅	70.5	7.3	70.5	7.2	261	55
Me	Et	154	C ₂₄ H ₃₃ NO ₅	71.0	7.5	71.2	7.6	252	
Me	<i>n</i> -Pr	196	C ₂₇ H ₃₅ NO ₅	71.5	7.7	71.3	7.7	206	8700
Me	<i>i</i> -Bu	152	C ₂₈ H ₃₇ NO ₅	71.9	7.9	72.0	8.1	238	
Me	<i>i</i> -Am	126	C ₂₉ H ₃₉ NO ₅	72.3	8.1	73.1	8.1	244	1300
Me	Cyclohexyl	193	C ₃₀ H ₄₁ NO ₅ · H ₂ O	70.5	8.1	70.8	8.2	262	1700
Et	Et	179	C ₂₇ H ₃₅ NO ₅	71.5	7.7	71.2	7.6		

^a Morphine = 1.

derivatives listed in Tables I and II, many are more active than any of the benzimidazoles, and in particular the alcohol IV (R = Me, R' = *n*-Pr), which is about 12,000 times as active as morphine, is the most potent analgesic so far reported. The very high potency of the phenols of structures III and IV makes them eminently suitable for use in large animals and the base III (R = Me, R' = *n*-Pr) is already widely used for the immobilization of wild animals for game conservation and veterinary purposes.^{6,7}

Several of the bases of the tetrahydrooripavine series III and IV have proved to be inaccessible. Bases of either of these structures in which one of the groups R or R' contains the system CHC=C or CH—aryl directly attached to the hydroxyl-bearing carbon atom fail to survive the vigorous conditions necessary for the alkaline demethylation process, owing to the ease with which they suffer base-catalyzed dehydration to polymerizable derivatives.

(6) J. M. King and B. H. Carter, *East African Wild Life J.*, **3**, 19 (1965).

(7) A. M. Harthoorn and J. Bligh, *Res. Vet. Sci.*, **6**, 290 (1965); A. M. Harthoorn, *J. S. African Vet. Med. Assoc.*, **36**, 45 (1965).

Esterification of the phenolic hydroxyl group of the tetrahydrooripavine derivatives is very easily accomplished by the conventional methods and, in general, results in some reduction in analgesic activity, though the 3-O-acetyl derivative of the base III (R = Me, R' = *n*-Pr) is more than twice as active as the parent phenol. The esters are very readily hydrolyzed even on heating aqueous solutions of their salts. The esters prepared are listed in Table III.

Derivatives of Nor Bases

It has been shown that N-allylnormorphine⁸ (nalorphine) (V, R = CH₂CH=CH₂) antagonizes the action of morphine (V, R = Me) in animals and in man,⁹ and that its administration to narcotics addicts precipitates withdrawal symptoms. Physical dependence on the drug does not appear to develop after prolonged administration, and it is widely believed to be non-addicting.¹⁰ Although the compound does not show

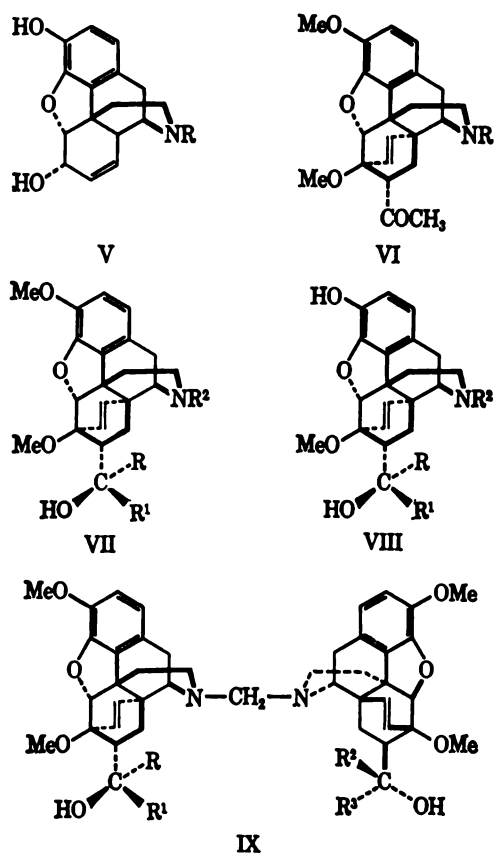
(8) J. Weijlard and A. E. Erickson, *J. Am. Chem. Soc.*, **64**, 869 (1942).

(9) K. Unna, *J. Pharmacol. Exptl. Therap.*, **79**, 27 (1943).

(10) H. Isbell, *Federation Proc.*, **15**, 442 (1956).

up as an analgesic when tested by the conventional techniques in laboratory animals, it has been shown to be an analgesic effective against natural pain in man, and to have a potency in such conditions about equal to that of morphine itself.¹¹ It has been very widely studied in clinical investigations, but has been found to produce bizarre and often distressing mental effects in a number of patients, with the result that it has found little clinical use as an analgesic.

The series of alcohols of general structures III and IV, and their 3-O-methyl ethers described in the previous paper, having a very wide range of morphine-like activity, provide a large number of starting materials, and many of these have been converted into analogs of nalorphine. Normorphine (V, R = H), from which other tertiary bases in the morphine series are prepared, is obtained from diacetylmorphine by treatment with cyanogen bromide and hydrolysis of the resulting N-cyanonor compound with dilute hydrochloric acid.⁸ Cyanogen bromide reacts with the ketone VI (R = Me) and its analogs, the phenols of general structures III and IV, and their methyl ethers to give the corresponding N-cyanonor compounds in very good yield. Since the rate of quaternization of all of the bases in this series is very low, quaternary salt formation with liberated methyl bromide is not a complicating factor in the reaction.



The alcohols of general structures VII and VIII and the corresponding 6,14-ethano compounds, being very readily rearranged by acids, can only be hydrolyzed at the N-cyano group under alkaline conditions, most conveniently by heating with potassium hydroxide in diethylene glycol at 160° for 5–10 min, or at 200–220°

for longer periods if the simultaneous O-demethylation of VII to VIII is also required. The ketones of structure VI are, however, unstable to alkalis, and hydrolysis of the N-cyano group of the cyanamide VI (R = CN) must be effected with dilute mineral acid, to which the ring structure is stable. The hydrolysis is, however, incomplete, and the principal product is the substituted urea VI (R = CONH₂). The required secondary base VI (R = H) is, however, preparable by the action of nitrous acid on the urea in 50% yield.

The preferred method of preparation of the ketonic secondary base VI (R = H) is the reaction of the tertiary base VI (R = Me) with methyl azodicarboxylate. The initial product of this reaction, which is presumably the substituted hydrazo ester VI (R = CH₂N(COOMe)—NHCOOMe), is very readily hydrolyzed by cold aqueous 1 N hydrochloric acid, with the separation of the sparingly soluble hydrochloride of the secondary base VI (R = H) and the liberation of formaldehyde and methyl hydrazodicarboxylate. Norcodeine has been prepared by this general process, but the yield is poor.^{12,13} The application of this reaction to the alcohols of general structure VII (R² = Me) and their 6,14-ethano analogs does not lead directly to the production of the corresponding secondary bases VII (R² = H). These alcohols react readily with methyl or ethyl azodicarboxylate in acetone solution, but the hydrolysis of the primary reaction products with mineral acid in the cold affords solutions from which no salt separates. The basification of these solutions affords products that initially are very soluble in methanol, but are rapidly converted in hot methanol into sparingly soluble, high-melting bases. Similar results are obtained, though more slowly, when the primary reaction products are hydrolyzed with aqueous methanol instead of acid.

The final high-melting products are not carbinolamines VII (R² = CH₂OH), as these are lower melting, more soluble bases preparable by the action of formaldehyde on the secondary bases, but they are obtained from the carbinolamines by heating these alone, or better with secondary base, in solution. Whereas on heating with an aqueous acid solution of 2,4-dinitrophenylhydrazine, the carbinolamines give 1 molecular equiv of formaldehyde dinitrophenylhydrazone, the high-melting products under similar conditions afford only 0.5 equiv of the hydrazone. It is clear from these facts that the high-melting bases are N,N'-methylenebis-nor bases of general structure IX, and nmr spectral studies support this conclusion. The spectra of the base VII (R = R¹ = R² = Me) and the bis compound IX (R = R¹ = R² = R³ = Me) are identical in all important respects apart from the absence from the spectrum of the latter base of the characteristic signal due to NCH₃.

Unsymmetrical bis compounds of structure IX can be prepared by the interaction of carbinolamines VII (R² = CH₂OH) and secondary bases VII (R² = H) differing in the nature of the HOCRR¹ substituent at C-7; for example, the same unsymmetrical base is obtained by heating the carbinolamine VII (R = R¹ = Me, R² = CH₂OH) with the secondary base VII (R = Me, R¹ = CH₂CH₂Ph, R² = H) or the carbinolamine VII

(11) L. Lasagna and H. K. Beecher, *J. Pharmacol. Exptl. Therap.*, **112**, 356 (1954); A. S. Keats and J. Telford, *ibid.*, **117**, 190 (1956).

(12) O. Diels and M. Paquin, *Ber.*, **46**, 2000 (1913).

(13) O. Diels and E. Fischer, *ibid.*, **47**, 2043 (1914).

Table IV. N,N'-Methylenebis Compounds of Structure IX




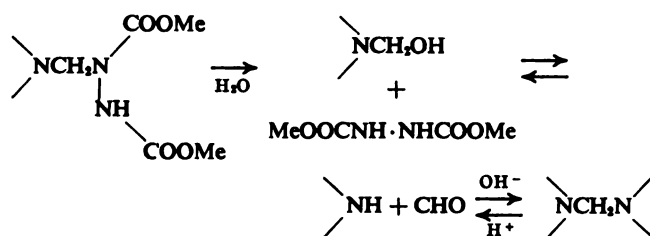
R	R ¹	R ²	R ³	Mp, °C	Composition	Calcd, %		Found, %	
						C	H	C	H
Me	Me	Me	Me	286	C ₆₇ H ₅₈ N ₂ O ₈	72.5	7.4	72.3	7.5
Me	Et	Me	Et	252	C ₄₅ H ₄₀ N ₂ O ₈	73.0	7.7	73.1	7.8
Me	<i>n</i> -Pr	Me	<i>n</i> -Pr	269	C ₅₃ H ₅₀ N ₂ O ₈	73.4	8.0	73.2	8.4
Me	<i>i</i> -Bu	Me	<i>i</i> -Bu	224	C ₅₅ H ₅₆ N ₂ O ₈	73.8	8.1	73.7	8.3
Me	<i>n</i> -Am	Me	<i>n</i> -Am	186	C ₅₅ H ₇₄ N ₂ O ₈	74.1	8.4	74.2	8.2
Me	<i>i</i> -Am	Me	<i>i</i> -Am	200	C ₅₅ H ₇₄ N ₂ O ₈	74.1	8.4	74.0	7.9
Me		Me		228	C ₅₇ H ₇₄ N ₂ O ₈	74.8	8.2	75.1	8.0
Me	CH ₂ CH ₂ Ph	Me	CH ₂ CH ₂ Ph	243	C ₆₁ H ₇₀ N ₂ O ₈	76.4	7.4	76.4	7.8
Me	Me	Me	CH ₂ CH ₂ Ph	220	C ₅₄ H ₆₄ N ₂ O ₈	74.6	7.4	74.3	7.2

Table V. Ketones of Structure VI

R	Mp, °C	Composition	Calcd, %		Found, %		Mp, °C, HCl
			C	H	C	H	
H	74	C ₂₅ H ₂₅ NO ₄ ·H ₂ O	68.8	7.0	68.8	7.2	350
CN	236	C ₂₅ H ₂₄ N ₂ O ₄	70.4	6.2	70.2	6.2	...
COCH ₃	101	C ₂₆ H ₂₇ NO ₄ ·H ₂ O	67.4	6.8	67.3	6.8	...
CH ₂ CH ₂ CH ₃	...	C ₂₅ H ₂₅ NO ₄ ·HCl·H ₂ O	64.7	7.3	64.4	7.2	263
CH ₂ CH=CH ₂	...	C ₂₅ H ₂₅ NO ₄ ·HCl·22.5H ₂ O	61.3	7.1	61.3	7.1	233
CH ₂ C≡CH	...	C ₂₆ H ₂₇ NO ₄ ·HCl	68.1	6.4	67.6	6.3	225
CH ₂ CHMe ₂	...	C ₂₆ H ₂₉ NO ₄ ·HCl·H ₂ O	65.2	7.5	65.4	7.5	305
CH ₂ CH=CMe ₂	...	C ₂₇ H ₂₉ NO ₄ ·HCl·1.5H ₂ O	65.0	7.5	65.0	7.5	256
CH ₂ CMe=CH ₂	...	C ₂₆ H ₂₉ NO ₄ ·HCl·1.5H ₂ O	64.5	7.2	64.5	7.0	308
CH ₂ CH ₂ Ph	137	C ₃₀ H ₂₉ NO ₄ ·0.5H ₂ O	75.0	7.1	75.3	7.0	245
∞- 	197	C ₂₆ H ₂₉ NO ₄	71.7	6.7	71.8	6.8	...

(R = Me, R¹ = CH₂CH₂Ph, R² = CH₂OH) with the secondary base VII (R = R¹ = Me, R² = H). The symmetrical bis compounds IX (R = R², R¹ = R³) presumably arise in this way after hydrolysis of the substituted hydrazo ester as follows.



In the hydrolysis of the hydrazo ester derived from the ketone VI (R = Me) the secondary base VI (R = H) is obtained rather than the bis compound as a result of the low solubility of its hydrochloride. The bis compounds are soluble in aqueous acids in which they are converted into carbinolamines and secondary bases which revert to the bis compounds on standing or heating in solution. When the compounds are heated in solution in dilute acetic acid, formaldehyde is slowly lost, and the secondary bases may be recovered from the solution; mineral acid solutions cannot be used for this purpose owing to the ease with which the alcohols of these series are rearranged in warm solutions of strong acids. The bis compounds of general structure IX prepared by these processes are listed in Table IV.

The secondary base VI (R = H) has been converted into a series of analogs of nalorphine V (R = CH₂CH=CH₂) by treatment with alkyl, alkenyl, or alkynyl halides RX under reflux in inert solvents. Quaternary salt formation with the 6,14-etheno and ethano tetrahydrothebaine derivatives is so slow that

excellent yields of tertiary bases may be obtained without difficulty. A list of ketones of general structure VI and corresponding 6,14-ethano compounds is given in Table V.

Nonphenolic and phenolic alcohols of general structures VII and VIII in which R² is other than methyl or hydrogen, which also are analogs of nalorphine, have been prepared by one or other of the following general processes.

(a) Conversion of the appropriate N-substituted nor ketone VI, in which R has the desired value, into alcohols by reduction with sodium borohydride or aluminum isopropoxide, or treatment with the appropriate Grignard reagent or lithium alkyl: in general, this process leads to mixtures of alcohols containing, in many cases, appreciable quantities of the product of Grignard reduction (see preceding paper), and the separation of pure products is frequently tedious. It does not give phenols directly.

(b) Alkylation, alkenylation, or alkynylation of the appropriate secondary bases VII (R² = H) and VIII, (R² = H) may be achieved by heating under reflux with the desired halide R²X or alternatively by acylation with an acyl halide R²COCl, followed by reduction of the resulting amide with lithium aluminum hydride. These processes readily afford pure isomers of the alcohols, since the separation of pure starting materials VII (R² = Me) and VIII (R² = Me) may be accomplished relatively easily before N-demethylation to secondary base. Phenolic bases are readily obtained in this way.

(c) Tertiary bases are obtained by heating the N,N'-methylenebisnor compounds of general structure IX (R = R², R¹ = R³) with the appropriate halide and, since the bis compounds are prepared from pure al-

ls of the N-methyl series, this process also affords chemically pure products. However, this process is generally less satisfactory than the alkylation of the tertiary bases since only the most reactive halides react readily with the bis compounds; in other cases prolonged periods of heating with the halide is necessary and some quaternization of the resulting tertiary base takes place under these conditions. Alternatively, tertiary bases are obtainable from the bis compounds by action of these with acyl halides, which proceeds readily, followed by reduction of the resulting amides with lithium aluminum hydride. Neither of these alternatives yields phenols directly since the phenolic compounds are not accessible by the action of methyl isocarbonylate on the phenolic N-methyl bases VIII (R = Me).

Phenolic bases of general structure VIII, when not prepared directly as in b above, may be obtained by the demethylation of the corresponding base VII as previously described in the case of the N-methyl compounds.

Bases corresponding to those of series VII and VIII containing a 6,14-ethano instead of an etheno bridge can be prepared by analogous processes to those set out above, starting from the corresponding 6,14-ethanol or alcohols.

Bases prepared by these methods are listed in Tables X. The pharmacological testing of the compounds listed in Tables V-IX presents certain difficulties since nalorphine-like substances are not revealed as analgesics by the conventional screening techniques in experimental animals, and the results of pharmacological studies are being and will be reported in detail here.¹⁴ It may, however, be stated here that the structure-activity relationships in the various series are complex, and that the physiological activity of each base is dependent on the nature of the substituents on the nitrogen atom, the C-3 oxygen atom, and in the alkoxy group. No group has been found that, when substituted for methyl attached to the nitrogen atom, reverses morphine-antagonist properties on all of the bases, and each of the series represented in Tables VI-IX contains potent morphine-like analgesics, as well as morphine antagonists and also several bases resembling morphine in some and nalorphine in other respects. For example, the base VIII (R = Me, R¹ = *n*-Pr, R² = CH₂CH=CMe₂) is a potent morphine-like agent, while base VIII (R = R¹ = Me, R² = CH₂C₃H₇, 6,14-ethano) is the most potent morphine antagonist so far tested, being some 150 times more potent than morphine. The base VIII (R = Me, R¹ = *i*-Am, R² = CH₂C₃H₇), however, shows morphine-like analgesic properties which are reversed by nalorphine only if nalorphine is given very soon after the drug, but, if nalorphine, it causes an increase in urinary output (morphine causes a decrease) and a decrease in locomotor activity in mice (morphine causes an increase). The physiological activity of the last mentioned base is tested in animals for up to 3 days.

Some information concerning certain of the bases of this group has already been published: D. Campbell, R. E. Lister, and G. W. Bentley, *Clin. Pharmacol. Therap.*, **5**, 193 (1964); R. E. Lister, J. Bentley, *J. Pharmacol.*, **16**, 364 (1964); K. W. Bentley, A. L. Boura, A. E. Hardy, D. G. Hardy, A. McCoubrey, M. L. Aikman, and R. E. Bentley, *Nature*, **206**, 102 (1965); A. L. A. Boura and A. E. Fitzgerald, *J. Pharmacol.*, **26**, 307 (1966).

Even the secondary bases in the series have been found to be unusual. Many of them are morphine-like analgesics, and this is without precedent in the morphine, morphinan, benzomorphan, and pethidine series; indeed secondary bases in general are inactive in the conventional tests.

The unprecedented potency of some members of the series I, II, III, and IV requires some comment. The bases would not be expected to be more acceptable than morphine at the receptor surface depicted by Beckett¹⁵ since the added portions of the molecule would be expected to project outside the limited area of such a surface. Two alternative explanations of the high activities are possible. Either the receptor surface is more extensive than that depicted by Beckett and has additional points of possible attachment by which the more extensive molecules of the bases I-IV, but not morphine or simpler bases, can be bound, or the molecules are no more acceptable than morphine at the receptor but arrive there in vastly greater numbers as a result of selective concentration in the tissues of the central nervous system. There is some evidence from preliminary distribution studies using labeled material that relatively high concentrations of the base III (R = Me, R¹ = *n*-Pr) are found in the brain about 0.5 hr after intramuscular or subcutaneous injection, but this alone cannot account for the very high potency of the base, and the problem clearly requires further study.

Experimental Section

The O-demethylation of the alcohols of general structures I and II were effected by the following general method.

7 α -(1-Hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydrooripavine (III, R = R¹ = Me). 7 α -(1-Hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydrothebaine (I, R = R¹ = Me) (8 g) was added to a solution of potassium hydroxide (60 g) in diethylene glycol (150 ml) boiling under reflux at 200-210°. The mixture was boiled and stirred vigorously under reflux until a test portion on dilution with ten times its volume of water gave a homogeneous solution. The mixture was then diluted with five times its volume of water and a solution of ammonium chloride was added until precipitation of the phenol ceased. The product was isolated by ether extraction and recrystallized from aqueous 2-ethoxyethanol with charcoal treatment, when the oripavine derivative was obtained as elongated plates, mp 266° (4.2 g).

Anal. Calcd for C₂₃H₂₉NO₄: C, 72.1; H, 7.6. Found: C, 72.4; H, 7.5.

The 3-O-acetyl ester was precipitated on the addition of acetic anhydride to a solution of the phenol in aqueous sodium hydroxide and was obtained as white prisms, mp 191°, from ethanol.

Anal. Calcd for C₂₅H₃₁NO₄: C, 70.5; H, 7.3. Found: C, 70.5; H, 7.2.

7 α -(1-(*R*)-Hydroxy-1-methylbutyl)-6,14-endo-ethenotetrahydrooripavine (III, R = Me; R¹ = *n*-Pr). 7 α -(1-(*R*)-Hydroxy-1-methylbutyl)-6,14-endo-ethenotetrahydrothebaine (I, R = Me; R¹ = *n*-Pr) (50 g) was demethylated with potassium hydroxide (360 g) and diethylene glycol (950 ml) at 205-215° until a test portion of the reaction mixture on dilution with ten times its volume of water gave a homogeneous solution. The mixture was diluted with water (4500 ml), and the solution was filtered through charcoal and aqueous ammonium chloride was added until precipitation of the phenol ceased. The solid (32 g) was collected, washed well with water, and recrystallized from aqueous 2-ethoxyethanol, when it was obtained as off-white prisms, mp 215-216°.

Anal. Calcd for C₂₅H₃₃NO₄·H₂O: C, 70.0; H, 8.1. Found: C, 70.0; H, 7.9.

The 3-O-acetyl ester was prepared by heating the phenol under reflux with acetic anhydride and anhydrous sodium acetate and was obtained as off-white prisms, mp 196°, from ethanol.

Anal. Calcd for C₂₇H₃₅NO₄: C, 71.5; H, 7.7. Found: C, 71.3; H, 7.7.

(15) A. H. Beckett, *Progr. Drug Res.*, **1**, 527 (1959).

Table VI. Alcohols of Structure VII^a

R	R ¹	R ²	Mp, °C	Composition	Calcd, C	% H	Found, C	% H	Mp, °C HCl
H	H	H	131	C ₂₅ H ₃₃ NO ₄	71.0	7.1	71.0	7.4	
H	Me	H	...	C ₂₆ H ₃₇ NO ₄ ·HCl	65.2	6.9	65.0	6.6	275
H	Me	CN	200	C ₂₅ H ₃₁ N ₂ O ₄	70.0	6.6	70.2	6.9	...
H	Me	CH ₂ CH=CH ₂	...	C ₂₅ H ₃₃ NO ₄ ·HCl·H ₂ O	64.7	7.3	64.8	7.3	293
H	Me	∞-△	185	C ₂₅ H ₃₃ NO ₅	71.4	7.1	71.3	7.4	...
H	Me	CH ₂ -△	...	C ₂₅ H ₃₃ NO ₄ ·HCl	67.9	7.5	67.6	7.7	254
Me	H	H	102	C ₂₆ H ₃₇ NO ₄	71.6	7.3	71.3	7.3	218
Me	H	CN	208	C ₂₅ H ₃₁ N ₂ O ₄	70.0	6.6	70.2	6.5	...
Me	H	CH ₂ CH ₂ CH ₃	...	C ₂₅ H ₃₃ NO ₄ ·HCl	67.1	7.6	67.6	7.9	315
Me	H	CH ₂ CHMe ₂	...	C ₂₅ H ₃₃ NO ₄ ·HCl	67.6	7.8	67.5	7.9	300
Me	H	CH ₂ CH=CH ₂	...	C ₂₅ H ₃₃ NO ₄ ·HCl·H ₂ O	64.7	7.3	64.6	7.4	277
Me	H	CH ₂ C≡CH	...	C ₂₅ H ₃₃ NO ₄ ·HCl·H ₂ O	65.0	6.9	64.9	7.1	260
Me	H	∞-△	180	C ₂₅ H ₃₃ NO ₅	71.4	7.1	71.3	7.4	
Me	H	CH ₂ -△	...	C ₂₅ H ₃₃ NO ₄ ·HCl	67.9	7.5	67.6	7.7	254
Me	H	CH ₂ CH=CMMe ₂	115	C ₂₇ H ₃₅ NO ₄	74.1	8.0	74.3	7.7	230
Me	Me	H	79 (163)	C ₂₅ H ₃₃ NO ₄	72.1	7.6	72.3	7.8	290
Me	Me	CN	228	C ₂₄ H ₂₉ N ₂ O ₄	70.9	7.1	70.7	7.1	...
Me	Me	Et	142	C ₂₅ H ₃₃ NO ₄	73.0	8.0	72.6	7.8	
Me	Me	<i>n</i> -Pr	157	C ₂₅ H ₃₃ NO ₄	73.4	8.2	73.6	8.3	286
Me	Me	<i>n</i> -Bu	124	C ₂₇ H ₃₇ NO ₄ ·0.5MeOH	72.5	8.6	72.0	8.8	
Me	Me	<i>i</i> -Bu	76	C ₂₇ H ₃₇ NO ₄	73.7	8.4	73.5	8.5	294
Me	Me	<i>n</i> -Am	135	C ₂₈ H ₃₉ NO ₄	74.1	8.7	74.3	8.7	
Me	Me	CH ₂ CH=CH ₂	104	C ₂₅ H ₃₃ NO ₄	73.7	7.9	74.0	8.0	
Me	Me	CH ₂ C≡CH	163	C ₂₅ H ₃₃ NO ₄ ·1.5H ₂ O	72.5	7.4	72.7	7.5	276
Me	Me	CH ₂ CMe=CH ₂	...	C ₂₇ H ₃₅ NO ₄ ·HCl	68.4	7.6	68.3	7.7	248
Me	Me	CH ₂ CH=CMMe ₂	...	C ₂₅ H ₃₃ NO ₄ ·HCl	68.8	7.8	69.0	8.1	172
Me	Me	CH ₂ COPh	170	C ₂₈ H ₃₅ NO ₅	74.2	7.0	73.7	6.9	
Me	Me	∞-△	214	C ₂₇ H ₃₅ NO ₅	71.7	7.3	71.9	7.3	...
Me	Me	CH ₂ -△	124	C ₂₇ H ₃₅ NO ₄ ·HCl	68.4	7.6	68.4	7.8	266
Me	Me	CH ₂ -◇	179	C ₂₈ H ₃₇ NO ₄	74.8	8.3	74.3	8.2	
Me	Et	H	155	C ₂₄ H ₂₉ NO ₄	72.5	7.8	72.3	7.8	
Me	Et	CN	198	C ₂₄ H ₂₉ N ₂ O ₄	71.1	7.2	70.8	7.5	...
Me	Et	Et	150	C ₂₅ H ₃₃ NO ₄	73.4	8.3	73.2	8.3	
Me	Et	<i>n</i> -Pr	142	C ₂₇ H ₃₇ NO ₄	73.7	8.4	73.8	8.2	282
Me	Et	<i>n</i> -Bu	100	C ₂₅ H ₃₃ NO ₄	71.1	8.7	74.5	8.7	
Me	Et	<i>i</i> -Bu	...	C ₂₅ H ₃₃ NO ₄ ·HCl·H ₂ O	66.1	8.3	66.5	8.5	268
Me	Et	CH ₂ CH=CH ₂	...	C ₂₇ H ₃₅ NO ₄ ·HCl	68.5	7.6	68.8	7.9	286
Me	Et	CH ₂ C≡CH	158	C ₂₇ H ₃₅ NO ₄	74.4	7.6	74.2	7.7	293
Me	Et	CH ₂ CMe=CH ₂	124	C ₂₅ H ₃₃ NO ₄	74.5	8.2	74.7	8.1	277
Me	Et	CH ₂ CH=CHMe	...	C ₂₆ H ₃₇ NO ₄ ·C ₄ H ₉ O ₄ ·H ₂ O ^b	62.0	7.3	61.7	7.5	242 ^b
Me	Et	CH ₂ CH=CMMe ₂	126	C ₂₅ H ₃₃ NO ₄	74.8	8.4	74.7	8.4	...
Me	Et	∞-△	212	C ₂₈ H ₃₅ NO ₅	72.2	7.6	72.0	7.6	...
Me	Et	CH ₂ -△	113	C ₂₆ H ₃₇ NO ₄	74.5	8.3	74.1	8.3	...
Me	Et	CH ₂ COCH ₃	160	C ₂₇ H ₃₅ NO ₅	71.5	7.8	71.5	7.7	125
Me	Et	CH ₂ COPh	166	C ₂₈ H ₃₇ NO ₅	74.5	7.2	74.4	7.1	155
Me	<i>n</i> -Pr	H	173	C ₂₅ H ₃₃ NO ₄	73.0	8.0	73.2	8.2	260
Me	<i>n</i> -Pr	CN	200	C ₂₄ H ₂₉ N ₂ O ₄	71.6	7.3	71.6	7.3	
Me	<i>n</i> -Pr	Et	...	C ₂₇ H ₃₇ NO ₄ ·HCl	68.1	8.0	68.1	8.2	189
Me	<i>n</i> -Pr	<i>n</i> -Pr	...	C ₂₆ H ₃₅ NO ₄ ·C ₄ H ₉ O ₄ ·H ₂ O ^b	61.8	7.2	61.3	7.6	254 ^b
Me	<i>n</i> -Pr	<i>n</i> -Bu	110	C ₂₅ H ₃₃ NO ₄	74.5	8.9	74.1	8.8	
Me	<i>n</i> -Pr	<i>i</i> -Bu	174	C ₂₅ H ₃₃ NO ₄	74.5	8.9	74.7	8.7	310
Me	<i>n</i> -Pr	<i>n</i> -Am	123	C ₂₆ H ₃₅ NO ₄	74.8	9.1	74.5	9.0	
Me	<i>n</i> -Pr	CH ₂ CH=CH ₂	118	C ₂₆ H ₃₇ NO ₄	74.5	8.2	74.2	8.1	163
Me	<i>n</i> -Pr	CH ₂ C≡CH	162	C ₂₅ H ₃₃ NO ₄	74.8	7.8	75.1	8.0	
Me	<i>n</i> -Pr	CH ₂ CMe=CH ₂	...	C ₂₅ H ₃₃ NO ₄ ·HCl	69.4	8.0	69.0	8.3	277
Me	<i>n</i> -Pr	CH ₂ CH=CMMe ₂	106	C ₂₅ H ₃₃ NO ₄	75.1	8.5	75.0	8.7	160
Me	<i>n</i> -Pr	∞-△	185	C ₂₈ H ₃₇ NO ₅	72.6	7.7	72.6	7.8	
Me	<i>n</i> -Pr	CH ₂ -△	130	C ₂₅ H ₃₃ NO ₄	74.9	8.4	74.7	8.6	
Me	<i>i</i> -Pr	CN	230	C ₂₃ H ₂₉ N ₂ O ₄	71.5	7.4	71.1	7.5	
Me	<i>i</i> -Pr	H	169	C ₂₅ H ₃₃ NO ₄	73.0	8.1	73.1	8.0	
Me	<i>i</i> -Pr	∞-△	177 (191)	C ₂₅ H ₃₃ NO ₅	72.6	7.8	73.0	7.9	
Me	<i>i</i> -Pr	CH ₂ -△	132	C ₂₅ H ₃₃ NO ₄	84.7	8.4	74.0	8.6	
Me	<i>n</i> -Bu	H	110	C ₂₆ H ₃₅ NO ₄	73.4	8.3	73.4	8.6	285

Table VI (Continued)























R	R ¹	R ²	Mp, °C	Composition	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Mp, °C, HCl
Me	<i>n</i> -Bu	CN	144	C ₂₇ H ₃₄ N ₂ O ₄	71.9	7.5	72.2	7.7	
Me	<i>n</i> -Bu	CH ₂ CH=CH ₂	102	C ₂₈ H ₃₈ NO ₄ ·0.5H ₂ O	73.4	8.5	73.2	8.7	255
Me	<i>n</i> -Bu	CH ₂ C≡CH	152	C ₂₈ H ₃₇ NO ₄	75.1	8.0	75.1	8.1	267
Me	<i>i</i> -Bu	H	131	C ₂₈ H ₃₈ NO ₄	73.4	8.3	73.5	8.4	284
Me	<i>i</i> -Bu	CN	170	C ₂₇ H ₃₄ NO ₄	71.9	7.5	72.0	7.6	
Me	<i>i</i> -Bu	CH ₂ CH=CH ₂	102	C ₂₈ H ₃₈ NO ₄	74.8	8.4	74.5	8.5	277
Me	<i>n</i> -Am	H	135	C ₂₇ H ₃₇ NO ₄	73.8	8.4	73.6	8.6	238
Me	<i>n</i> -Am	CN	129	C ₂₈ H ₃₈ NO ₄	72.4	7.8	72.5	7.9	
Me	<i>n</i> -Am	CH ₂ CMc=CH ₂	100	C ₂₈ H ₄₀ NO ₄	74.5	8.8	75.2	8.8	
Me	<i>n</i> -Am	CH ₂ CH=CMc ₂	...	C ₂₈ H ₄₀ NO ₄ ·HCl·H ₂ O	68.5	8.5	68.4	8.6	230
Me	<i>n</i> -Am		118	C ₂₈ H ₄₄ NO ₄	75.7	8.9	75.6	8.8	
Me	<i>i</i> -Am	H	134	C ₂₇ H ₃₇ NO ₄	73.8	8.4	73.7	8.5	
Me	<i>i</i> -Am	CN	164	C ₂₈ H ₃₈ N ₂ O ₄	72.4	7.8	72.6	8.0	
Me	<i>i</i> -Am	Et	110	C ₂₈ H ₄₀ NO ₄	74.5	8.8	74.0	8.8	
Me	<i>i</i> -Am	<i>n</i> -Pr	90	C ₂₈ H ₄₂ NO ₄	74.8	9.0	74.7	9.0	220
Me	<i>i</i> -Am	<i>n</i> -Bu	...	C ₂₈ H ₄₄ NO ₄ ·HCl	70.0	8.7	70.1	8.5	201
Me	<i>i</i> -Am	<i>i</i> -Bu	72	C ₂₈ H ₄₄ NO ₄	75.2	9.1	75.0	9.4	301
Me	<i>i</i> -Am	<i>n</i> -Am	101	C ₂₈ H ₄₇ NO ₄	75.5	9.3	75.8	9.2	
Me	<i>n</i> -C ₈ H ₁₇	H	...	C ₂₈ H ₄₈ NO ₄ ·C ₈ H ₁₆ O ₃ ·H ₂ O ^b	62.9	7.9	62.5	8.2	286 ^a
Me	<i>n</i> -C ₈ H ₁₇	CN	108	C ₂₈ H ₄₈ N ₂ O ₄	73.5	8.3	73.6	8.6	
Me	<i>n</i> -C ₈ H ₁₇	CH ₂ CH=CMc ₂	96	C ₂₈ H ₄₈ NO ₄	76.5	9.3	76.8	9.5	
Me		H	110	C ₂₈ H ₃₈ NO ₄	74.1	8.0	74.2	7.9	
Me		CN	210	C ₂₈ H ₃₄ N ₂ O ₄	72.7	7.4	72.5	7.6	
Me		CH ₂ CH=CMc ₂	112	C ₂₈ H ₄₀ NO ₄ ·H ₂ O	73.4	8.6	73.5	8.8	
Me		H	203	C ₂₈ H ₃₇ NO ₄	74.5	8.3	74.7	8.5	288
Me		CN	213	C ₂₉ H ₃₆ N ₂ O ₄	73.1	8.6	73.2	8.5	
Me		Et	171	C ₂₉ H ₄₀ NO ₄	75.2	8.6	74.9	8.8	
Me		<i>n</i> -Pr	180	C ₂₈ H ₄₂ NO ₄	75.4	8.8	75.4	8.8	
Me		<i>n</i> -Bu	157	C ₂₈ H ₄₄ NO ₄ ·0.5H ₂ O	74.4	9.0	74.6	8.8	
Me		<i>n</i> -Am	151	C ₂₈ H ₄₇ NO ₄	76.0	9.1	76.1	9.0	
Me		CH ₂ CH=CH ₂	204	C ₂₈ H ₄₄ NO ₄ ·0.5H ₂ O	74.4	8.4	74.4	8.4	219
Me		CH ₂ C≡CH	172	C ₂₈ H ₃₉ NO ₄	76.0	8.0	75.8	8.2	
Me		CH ₂ CMc=CH ₂	203	C ₂₈ H ₄₂ NO ₄ ·0.5H ₂ O	74.7	8.6	74.7	8.5	
Me		CH ₂ CH=CMc ₂	190	C ₂₉ H ₄₄ NO ₄	76.1	8.7	76.0	8.8	
Me			220	C ₂₈ H ₄₄ NO ₄	73.9	7.9	73.7	8.1	
Me			228	C ₂₈ H ₄₈ NO ₄ ·H ₂ O	73.5	8.6	73.5	8.4	
Me			258	C ₃₀ H ₄₄ NO ₄	74.2	8.1	74.0	8.2	
Me			98	C ₃₂ H ₄₄ NO ₄	76.3	8.7	76.3	8.5	
Me	CH ₂ Ph	CN	216	C ₃₀ H ₃₈ N ₂ O ₄	74.4	6.6	74.5	6.9	
Me	CH ₂ Ph	H	85	C ₂₈ H ₃₈ NO ₄	75.8	7.2	75.7	7.3	
Me	CH ₂ Ph	CH ₂ CH=CH ₂	78	C ₂₈ H ₃₇ NO ₄ ·HCl·H ₂ O	70.5	7.2	70.2	7.4	148
Me	CH ₂ CH ₂ Ph	H	138	C ₂₈ H ₃₈ NO ₄	76.1	7.4	76.3	7.6	
Me	CH ₂ CH ₂ Ph	CN	98	C ₂₈ H ₃₄ N ₂ O ₄	74.6	6.8	74.7	6.8	
Me	CH ₂ CH ₂ Ph	Et	159	C ₂₈ H ₃₉ NO ₄	76.6	7.8	76.1	8.0	
Me	CH ₂ CH ₂ Ph	<i>n</i> -Pr	122	C ₂₈ H ₄₁ NO ₄	76.9	8.0	76.8	8.0	
Me	CH ₂ CH ₂ Ph	<i>n</i> -Bu	...	C ₂₈ H ₄₄ NO ₄ ·HCl·H ₂ O	69.9	7.9	69.9	7.9	195
Me	CH ₂ CH ₂ Ph	CH ₂ CH=CH ₂	127	C ₂₉ H ₃₉ NO ₄	77.2	7.7	76.7	7.6	

Table VI (Continued)

R	R ¹	R ²	Mp, °C	Composition	Calcd, % C
Me	CH ₂ CH ₂ Ph	CH ₂ CH=CM ₂	...	C ₂₂ H ₂₂ NO ₄ ·HCl	72.7
Me	(CH ₂) ₃ Ph	H	138	C ₂₂ H ₂₇ NO ₄	76.4
Me	(CH ₂) ₃ Ph	CN	212	C ₂₂ H ₂₂ N ₂ O ₄	74.9
Me	(CH ₂) ₃ Ph	CH ₂ CH=CM ₂	189	C ₂₂ H ₂₂ NO ₄	77.9
Me	CH ₂ CH=CH ₂	CH ₂ CH=CH ₂	...	C ₂₂ H ₂₂ NO ₄ ·HCl	69.2
Me	(CH ₂) ₃ OE _t	CH ₂ CH=CH ₂	...	C ₂₂ H ₂₂ NO ₄ ·HCl·H ₂ O	65.5
Me	(CH ₂) ₃ OPh	CH ₂ CH=CH ₂	136	C ₂₂ H ₂₂ NO ₄	75.5
Me	<i>p</i> -Tolyl	H	190	C ₂₂ H ₂₂ NO ₄	75.8
Me	<i>p</i> -Tolyl	CN	210	C ₂₂ H ₂₂ N ₂ O ₄	74.4
Me	<i>p</i> -Tolyl	CH ₂ CN=CH ₂	201	C ₂₂ H ₂₇ NO ₄	76.9

* For bases where R² = Me, see Table I, ref 1a. ^b Bitartrate.

The 3-O-propionyl ester was obtained (from the phenol, propionic anhydride, and sodium propionate) as off-white prisms, mp 130°, from aqueous ethanol.

Anal. Calcd for C₂₂H₂₇NO₄: C, 71.9; H, 7.9. Found: C, 71.8; H, 7.9.

N-Cyano-7α-acetyl-6,14-endo-ethenotetrahydronorthebaine (VI, R = CN). 7α-Acetyl-6,14-endo-ethenotetrahydrothebaine (VI, R = Me) (50 g) was heated under reflux with cyanogen bromide (16 g) in dry alcohol-free chloroform (350 ml) for 12 hr. The chloroform was evaporated, and the residue was recrystallized from 2-ethoxyethanol, when the N-cyanonor compound (48 g) was obtained as colorless prisms, mp 236°, ν_{max} 2250 and 1715 cm⁻¹.

Anal. Calcd for C₂₂H₂₄N₂O₄: C, 70.4; H, 6.2. Found: C, 70.2; H, 6.4.

N-Aminocarbonyl-7α-acetyl-6,14-endo-ethenotetrahydronorthebaine (VI, R = CONH₂). N-Cyano-7α-acetyl-6,14-endo-ethenotetrahydronorthebaine (VI, R = CN) (40 g), finely powdered, was boiled under reflux with 2 N hydrochloric acid (400 ml), in the presence of a small amount of a neutral wetting agent to minimize frothing, until all the solid had dissolved (~2 hr). The solution was cooled, and a small portion was neutralized with ammonia, when a viscous gum was obtained, from which the crystalline N-aminocarbonyl compound was obtained with difficulty on crystallization from methanol as prisms, mp 220°.

Anal. Calcd for C₂₂H₂₆N₂O₅: C, 67.3; H, 6.4; N, 6.8. Found: C, 67.1; H, 6.4; N, 6.8.

7α-Acetyl-6,14-endo-ethenotetrahydronorthebaine (VI, R = H). a. The acid solution obtained by the hydrolysis of N-cyano-7α-acetyl-6,14-endo-ethenotetrahydronorthebaine (VI, R = CN) (40 g) as above was cooled to 0°, and an aqueous solution of sodium nitrite (8 g) was slowly added with vigorous stirring. When evolution of gas ceased, the mixture was made alkaline with ammonia and extracted with chloroform. Evaporation of the extract gave a viscous gum, which was converted into the crystalline hydrochloride with methanolic hydrogen chloride. The salt (25 g) was obtained as plates, mp 350°, from hot water.

Anal. Calcd for C₂₂H₂₈NO₄·HCl·0.5H₂O: C, 64.0; H, 6.6. Found: C, 63.9; H, 6.3.

The base recovered from the hydrochloride was obtained as needles, mp 73°, from water.

Anal. Calcd for C₂₂H₂₈NO₄·H₂O: C, 68.8; H, 7.0. Found: 68.8; H, 7.2.

The picrate was obtained as yellow prisms, mp 273°, from ethanol.

Anal. Calcd for C₂₂H₂₈N₄O₁₁: C, 56.4; H, 4.7; N, 9.4. Found: C, 56.0; H, 4.7; N, 9.4.

The N-acetyl compound was prepared by heating the base with acetic anhydride and was obtained as prisms, mp 101°, from aqueous methanol.

Anal. Calcd for C₂₄H₂₇NO₅·H₂O: C, 67.4; H, 6.8. Found: C, 67.3; H, 6.8.

The N-cyclopropylcarbonyl compound, from the base and cyclopropylcarbonyl chloride and anhydrous potassium carbonate in ether, was obtained as prisms, mp 197°.

Anal. Calcd for C₂₅H₂₉NO₅: C, 71.7; H, 6.7. Found: C, 71.8; H, 6.8.

b. A solution of 7α-acetyl-6,14-endo-ethenotetrahydrothebaine (10 g) (VI, R = Me) and methyl azodicarboxylate (3.84 g) in acetone (75 ml) was evaporated to dryness over about 30 min. The viscous yellow residue was dissolved in 1 N hydrochloric acid (40 ml) with vigorous stirring and the solution set aside until separation of solid

matter ceased (~1 hr). The hydrate was washed with ice water, and a water when the nor base (X, R = 1) as prisms, mp 350°, identical in infrared with material prepared as in part a.

N-Allyl-7α-acetyl-6,14-endo-ethenotetrahydronorthebaine (VI, R = CH₂CH=CH₂). 7α-Acetylthebaine (VI, R = H) (20 g), all sodium carbonate (10 g), and ethanol under reflux for 18 hr. The mixture leaving the base as an uncrystallizable hydrochloride (22 g) as plates, mp 2 hydrogen chloride.

Anal. Calcd for C₂₄H₂₈NO₄·HCl: Found: C, 64.8; H, 7.1.

Other N-substituted nor bases of the secondary base VI and are listed in Table V.

N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthebaine (VII, R = R¹ = 1-hydroxy-1-methylethyl) (15 g), cyanogen bromide (50 ml) were boiled for 24 hr. The solution was evaporated, the residue was finely powdered and stirred with hydrochloric acid, then collected, recrystallized from aqueous 2-ethoxyethanol nor compound (14.8 g) was obtained, ν_{max} 2250 cm⁻¹.

Anal. Calcd for C₂₄H₂₈N₂O₄: Found: C, 70.7; H, 7.1.

N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydrothebaine (VIII, R = R¹ = 1-hydroxy-1-methylethyl) (5.3 g), cyanogen bromide (5.3 g), 7α-endo-ethenotetrahydrothebaine (VI, R = H) (5 g) in dry methylene chloride was stirred for 24 hr. The product (14.8 g) isolated by extraction with acid washing of the powdered residue, mp 275°, from aqueous 2-ethoxyethanol.




















Anal. Calcd for C₂₄H₂₈N₂O₄: Found: C, 70.1; H, 6.4.

7α-(1-Hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydrothebaine (VII, R = R¹ = Me; R² = 1-hydroxy-1-methylethyl) (57 g) was dissolved in a solution of potassium hydroxide (100 ml) at 165–170°, and the mixture was stirred until evolution of ammonia ceased, was then poured into vigorously stirred crushed ice, and the precipitated solid was washed from water, when the secondary base was obtained as prisms, mp 163°. (A low-melting solid was obtained in initial experiments, and a ca. 50% solution by rapid cooling.)

Anal. Calcd for C₂₄H₂₈NO₄: Found: C, 72.3; H, 7.8.

The hydrolysis of other N-cyano-7α-substituted bases was effected in that they did not crystallize on dilution with water were isolated by ether extraction with organic solvents of the residue.

Table VII. Alcohols of Structure VIII^a

R	R ¹	R ²	Mp, °C	Composition	Calcd, %		Found, %		Mp, °C, HCl
					C	H	C	H	
H	H	H	...	C ₂₀ H ₂₃ NO ₄ ·HCl·H ₂ O	60.7	6.7	60.5	6.6	264
H	H	CH ₂ CH=CH ₂	...	C ₂₃ H ₂₇ NO ₄ ·HCl·2H ₂ O	60.9	7.1	60.8	7.2	281
H	Me	H	296	C ₂₁ H ₂₅ NO ₄	71.0	7.1	71.2	7.4	
H	Me	CH ₂ CH=CH ₂	265	C ₂₄ H ₂₉ NO ₄	72.8	7.3	72.8	7.5	
H	Me	CH ₂ — 	92	C ₂₅ H ₃₁ NO ₄ ·HCl·H ₂ O	64.6	7.3	64.6	7.2	251
Me	Me	H	284	C ₂₃ H ₂₇ NO ₄	71.5	7.3	71.3	7.4	308
Me	Me	Et	228	C ₂₄ H ₃₁ NO ₄	72.5	7.8	72.0	7.9	
Me	Me	<i>n</i> -Bu	172	C ₂₆ H ₃₅ NO ₄	73.4	8.3	73.3	8.2	
Me	Me	<i>n</i> -Am	...	C ₂₇ H ₃₇ NO ₄ ·HCl·0.5H ₂ O	66.9	8.1	67.0	8.0	196
Me	Me	CH ₂ CH=CH ₂	120 (210)	C ₂₅ H ₃₁ NO ₄	73.3	7.6	73.0	7.4	248
Me	Me	CH ₂ C≡CH	120	C ₂₅ H ₂₉ NO ₄	73.6	7.1	73.7	7.4	240
Me	Me	CH ₂ CH=CM ₂	...	C ₂₇ H ₃₅ NO ₄ ·HCl·2H ₂ O	63.6	7.9	63.4	8.0	212
Me	Me	CO— 	290	C ₂₆ H ₃₁ NO ₅	71.4	7.1	71.5	7.3	
Me	Me	CH ₂ — 	234	C ₂₆ H ₃₃ NO ₄	73.6	7.8	73.6	7.9	248
Me	Et	H	277	C ₂₃ H ₂₉ NO ₄	72.0	7.6	71.5	7.7	
Me	Et	Et	260	C ₂₅ H ₃₃ NO ₄	73.0	8.0	72.5	8.0	
Me	Et	<i>n</i> -Pr	187	C ₂₆ H ₃₅ NO ₄	73.4	8.3	73.5	8.4	
Me	Et	<i>n</i> -Bu	162	C ₂₇ H ₃₇ NO ₄	73.7	8.5	73.4	8.5	
Me	Et	CH ₂ CH=CM ₂	208	C ₂₈ H ₃₇ NO ₄	74.5	8.3	74.9	8.2	
Me	Et	CO— 	254	C ₂₇ H ₃₃ NO ₅	71.8	7.4	71.7	7.6	
Me	Et	CH ₂ — 	117	C ₂₇ H ₃₅ NO ₄	74.1	8.1	73.8	8.1	
Me	<i>n</i> -Pr	H	260	C ₂₄ H ₃₁ NO ₄	72.5	7.8	72.2	8.2	305
Me	<i>n</i> -Pr	Et	219	C ₂₆ H ₃₅ NO ₄	73.4	8.3	73.0	8.3	
Me	<i>n</i> -Pr	<i>n</i> -Pr	214	C ₂₇ H ₃₇ NO ₄	73.7	8.5	74.0	8.3	
Me	<i>n</i> -Pr	<i>n</i> -Bu	136	C ₂₈ H ₃₉ NO ₄	74.1	8.7	73.9	8.6	
Me	<i>n</i> -Pr	<i>n</i> -Am	141	C ₂₉ H ₄₁ NO ₄	74.5	8.9	74.4	9.2	
Me	<i>n</i> -Pr	CH ₂ CH=CH ₂	126	C ₂₇ H ₃₅ NO ₄	74.1	8.0	74.0	8.1	254
Me	<i>n</i> -Pr	CH ₂ CH=CM ₂	190	C ₂₉ H ₃₉ NO ₄	74.8	8.4	74.5	8.2	
Me	<i>n</i> -Pr	CO— 	270	C ₂₈ H ₃₅ NO ₅	72.2	7.5	72.0	7.8	
Me	<i>n</i> -Pr	CH ₂ — 	180	C ₂₈ H ₃₇ NO ₄	74.4	8.2	74.7	8.5	262
Me	<i>n</i> -Bu	H	210	C ₂₅ H ₃₃ NO ₄	73.0	8.0	72.9	8.2	
Me	<i>n</i> -Bu	CH ₂ CH=CH ₂	122	C ₂₈ H ₃₇ NO ₄	74.5	8.3	74.4	8.0	263
Me	<i>n</i> -Am	CO— 	236	C ₃₀ H ₃₉ NO ₅	73.0	8.0	72.8	7.8	
Me	<i>n</i> -Am	CH ₂ — 		C ₃₂ H ₄₁ NO ₄	75.1	8.6	74.9	8.6	
Me	<i>i</i> -Am	H	262	C ₂₈ H ₃₅ NO ₄	73.4	8.3	73.6	8.2	
Me	<i>i</i> -Am	Et	179	C ₃₀ H ₃₉ NO ₄	74.1	8.7	74.0	8.6	
Me	<i>i</i> -Am	<i>n</i> -Pr	175	C ₂₉ H ₄₁ NO ₄	74.5	8.9	74.5	8.9	
Me	<i>i</i> -Am	<i>n</i> -Bu	141	C ₃₀ H ₄₃ NO ₄ ·0.5H ₂ O	73.5	9.0	73.8	9.0	
Me	<i>i</i> -Am	<i>n</i> -Am	122	C ₃₁ H ₄₅ NO ₄ ·0.5H ₂ O	73.8	9.2	74.3	9.4	
Me	<i>i</i> -Am	CH ₂ CH=CM ₂	225	C ₃₁ H ₄₃ NO ₄	75.4	8.8	75.4	8.8	
Me	<i>i</i> -Am	CO— 	240	C ₃₃ H ₃₉ NO ₅	73.0	7.9	73.2	8.1	
Me	<i>i</i> -Am	CH ₂ — 	110	C ₃₀ H ₄₁ NO ₄	75.1	8.6	75.3	8.8	258
Me		H	310	C ₂₇ H ₃₅ NO ₄	74.1	8.0	74.3	8.2	
Me		<i>n</i> -Pr	...	C ₃₀ H ₄₁ NO ₄ ·HCl	69.8	7.9	69.9	8.1	275
Me		CH ₂ CH=CH ₂	...	C ₃₄ H ₃₉ NO ₄ ·HCl	70.1	7.6	70.0	7.9	251
Me		CH ₂ C≡CH	...	C ₃₀ H ₂₇ NO ₄ ·HCl	70.3	7.2	70.0	7.5	202
Me		CO— 	268	C ₃₁ H ₃₉ NO ₅	73.6	7.7	73.8	7.9	
Me		CH ₂ — 	134 (198)	C ₃₁ H ₄₁ NO ₄	75.6	8.4	75.5	8.6	180













^a For bases where R² = Me, see Table I, ref 1a.

generally resulted in crystallization of the product, but a few secondary bases could not be induced to crystallize and were characterized as the hydrochloride or acid tartrate.

7 α -(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorripavine (VIII, R = R¹ = Me; R² = H). a. N-Cyano-7 α -




(1-hydroxy-1-methylethyl)-6,14-*endo*-ethenotetrahydronorthebaine (VII, R = R¹ = Me; R² = CN) (100 g) was added to a vigorously stirred solution of potassium hydroxide (250 g) in diethylene glycol (1200 ml) at 200° under an atmosphere of nitrogen. The mixture was heated at 200–220° until a test portion on

Table VIII. 6,14-Ethano Analogs of Alcohols of Structure VII^a

R	R ¹	R ²	Mp, °C	Composition	Calcd, % C	H	Found, % C	H	Mp, °C HCl
H	H	CH ₂ — 	107	C ₂₅ H ₃₃ NO ₄	73.0	8.1	73.4	8.5	
Me	Me	H	146	C ₂₃ H ₃₁ NO ₄	71.6	8.1	72.1	8.3	
Me	Me	CN	205	C ₂₄ H ₃₀ N ₂ O ₄	70.2	7.4	69.6	7.0	
Me	Me	CH ₂ — 	123	C ₂₇ H ₃₇ NO ₄	73.8	8.5	73.4	8.5	
Me	Et	H	143	C ₂₄ H ₃₃ NO ₄	72.1	8.3	72.0	8.1	
Me	Et	CN	170	C ₂₅ H ₃₂ N ₂ O ₄	70.7	7.6	70.8	7.7	
Me	Et	CH ₂ — 	100	C ₂₈ H ₃₉ NO ₄	72.1	8.3	72.0	8.1	
Me	<i>n</i> -Pr	H	168	C ₂₅ H ₃₅ NO ₄ ·HCl·0.5H ₂ O	65.4	8.1	64.9	7.8	265
Me	<i>n</i> -Pr	CN	199	C ₂₆ H ₃₄ N ₂ O ₄	71.2	7.8	71.4	7.9	
Me	<i>n</i> -Pr	CH ₂ — 	99	C ₂₉ H ₄₁ NO ₄	74.5	8.8	74.4	8.6	
Me	<i>n</i> -Bu	H	136	C ₂₆ H ₃₇ NO ₄	73.1	8.7	73.0	8.7	
Me	<i>n</i> -Bu	CN	153	C ₂₇ H ₃₆ N ₂ O ₄	71.6	8.0	72.1	8.0	
Me	<i>n</i> -Bu	CH ₂ — 	102	C ₃₀ H ₄₃ NO ₄	74.8	9.0	74.9	9.0	
Me	<i>i</i> -Bu	H	128	C ₂₇ H ₃₇ NO ₄	73.1	8.7	72.6	8.5	
Me	<i>i</i> -Bu	CN	180	C ₂₇ H ₃₆ N ₂ O ₄	71.6	8.0	71.5	8.3	
Me	<i>i</i> -Bu	H	199	C ₂₈ H ₃₇ NO ₄	73.1	8.7	72.6	8.6	
Me	<i>i</i> -Bu	CN	207	C ₂₇ H ₃₆ N ₂ O ₄	71.6	8.0	71.3	8.2	
Me	<i>i</i> -Bu	CO— 	176	C ₃₀ H ₄₁ NO ₃	72.7	8.3	72.7	8.3	
Me	<i>i</i> -Bu	CH ₂ — 	109	C ₃₀ H ₄₃ NO ₄	74.8	9.0	74.5	9.0	
Me	<i>n</i> -Am	H	...	C ₂₇ H ₃₉ NO ₄ ·HCl	67.8	8.4	68.1	8.5	241
Me	<i>n</i> -Am	CN	142	C ₂₈ H ₃₈ N ₂ O ₄	72.0	8.2	71.5	8.5	
Me	<i>n</i> -Am	CH ₂ — 	78	C ₃₁ H ₄₅ NO ₄	75.1	9.2	74.5	9.6	
Me	<i>i</i> -Am	CN	152	C ₂₈ H ₃₈ N ₂ O ₄	72.0	8.2	71.9	8.4	
Me		H	174	C ₂₈ H ₃₉ NO ₄	74.1	8.7	74.3	8.5	
Me		CN	216	C ₂₉ H ₃₈ N ₂ O ₄	72.8	8.0	72.9	8.1	
Me		CO— 	235	C ₂₉ H ₄₂ NO ₃	73.7	8.3	74.0	8.3	

^a For bases where R² = Me, see Table II, ref 1a.

Table IX. 6,14-Ethano Analogs of Alcohols of Structure VIII

R	R ¹	R ²	Mp, °C	Compo- sition	Calcd, % C	H	Found, % C	H
Me	Me	CH ₂ — 	185	C ₂₆ H ₃₃ NO ₄	73.4	8.3	72.8	8.3
Me	<i>n</i> -Pr	H	239	C ₂₄ H ₃₁ NO ₄	72.1	8.3	72.1	7.9
Me	<i>n</i> -Pr	CH ₂ — 	179	C ₂₈ H ₃₉ NO ₄	74.1	8.7	74.1	8.5
Me	<i>n</i> -Bu	CH ₂ — 	178	C ₂₉ H ₄₁ NO ₄	74.5	8.9	74.5	8.8

dilution with ten times its volume of water gave a homogeneous solution (~30–40 min). The mixture was rapidly cooled and poured with vigorous stirring into ice-water (2500 ml), and the phenol was then precipitated by the addition of saturated aqueous ammonium chloride. The product (80 g), mp 280–282°, was collected, washed well with water, and recrystallized from methanol, when the phenolic base XII (R = R¹ = Me, R² = H) was obtained as prisms, mp 284°.

Anal. Calcd for C₂₂H₂₇NO₄: C, 71.5; H, 7.3. Found: C, 71.3; H, 7.4.

b. N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronoripavine (VIII, R = R¹ = Me; R² = CN) (5 g) was hydrolyzed with potassium hydroxide (5 g) and diethylene glycol (40 ml) at 160–170° for 10 min. The mixture was poured into water (250 ml) and the phenol was precipitated with ammonium chloride, collected, washed, and recrystallized from aqueous 2-ethoxyethanol, when it was obtained (3.1 g) as prisms, mp 284°, identical in infrared absorption, mixture melting point, and R_f value with material obtained as in part a above.

c. 19-Methylnorthevinol (VII, R = R¹ = Me; R² = H) (2 g) was O-demethylated by heating with potassium hydroxide

(2.5 g) and diethylene glycol (12.5 ml) at 210° until a test portion gave a homogeneous solution on dilution with water. The mixture was then diluted with water (65 ml), and the product was precipitated with ammonium chloride, when 19-methylnororvinol (VIII, R = R¹ = Me; R² = H) (0.8 g) was obtained as prisms, mp 284°, from 2-ethoxyethanol, identical with the base obtained in a and b above.

Other phenolic secondary bases of structure VIII, (R² = H) were prepared by the combined hydrolysis and O-demethylation of N-cyano compounds of the tetrahydrothebaine series VII, (R¹ = CN) by the process given in part a above.

N-Allyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthebaine (VII, R = R¹ = Me; R² = CH₂CH=CH₂) (N-Allyl-19-methylnorthevinol). a. 19-Methylnorthevinol (VII, R = R¹ = Me; R² = H) (3.4 g), allyl bromide (1 g), anhydrous sodium carbonate (2 g), and ethanol (40 ml) were boiled together under reflux for 18 hr. The mixture was filtered and evaporated, leaving a viscous gum that crystallized on standing. It was recrystallized from petroleum ether (bp 40–60°), when N-allyl-19-methylnororvinol was obtained (3.0 g) as white prisms, mp 104°.

Anal. Calcd for C₂₆H₃₃NO₄: C, 73.7; H, 7.9. Found: C, 74.0; H, 8.0.

b. N-Allyl-7α-acetyl-6,14-endo-ethenotetrahydrothebaine (N-allylnorthevinone, VI, R = CH₂CH=CH₂) (10 g) in ether (350 ml) was slowly added to a vigorously stirred solution of methylmagnesium iodide (from 1.67 g of magnesium and 9.9 g of methyl iodide) in ether (200 ml). The mixture was stirred and heated under reflux for 2 hr and poured into aqueous ammonium chloride. The ether layer was separated, dried, and evaporated, leaving a residue that crystallized on standing. Recrystallization of the product from petroleum ether (bp 40–60°) afforded N-allyl-19-methylnorthevinol (8.9 g) as white prisms, mp 104°, identical in infrared absorption, mixture melting point, and R_f value with the base prepared as in part a above.

The base was also obtained from *N,N'*-methylenebis(19-methylnorthevinol) (IX, $R = R^1 = R^2 = R^3 = \text{Me}$) and allyl iodide (see below).

Other *N*-substituted nor bases of the general formula VII were prepared from the corresponding secondary bases by heating the appropriate alkyl, alkenyl, or alkynyl halide, sodium cyanate, and a solvent, generally ethanol, though acetone or ethyl methyl ketone was the preferred solvent for 3,3-dimethylbromide since solvolysis of the halide appeared to occur when iodide was used.

***N*-Allyl-7 α -(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthevinol (VIII, $R = R^1 = \text{Me}$; $R^2 = \text{CH}_2\text{CH}=\text{CH}_2$)** (19-methylnorvinol). *a.* 7 α -(1-Hydroxy-1-methylethyl)-endo-ethenotetrahydronorthevinol (VIII, $R = R^1 = \text{Me}$; $R^2 = \text{H}$) (19-methylnorvinol) (3.4 g), allyl bromide (1 g), anhydrous sodium carbonate (2 g), and ethanol (80 ml) were boiled under reflux for 18 hr. The mixture was filtered and the residue was recrystallized from methanol, when the allyl compound (3.0 g) was obtained as white prisms, mp on slow heating, 210° on plunging into a bath heated above

lit. Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_2$: C, 73.3; H, 7.6. Found: C, 73.4; H, 7.4.

***N*-Allyl-7 α -(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthevinol (N-allyl-19-methylnorthevinol, VII, $R = R^1 = \text{Me}$; $R^2 = \text{CH}_2\text{CH}=\text{CH}_2$)** (2 g) was demethylated by heating with potassium hydroxide (2.5 g) and diethylene glycol (ml) at 200–210° until a homogeneous solution was obtained on addition of a test portion with ten times its volume of water. The mixture was then poured into aqueous ammonium chloride, and the mixture was isolated by ether extraction, when it was obtained, after recrystallization from methanol, as white prisms (0.8 g), mp 120–121°, identical with material prepared as in part a above.

Other *N*-substituted nor bases of the phenolic series VIII were prepared as in a by the action of alkyl, alkenyl, or alkynyl halides on the appropriate secondary base VIII ($R^3 = \text{H}$), though with methylallyl bromide acetone was used as the solvent.

Cyclopropylcarbonyl-7 α -(1-hydroxy-1-methylethyl)-6,14-endo-tetrahydronorthevinol (N-Cyclopropylcarbonyl-19-methylnorvinol, VII, $R = R^1 = \text{Me}$; $R^2 = \text{cyclopropylcarbonyl}$). Secondary base 19-methylnorthevinol (VII, $R = R^1 = \text{Me}$; $R^2 = \text{H}$) (5 g) was stirred in dry ether (150 ml) with anhydrous potassium carbonate (5 g) and cyclopropyl carbonyl chloride (1.4 g) for 5 hr. Water and dilute hydrochloric acid were then added, and the ether layer was separated, washed with water, dried, and evaporated, leaving the nonbasic amide as prisms, mp 212° (3.5 g) lit to 214°, ν_{max} 1640 cm^{-1} , on recrystallization from methanol.

lit. Calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_3$: C, 71.7; H, 7.3. Found: C, 71.8; H, 7.3.

***N*-Cyclopropylmethyl-7 α -(1-hydroxy-1-methylethyl)-6,14-endo-tetrahydronorthevinol (N-Cyclopropylmethyl-19-methylnorvinol, VII, $R = R^1 = \text{Me}$; $R^2 = \text{cyclopropylmethyl}$)**. The amide cyclopropylcarbonyl-19-methylnorthevinol (VII, $R = R^1 = \text{Me}$; $R^2 = \text{cyclopropylcarbonyl}$) (2 g) in tetrahydrofuran (40 ml) was stirred and heated under reflux with lithium aluminum hydride for 5 hr. The excess of hydride was cautiously destroyed by addition of an aqueous solution of potassium sodium tartrate, the tetrahydrofuran layer was separated. The aqueous layer was extracted with ether, and the combined organic solutions were dried and evaporated, when the tertiary base was obtained as a gum, which slowly crystallized. Recrystallization of the product from methanol afforded 1.4 g of colorless prisms, mp 124°.

lit. Calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_2$: C, 74.2; H, 8.0. Found: C, 74.3; H, 7.8.

The tertiary base was obtained by treating an ethanolic solution of the base with ethanolic hydrogen chloride and adding dry ether. The product was obtained as white prisms, mp 266°.

lit. Calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_2 \cdot \text{HCl}$: C, 68.4; H, 7.6. Found: C, 68.5; H, 7.8.

Other tertiary bases of general structure VII could be prepared by the same amide and reduction with lithium aluminum hydride in a similar manner to the above.

Cyclopropylcarbonyl-7 α -(1-hydroxy-1-methylethyl)-6,14-endo-tetrahydronorthevinol (N-Cyclopropylcarbonyl-19-methylnorvinol, VIII, $R = R^1 = \text{Me}$; $R^2 = \text{cyclopropylcarbonyl}$). The phenolic secondary base 19-methylnorvinol (VIII, $R = R^1 = \text{Me}$; $R^2 = \text{H}$) (5 g) was stirred in dry ether (150 ml) with anhydrous sodium carbonate (5 g) and cyclopropylcarbonyl chloride (2.4 g) for 5 hr. The solution was stirred with 1 *N* hydrochloric acid (ml) for 5 min, the ether layer was separated, washed, dried,

and evaporated, leaving the amide as a solid residue. This was recrystallized from ethanol, when it was obtained as white prisms, mp 290°, giving a blue color with ferric chloride and instantly soluble when an ethanolic solution was added to an excess of cold aqueous sodium hydroxide.

Anal. Calcd for $\text{C}_{26}\text{H}_{31}\text{NO}_3$: C, 71.4; H, 7.1. Found: C, 71.5; H, 7.3.

***N*-Cyclopropylmethyl-7 α -(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthevinol (N-Cyclopropylmethyl-19-methylnorvinol, VIII, $R = R^1 = \text{Me}$; $R^2 = \text{cyclopropylmethyl}$)**. The amide VIII ($R = R^1 = \text{Me}$; $R^2 = \text{cyclopropylcarbonyl}$) (4 g) was reduced with lithium aluminum hydride (2.15 g) in tetrahydrofuran under reflux over 5 hr. The product was isolated by the cautious addition of an aqueous solution of potassium sodium tartrate and ether extraction, when the tertiary base was obtained as white prisms, mp 234°, on recrystallization from methanol.

Anal. Calcd for $\text{C}_{26}\text{H}_{33}\text{NO}_2$: C, 73.6; H, 7.8. Found: C, 73.6; H, 7.9.

Other *N*-substituted bases of the phenolic series VIII were prepared by the amide and reduction with lithium aluminum hydride by the same method described above.

***N,N'*-Methylenebis(7 α -(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthevinol) (N,N'-Methylenebis(19-methylnorvinol), IX, $R = R^1 = R^2 = R^3 = \text{Me}$)**. *a.* A solution of 19-methylnorvinol (I, $R = R^1 = \text{Me}$) (10 g) and methyl azodicarboxylate (3.64 g) in acetone (75 ml) was evaporated to dryness over 30 min. The viscous yellow product was dissolved in cold 1 *N* hydrochloric acid (100 ml) and the solution kept at room temperature for 45 min. The base was precipitated with ammonia and rapidly extracted with ether. The undried extract was evaporated, the viscous residue dissolved in methanol (50 ml), and the solution heated to boiling. A white solid (8.4 g) rapidly separated and was collected and recrystallized from 2-ethoxyethanol, when the *N,N'*-methylenebis compound was obtained as white prisms, mp 286°.

Anal. Calcd for $\text{C}_{67}\text{H}_{88}\text{N}_2\text{O}_4$: C, 72.5; H, 7.4. Found: C, 72.3; H, 7.5.

b. Aqueous formaldehyde (30%, 1 ml) was added to a solution of 19-methylnorvinol (VII, $R = R^1 = \text{Me}$; $R^2 = \text{H}$) (2 g) in ethanol (15 ml). The mixture was kept at the room temperature for 45 min, diluted with water, and extracted with ether. The ether extract on evaporation yielded a viscous gum (2.01 g), 1 g of which on heating under reflux in methanol (5 ml) gave 0.85 g of the above *N,N'*-methylenebis compound (IX, $R = R^1 = R^2 = R^3 = \text{Me}$). The remaining 1 g on heating with 19-methylnorvinol (1 g) in methanol (10 ml) afforded 1.8 g of the same *N,N'*-methylenebis compound, mp 286°.

***N*-Hydroxymethyl-7 α -(1-(*R*)-hydroxy-1-methyl-3-phenylpropyl)-6,14-endo-ethenotetrahydronorthevinol (N-Hydroxymethyl-19-phenethylnorthevinol, VII, $R = \text{Me}$; $R^1 = \text{CH}_2\text{CH}_2\text{Ph}$; $R^2 = \text{CH}_2\text{OH}$)**. Aqueous formaldehyde (30%, 1 ml) was added to a warm solution of 19-phenethylnorthevinol (VII, $R = \text{Me}$; $R^1 = \text{CH}_2\text{CH}_2\text{Ph}$; $R^2 = \text{H}$) (2 g) in ethanol (15 ml) and the mixture kept at 45° for 30 min during which time a crystalline solid separated. The mixture was cooled, and the solid (1.9 g) was collected and recrystallized from methanol containing 10% of aqueous 30% formaldehyde, when the carbinolamine (1.6 g) was obtained as white prisms, mp 123°.

Anal. Calcd for $\text{C}_{28}\text{H}_{37}\text{NO}_3$: C, 74.1; H, 7.4. Found: C, 74.6; H, 7.8.

***N,N'*-Methylenebis(7 α -(1-(*R*)-hydroxy-1-methyl-3-phenylpropyl)-6,14-endo-ethenotetrahydronorthevinol) (N,N'-Methylenebis(19-phenethylnorthevinol), IX, $R = R^1 = \text{Me}$; $R^2 = R^3 = \text{CH}_2\text{CH}_2\text{Ph}$)**.

a. A solution of 19-phenethylnorthevinol (60 g) and ethyl azodicarboxylate (24 g) in acetone (450 ml) was boiled under reflux for 1 hr. The acetone was then evaporated, and the residue was dissolved in methanol (600 ml) and water (75 ml) added. The solution was heated to boiling when a crystalline solid rapidly separated. The mixture was cooled, and the solid (42 g) was collected and a portion recrystallized from 1-propanol, when the *N,N'*-methylenebis compound was obtained as white prisms, mp 241–243°.

Anal. Calcd for $\text{C}_{68}\text{H}_{90}\text{N}_2\text{O}_4$: C, 76.4; H, 7.4; N, 2.9. Found: C, 76.4; H, 7.8; N, 2.9.

b. *N*-Hydroxymethyl-19-phenethylnorthevinol (VII, $R = \text{Me}$; $R^1 = \text{CH}_2\text{CH}_2\text{Ph}$; $R^2 = \text{CH}_2\text{OH}$) (1 g) was heated in boiling ethanol (20 ml) until separation of crystalline material appeared to have ceased. The mixture was cooled and the solid (0.8 g) collected, when the *N,N'*-methylenebis compound was obtained as prisms, mp 238–240°, raised to 241–242° on recrystallization from 1-propanol.

c. N-Hydroxymethyl-19-phenethylnorthevinol (VII, R = Me; R¹ = CH₂CH₂Ph; R² = CH₂OH) (1 g) and 19-phenethylnorthevinol (VII, R = Me; R¹ = CH₂CH₂Ph; R² = H) (0.93 g) were heated together in ethanol (25 ml) until separation of crystalline material appeared to have ceased. The mixture was cooled and the N,N'-methylenebis compound (1.7 g) was collected and recrystallized from 1-propanol, when it was obtained as white prisms, mp 241–243°.

N,N'-Methylene-7 α -(1-hydroxy-1-methylethyl)-7' α -(1-(R)-hydroxy-1-methyl-3-phenylpropyl)bis(6,14-endo-ethenotetrahydronorthebaine) (N,N'-Methylene-19-methyl-19'-phenethylbis(northevinol), IX, R = R¹ = R² = Me; R³ = CH₂CH₂Ph). a. N-Hydroxymethyl-19-phenethylnorthevinol (VII, R = Me; R¹ = CH₂CH₂Ph; R² = CH₂OH) (1 g) and 19-methylnorthevinol (VII, R = R¹ = Me; R² = H) (0.76 g) were heated together in boiling ethanol until separation of the solid ceased. The mixture was cooled, and the product was collected (1.41 g) and recrystallized from 1-propanol, when it was obtained as white prisms, mp 218–220°.

Anal. Calcd for C₃₄H₄₄N₂O₄: C, 74.6; H, 7.7. Found: C, 74.3; H, 7.2.

b. Aqueous formaldehyde (30%, 1 ml) was added to a solution of 19-methylnorthevinol (VII, R = R¹ = Me; R² = H) (1 g) in ethanol (10 ml), and after 30 min the solution was diluted with water (50 ml) and rapidly extracted with ether. The ether extract was evaporated at 20° *in vacuo*; the residue was dissolved in ethanol (20 ml) and heated with 19-phenethylnorthevinol (VII, R = Me, R¹ = CH₂CH₂Ph; R² = H) (1.24 g) until precipitation of solid ceased. The mixture was cooled and the above unsymmetrical bis compound (1.9 g) was collected and obtained as prisms, mp 218–220°, after recrystallization from 1-propanol.

Hydrolysis of N,N'-Methylenebis(7 α -(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthebaine) (IX, R = R¹ = R² = R³ = Me). a. The N,N'-methylenebis compound (500 g) was dissolved in 1 N hydrochloric acid (5 ml), and the solution was added to a solution of 2,4-dinitrophenylhydrazine (500 mg) in 3 N hydrochloric acid (10 ml). The mixture was warmed until separation of solid matter ceased. The solid was collected, washed with water, and dried (125 mg). On recrystallization from aqueous ethanol, it was obtained as orange needles, mp 165°, undepressed on mixing with formaldehyde 2,4-dinitrophenylhydrazone, mp 166°.

b. A solution of dimedone (0.2 g) in ethanol (5 ml) was added to a hot solution of the N,N'-methylenebis compounds (1 g) in 6% acetic acid. Methylenedimedone (0.19 g) was precipitated almost at once and was collected, when it was obtained as white prisms, mp 189° undepressed on mixing with an authentic specimen prepared from formaldehyde. The filtrate, after removal of this derivative, was basified with ammonia, and the precipitated base

was collected and recrystallized from aqueous methanol, when the secondary base (VII, R = R¹ = Me; R² = H) (0.8 g) was obtained as needles, mp 163°, identical with material prepared by the hydrolysis of the N-cyanonor compound (VII, R = R¹ = Me; R² = CN) as described above.

Reaction of N,N'-Methylenebis(7 α -(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydrothebaine) (IX, R = R¹ = R² = R³ = Me) with Alkyl and Acyl Halides. a. The N,N'-methylenebis compound (1 g), methyl iodide (2 ml), anhydrous potassium carbonate (1 g), and ethanol (20 ml) were boiled together under reflux for 6 hr. Filtration and concentration of the solution afforded 19-methylthevinol (I, R = R' = Me) (1 g), mp 166° alone or mixed with an authentic specimen.

b. The bis compound (1 g), allyl bromide (2 ml), anhydrous potassium carbonate (1 g), and ethanol (20 ml) were boiled together under reflux for 16 hr. Filtration and evaporation of the solution yielded N-allyl-19-methylnorthevinol (VII, R = R¹ = Me; R² = CH₂CH=CH₂) (1 g), mp 104° on recrystallization from petroleum ether (bp 40–60°).

Other N-alkenylations and alkynylations of this and other methylenebis compounds using reactive halides such as propargyl bromide, allyl bromide, and dimethylallyl bromide were achieved under similar conditions. Less reactive alkyl halides, however, such as ethyl bromide, *n*-propyl iodide, etc., reacted less readily, and reflux periods of up to 3 days were necessary for complete reaction, and under such conditions quaternary salt formation was also observed.

c. The N,N'-methylenebis compound (1 g), anhydrous potassium carbonate (1 g), and cyclopropylcarbonyl chloride (0.5 g) were stirred together in dry ether (50 ml) for 6 hr. Water (10 ml) and 2 N hydrochloric acid (20 ml) were added, and the ether layer was separated and evaporated, when N-cyclopropylcarbonyl-19-methylnorthevinol (VII, R = R¹ = Me; R² = cyclopropylcarbonyl) (1.0 g) was obtained after recrystallization from methanol, mp 214°, undepressed on mixing with an authentic specimen prepared from the secondary base VII (R = R¹ = Me, R² = H).

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Novel Analgesics and Molecular Rearrangements in the Morphine-Thebaine Group. IV.¹ Acid-Catalyzed Rearrangements of Alcohols of the 6,14-*endo*-Ethenotetrahydrothebaine Series

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Abstract: Alcohols of general structure I have been dehydrated to olefins II which have been further converted into 14-alkenylcodeinones V, themselves transformed by further acid-catalyzed reactions into recyclized products VII and IX and derivatives of 5,14-thebainone (XV). 14-(3-Methylbut-2-enyl)codeine (XXVII) has been converted into a derivative XXIX of (–)-sinomenilan, the structure of which has been demonstrated by spectral studies and by conversion *via* the bases XXX and XXXIII into the olefin XXXIV.

Alcohols of the 6,14-etheno- and -ethanotetrahydrothebaine and -oripavine groups described in preceding two papers in this series² are all unstable in media, in which they suffer dehydration and rearrangement, the speed, extent, and course of which depends on the nature of the alcoholic group and the bridge and on the conditions of the reaction. In these cases the first product appears to be an olefin. These olefins are generally preparable in good yield by heating alcohols in 98–100% formic acid, though in some cases a further reaction takes place before complete dehydration occurs. In no case was evidence obtained for the production of more than one olefin, and in the cases examined the olefin is the product of dehydration of the side chain rather than toward C-7.

Olefin II ($R^1 = R^2 = H$) on ozonolysis affords propionaldehyde and the ketone III, and the olefin II ($R^1 = H, R^2 = Et$) yields propionaldehyde, thus confirming the structures assigned to these bases. Structure II ($R^1 = R^2 = H$) for the olefin derived from the alcohol I ($R = Me$) is further confirmed by its formation from the ketone III by the Wittig reaction, by its nmr spectrum, which shows a two-proton signal at δ 4.80 ($H_2C=C<$) and a three-proton signal at δ 6.60 ($=CCH_3$). The production of the same olefin II ($R^1 = H, R^2 = Me$) from two diastereoisomeric alcohols of structure I ($R = Et$) and of the olefin II ($R^1 = H, R^2 = Et$) from two alcohols of structure I ($R = n-Pr$) shows that the alcohols in each case are diastereoisomers at the asymmetric alcoholic carbon and do not differ at C-7.³

Olefins analogous to those of structure II, but bearing a 6,14-ethano bridge are preparable by the dehydration of 6,14-ethano analogs of the alcohols of structure I. Acid-catalytic reduction of the olefins II in general results in the saturation of the 6,14-etheno bridge, which is appreciably less hindered than in the alcohols I, but in the case of the methylene group in the olefin II ($R^1 =$

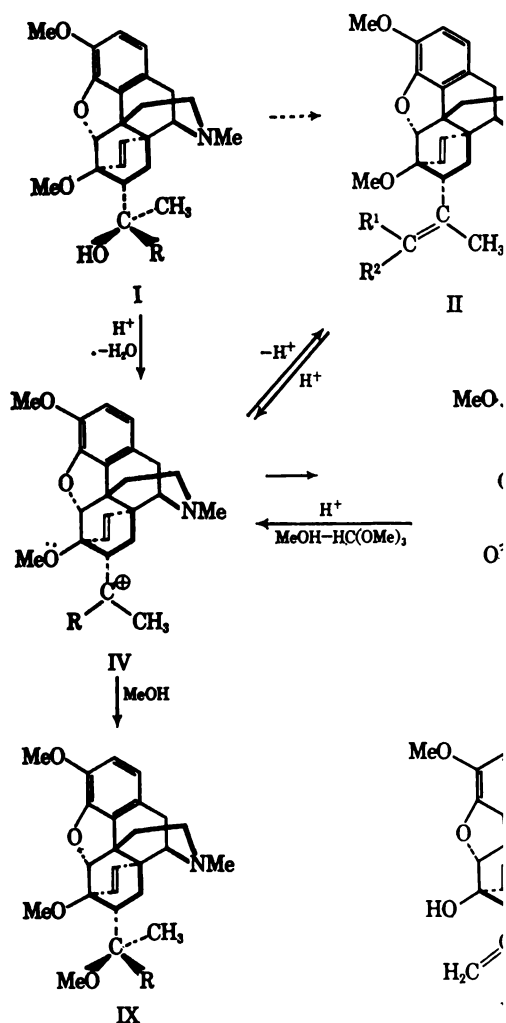
$R^2 = H$) is also reduced; the more heavily substituted double bond in the olefin II ($R = H, R^1 = n-Pr$) is more resistant to reduction.

The olefins themselves are unstable under acid conditions, but the ease of rearrangement appears to depend on the degree of substitution of the double bond. For example, the olefin II ($R^1 = R^2 = H, CH_3 = Ph$) is completely rearranged after 10-min boiling in 98–100% formic acid, and the olefin II ($R^1 = R^2 = H$) after 3 hr-boiling, whereas the trisubstituted olefins II ($R^1 = H$) are stable to boiling formic acid and require heating with dilute mineral acid before rearrangement can be effected. Presumably the ease of rearrangement is dependent on the ease of protonation of the double bond to give the carbonium ion IV, which can either revert to the olefin II with the loss of a proton, or can suffer ring fission to give the 14-alkenylcodeinone (V). Compounds of this structure V ($R = Me$ and Ph) have been isolated from the products of rearrangement of the alcohols I ($R = Me$ and Ph) and the derived olefins, and the ketone V ($R = Ph, CH_3 = Et$) has been obtained from the alcohol I ($R = Ph, CH_3 = Et$). In each of these cases, rearrangement to the codeinone was complete in refluxing 98–100% formic acid. In other cases, the alkenylcodeinones are only obtained when the alcohols or olefins are heated with dilute mineral acid. Under these conditions, however, the unsaturated ketones are themselves susceptible to further rearrangement (see following paper), and hence the yields of the codeinones in these cases are very poor, and the isolation of pure materials from the reaction mixtures is difficult.

The structures assigned to the 14-alkenylcodeinones (V) are in accord with their chemical properties and absorption spectra. They are insoluble in alkalis and do not couple with diazonium salts. Their infrared spectra show carbonyl absorption at 1690 cm^{-1} , and the ultraviolet spectra of the bases V ($R = Ph$ and also $R = Ph, CH_3 = Et$) are styrenoid. The nmr spectrum of the base V ($R = Ph$) shows signals (in δ units) at 7.23 (five aromatic H), 6.52 (C-1 and C-2 H), doublets centered at 6.52 (C-8 H) and 6.05 (C-7 H) ($J_{7,8} = 10$ cps), a triplet centered at 5.58 ($CH=CMePh$), and singlets at 4.65 (OCH_3), 3.78 (C-3 OCH_3), 2.40 (NCH_3), and 2.02 ($C=CHPh$). The spectrum of the base V ($R = Me$) is similar to that of the base ($R = Ph$), but

¹ Part III: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, 89, 1 (1967). (b) A preliminary report of part of this work has been given by K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1963); the publication of this report some similar work on a simpler system has been reported by A. J. Birch and J. S. Hill, *J. Chem. Soc.*, 419 (1963).

² Part II: K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, 89, 3273 (1967).
³ K. W. Bentley and J. C. Ball, *J. Org. Chem.*, 23, 1720 (1958).



lacks the signals at 7.23 and 2.02 and shows instead signals at 1.68 (3 H) and 1.47 (3 H) attributed to the methyl groups in the system $C=CMe_2$.

Catalytic reduction of the 14-alkenylcodeinones proceeds very sluggishly and affords poor yields of 14-alkyldihydrocodeinones (X), but isolation of pure materials is difficult since mixtures of isomers appear to be formed in most cases. Reduction only of the α,β -unsaturated ketone system of the base V ($R = Me$) could not be accomplished with zinc and acetic acid or with sodium amalgam, both of which reagents yielded mixtures containing phenols resulting from opening of the 4,5-oxygen bridge. The dihydro compound XI ($R = Ph$) was, however, obtained, together with the alcohol XII ($R = Ph$), by the reduction of the unsaturated ketone with sodium borohydride in pyridine.⁴ The alkenyldihydrocodeinones XI are not accessible by the rearrangement of the 6,14-ethano alcohols analogous to those of structure I, since they appear to suffer further rearrangement in acid media very much more readily than their α,β -unsaturated counterparts, and the rearrangements only furnish either olefins or phenolic bases. The C-6 carbonyl group in the 14-alkenylcodeinones and their reduction products can be reduced very readily with sodium borohydride to give the related derivatives of codeine, for example, the 14-alkenylcodeines (XII). In this reduction there is no evidence

(4) We are indebted to Dr. J. W. Lewis and Mr. M. J. Readhead of this laboratory for details of this reaction, the further implications of which will be discussed in a subsequent publication.

The 14-alkenylcodeinones and morphinones are, however, only intermediates in the complex rearrangements of the alcohols of structure I and their phenolic analogs undergo in acid media. When the alcohol I ($R = \text{Me}$) is warmed at 45° with 6 *N* hydrochloric acid 6–7 hr or kept in the same medium at 25° for 3 days, it is converted in good yield into the 6-hydroxy analog (R = Me), the infrared spectrum of which is very similar to that of the parent alcohol I (R = Me) and shows no carbonyl absorption. The nmr spectrum shows no band attributable to the C-6 methoxyl group, but does show two bands at δ 4.71 and 4.48 that disappear after shaking the base with deuterium oxide and must, therefore, be due to two hydroxyl groups, the rest of the spectrum being virtually identical with that of the parent alcohol. Since the ketones III (also $R = \text{Ph}$) are unaffected under the conditions under which the alcohol I (R = Me) is demethylated, this demethylation may be assumed to proceed through the enylcodeinone V (R = Me), by recyclization to the oxonium ion VI (R = Me), which can then either add a proton to give the 6-hydroxyolefin VIII, or react with a water molecule to give the alcohol VII (R = Me). This process has, indeed, been accomplished separately starting with the codeinone V (R = Me), which on heating in cold 6 *N* hydrochloric acid affords the alcohol VII (R = Me) in good yield. The olefin VIII has not yet been isolated. Further support for this mechanism is forthcoming from the action of methyl formate, methanol, and perchloric acid on the enone V (R = Me) which leads, presumably *via* a carbonium ion, to the carbinol methyl ether IX (R = Me) (40%) and the olefin II ($R^1 = R^2 = \text{H}$) (2%).⁶ The alcohol VII (R = Me) can be converted back into the alkenylcodeinone V (R = Me) by heating in 100% formic acid. From the alkenylcodeinone V (R = Me), the alcohols VI (R = Me) and VII (R = Me), or the olefin II ($R^1 = R^2 = \text{H}$) is heated with 6 *N* hydrochloric acid at 100° for a short period, further rearrangement occurs, and the major product is a phenolic base isomeric with the enone V (R = Me) and, like the latter, an α,β -unsaturated ketone. The phenolic hydroxyl must appear as the result of fission of the 4,5-oxide bridge, in which case a new bond must be formed to C-5, and the base is clearly an analog of flavonepenthone (XV, R = H, $R^1 = \text{Ph}$)^{3,7} and may be assigned the structure XV ($R = R^1 = \text{Me}$). This is supported by the nmr spectrum of the base which shows signals (in δ units) at 3.567 (two aromatic H), doublets centered at 6.77 (C-8 H) and 5.67 (C-7 H) ($J_{7,8} = 10$ cps), singlets at 4.42 (C-5 H), 2.36 (aromatic OCH_3), 2.36 (NCH_3) and 1.86 and 1.70 (CMe_2), and by the ozonolysis of the base, which affords acetone.

The ultraviolet spectrum of the base XV ($R = R^1 = \text{Me}$) further supports the assigned structure, showing as does the long wavelength absorption band λ_{max} 3350 m μ which is a characteristic feature of the spectra of thebaone (XIX),⁸ benzflavothebaone (XX),⁹ and flavonepenthone (XV, R = H, $R^1 = \text{Ph}$),³ though the

intensity of absorption at this wavelength is somewhat less than in these three bases. This absorption band in flavothebaone has been attributed by Meinwald and Wiley¹⁰ to charge transfer between the quinol nucleus and the enone system as shown in formula XXI, but such charge transfer is not possible in bases of general structure XV, in which no oxygen atom is available to supply electrons. Bentley, Dominguez, and Ringe,⁸ however, have suggested that this long wavelength absorption band is simply the absorption band of the α,β -unsaturated ketone system, which normally appears in this region but which in normal circumstances is very weak ($\epsilon_{\text{max}} \sim 50$) intensified ($\epsilon_{\text{max}} \sim 2000$) as a result of the perturbation of the enone system by the spatially proximate π orbitals of the unsaturated system, the precise nature of which (quinol, naphthaquinol, styrene, or isolated double bond) appears to be of little importance.

Bases of general structure XV can arise from the 14-alkenylcodeinones by protonation of the oxide bridge, bridge fission, and Markovnikov addition of the resulting carbonium ion to the side-chain double bond, as in XIII \rightarrow XV.³ Non-Markovnikov addition, clearly unlikely, would lead to a base of structure XVI, which is demonstrably not that of the product. Alternatively, since the alkenylcodeinone is in equilibrium with the recyclized carbonium ion VI in acid solution, rearrangement may take place by way of such an ion and the olefin XVII, in which concerted bridge fission and migration in a pinacolone type rearrangement can occur. The geometry of the molecule of the olefin XVII is particularly favorable for such a 1,2 shift. In view of the formation of the olefin II from the carbonium ion IV, the ion XIV might be expected to give the olefin XVIII instead of the actual product XV.

Other bases analogous to the base XV ($R = R^1 = \text{Me}$), bearing substituents other than a methyl group on the nitrogen atom, are preparable in about 40–50% yield by the rearrangement of the corresponding analogs of the alcohol I (R = Me), and the related 3-hydroxy compounds may be obtained either by the demethylation of the 3-methoxy bases with 48% hydrobromic acid or by the combined rearrangement and demethylation of the appropriate alcohol with this reagent.

Zinc and acetic acid reduction of the unsaturated ketone XV ($R = R^1 = \text{Me}$) affords the saturated ketone,¹¹ which is the sole end product of the rearrangement of the 6,14-ethano analog of the alcohol I (R = Me). In this reaction, the 14-alkenyldihydrocodeinone (X, R = Me) has not been detected as an intermediate in the reaction and it may be concluded that this base is rearranged more rapidly than the corresponding codeinone.

During the rearrangement of the alcohol I (R = Me) and the codeinone V (R = Me), a second process competes with the formation of the phenol XV ($R = R^1 = \text{Me}$) giving rise to an isomer of the latter. This process,

(10) J. Meinwald and G. A. Wiley, *J. Am. Chem. Soc.*, **79**, 2569 (1957).

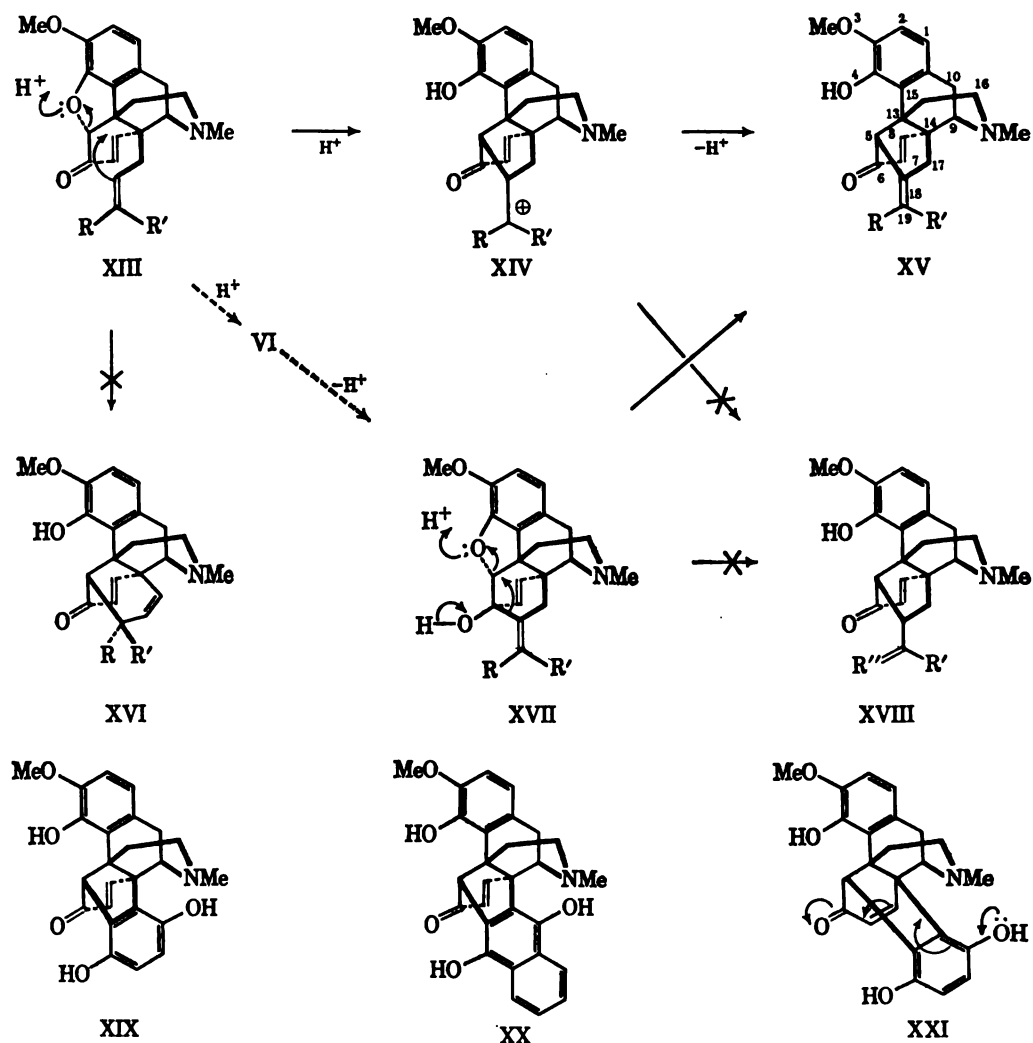
(11) 14-Hydroxycodeinone undergoes bimolecular coupling during reduction with zinc and acetic acid [L. J. Sargent and U. Weiss, *J. Org. Chem.*, **25**, 987 (1960)], but the enone system present in the bases of general structure XV is so shielded by the other parts of the molecule that bimolecular coupling is very seriously hindered. In the 14-alkenylcodeinones of structure V the enone system is much less hindered, and bimolecular coupling may be assumed to be involved in part in the formation of the very complex product of reduction of these bases with zinc and acetic acid.

) We are indebted to Dr. J. J. Brown of Lederle Laboratories, Pearl River, N. Y., for details of this reaction.

) K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1725 (1958).

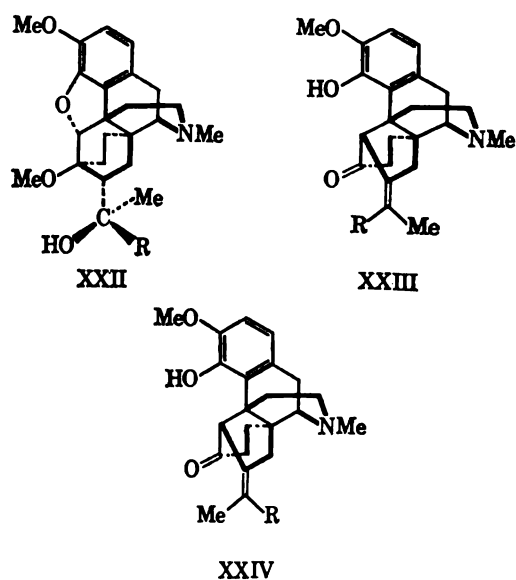
) K. W. Bentley, J. Dominguez, and J. P. Ringe, *ibid.*, **22**, 418 (1957).

) K. W. Bentley, J. C. Ball, and H. M. E. Cardwell, *ibid.*, **23**, 941 (1958).



which is discussed in the following paper,¹² becomes the dominant one in the rearrangement of alcohols I in which R is not a methyl group, with the result that bases of structure XV then become minor products of the reaction. For example, the rearrangement of the alcohol I (R = Ph) affords only 1.6% of the phenol XV (R = Me, R' = Ph). This competing reaction, however, involves the 14-alkenylcodeinone (V) as an essential intermediate and is not operative in the rearrangement of the 6,14-ethano alcohols. Rearrangement of the alcohols XXII (R = *n*-Pr), XXII (R = *n*-Bu), XXII (R = *n*-Am), however, affords mixtures in each case of two isomeric phenols. The products from the alcohol XXII (R = *n*-Bu) have identical infrared spectra, and these are presumably *cis-trans* isomers XXIII and XXIV, which could obviously arise from the intermediate carbonium ion, whether this be of the type XIV or VI.

The presence of the carbonyl group in the alkenylcodeinone V (R = Me) is essential for the rearrangement of this base to the phenol XV (R = R' = Me) by recyclization to the carbonium ion VI and concerted oxide bridge opening and rearrangement as in XVII, and may be necessary for activation of the 4,5-oxide bridge if the rearrangement proceeds as shown in formulas XIII → XV. The reaction of the 14-alkenyl-

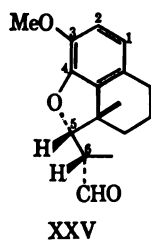


codeine (XII, R = Me), which contains no carbonyl group, with hot concentrated hydrochloric acid was accordingly examined. This reaction yielded a complex mixture of products from which a crystalline base "A," mp 200°, was recovered in 25% yield. Base "A" is isomeric with the codeine XII (R = Me), and infrared spectrum shows carbonyl absorption at 1710 cm⁻¹ but no hydroxyl absorption. It is very sparingly soluble in ethanol but dissolves readily on the addition

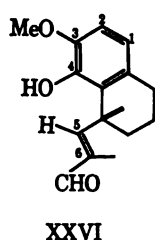
(12) Part V: K. W. Bentley, D. G. Hardy, C. F. Howell, W. Fulmor, J. E. Lancaster, J. J. Brown, G. O. Morton, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89**, 3303 (1967).

of sodium ethoxide to give a deep yellow solution, which couples readily with diazotized sulfanilic acid to give a blood red solution. Base "A" is recovered from the yellow ethoxide solution on the addition of water, but the addition of an excess of ammonium chloride solution results in the precipitation of a new base "B," which is isomeric with base "A" and shows phenolic hydroxyl absorption and carbonyl absorption at 1690 cm^{-1} in the infrared. Base "B" is readily soluble in ethanol, and the solution rapidly deposits base "A" on the addition of a small amount of aqueous sodium hydroxide. The reduction of base "A" with sodium borohydride in neutral solution affords a nonphenolic alcohol, whereas reduction in the presence of sodium ethoxide yields a phenolic alcohol, and both of these products are stable to alkalis.

Base "A" reacts relatively slowly with bromine and, hence, cannot contain an olefinic center, and this is confirmed by the failure of ozonolysis to yield either acetone or formaldehyde. The nmr spectra of bases "A" and "B" show that both of these bases are aldehydes. Both spectra show signals attributable to the C-1 C-2 aromatic protons and protons of the OCH_3 , NCN_3 , and two CCH_3 groups. The two CCH_3 peaks appear at δ 1.0 and 0.77 in the spectrum of base "A" and at δ 1.16 and 1.03 in the spectrum of base "B," indicating that neither base contains the system $=\text{CMe}_2$, and that some change in the distant environment of the two methyl groups occurs in the conversion of base "A" into base "B." The aldehyde proton signal in the spectrum of base "A" is a doublet at δ 9.35, $J = 2$ cps, suggesting that the system $>\text{CHCHO}$ is present in this base, whereas the corresponding signal in the spectrum of base "B" is a singlet at δ 9.76, which is consistent with the presence in this base of the system $\text{C}=\text{CCHO}$. This interpretation is consistent with the shift of carbonyl absorption frequency from 1730 to 1690 cm^{-1} in the conversion of base "A" into base "B." The reversible conversion of the system CCHCHO into $\text{C}=\text{CCHO}$ with the simultaneous appearance of a phenolic hydroxyl group suggests that base A and base B are related as shown in part structures XXV and XXVI, and in agreement with this the C-5 proton of XXV is revealed in the nmr spectrum of base A by a doublet centered at δ 5.15, $J_{5,6} = 9$ cps, which is absent from the spectrum of base B. The spectrum of base B, however, shows a one-proton signal at δ 7.68, which is absent from the spectrum of base A and is attributable to the C-5 proton in XXVI.



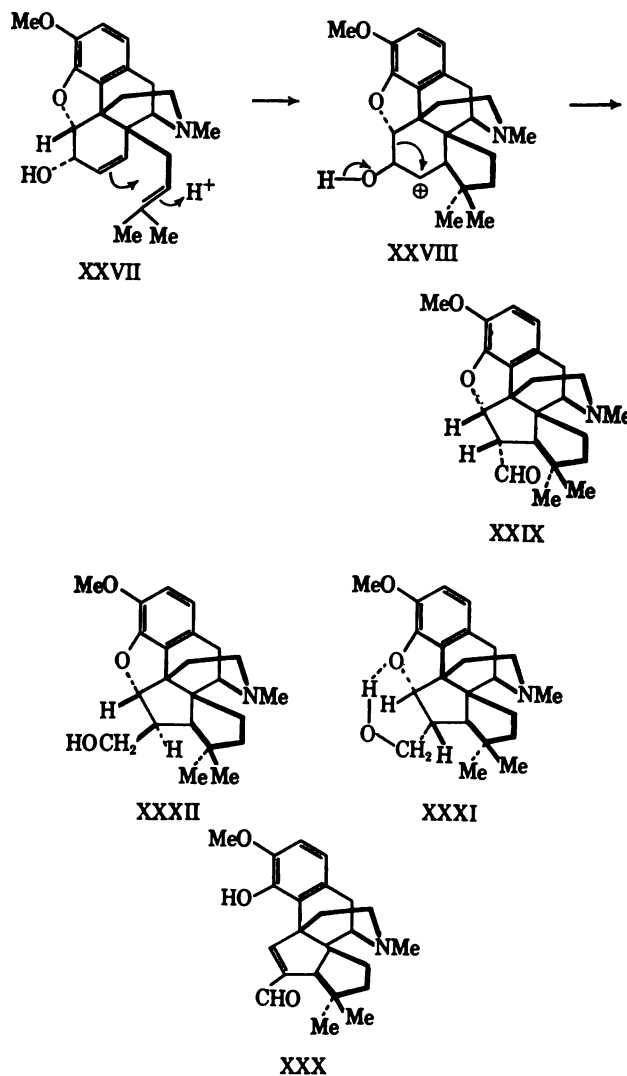
XXV



XXVI

The spectrum of base A shows no signal attributable to an olefinic proton and, hence, both of the double bonds in the base XII ($\text{R} = \text{Me}$) must be involved in a cyclization process, in which case the side-chain methyl groups would appear as a *gem*-dimethyl group in the product. The appearance of an aldehyde group in base A indicates the contraction of ring C of XII and

all of these requirements are met by the mechanism shown in formulas XXVII \rightarrow XXIX. The resulting structures for base A XXIX and base B XXX are in agreement with all of the known facts about these bases. A model of the structure XXIX, which can be constructed with very little strain, shows that steric hindrance is least with the CHO group disposed on the same side of the molecule as the oxide bridge, and it may be noted that the infrared spectrum of the alcohol XXXI derived from base A shows a band attributable to a hydrogen-bonded hydroxyl group and that hydrogen bonding is easily accommodated in the structure XXXI but is impossible in the epimeric structure XXXII.



The primary alcohol XXXIII, obtained by the reduction of base A in sodium ethoxide solution, might be expected to suffer dehydration in acids by the mechanism shown, with 4,5-oxide ring closure, to give the olefin XXXIV, by analogy with the way in which both isomers of the dienol XXXV are cyclized to thebaine.¹³⁻¹⁶

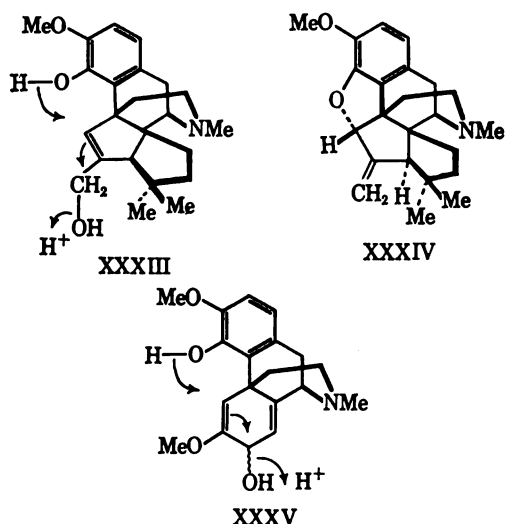
(13) D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 2423 (1965).

(14) A. Matthiessen and C. R. A. Wright, *Proc. Roy. Soc.*, (London), 18, 83 (1869); A. Matthiessen and C. R. A. Wright, *Ann. Suppl.*, 7, 364 (1870); L. Knorr and H. Horlein, *Ber.*, 40, 4883 (1907).

(15) L. Knorr and H. Horlein, *ibid.*, 41, 969 (1908).

(16) The numbering of the ring system is given in structure XV. The 5,14-ethano bridge is on the same side of the molecule as are the hydrogen atoms at C-5 and C-14 in thebainone, as is implied by the nomenclature used.

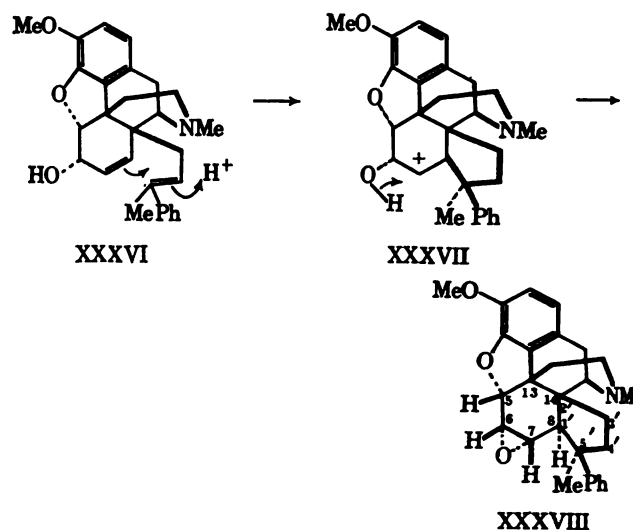
The alcohol is recovered unchanged from hot dilute hydrochloric acid but on heating with concentrated hydrochloric acid is converted into a crystalline base that shows no hydroxyl absorption in the infrared but does show nmr signals (in δ units) at 6.67 (two aromatic H), 3.92 (C-3 OCH₃), 2.46 (NCH₃), 1.07 (6 H, 2CH₃), a complex one-proton signal at 5.60 (C-5 H, split by the methylene protons), and a two-proton doublet at 4.95 showing further splitting, due to the system CHC(=CH₂)CH. There is little doubt that this base has the structure XXXIV.



The alkenylcodeine XXXVI, which is an analog of the base XXVII, on heating with concentrated hydrochloric acid gave a mixture from which about 10% of a crystalline solid was easily isolated. This base was isomeric with the codeine XXXVI, but the infrared spectrum showed no carbonyl group absorption. It did not react readily with bromine, and the nmr spectrum showed no signal attributable to an olefinic proton. This spectrum showed signals (in δ units) at about 7.2 (phenyl group protons), 6.72 (C-1 and C-2 H), 4.70 (doublet, C-5 H, $J_{5,6} = 9$ cps), 3.92 (C-3 OCH₃), 3.05 (2 H), 2.40 (NCH₃), and 1.39 (PhCCH₃). It is clear from this spectrum that both of the double bonds present in the codeine XXXVI have disappeared with the conversion of the system CH=CMePh into C-(C)-CMePh during the production of this new base, and a rational interpretation of this is that the reaction proceeds through the cyclized carbonium ion XXXVII, which is an analog of the ion XXVIII.

This carbonium ion could be converted into a neutral product in several ways, e.g., by the loss of a proton from C-6 or C-8, by reaction with a water molecule to give a glycol, by ring contraction to give an aldehyde similar to the aldehyde XXIX, or by the loss of a proton from the hydroxyl group with the formation of an epoxide ring XXXVIII. Since the infrared spectrum of the base shows neither carbonyl nor hydroxyl group absorption, and the nmr spectrum shows no signal attributable to olefinic or hydroxyl protons, only the structure XXXVIII seems tenable for this compound. The complex two-proton signal at about δ 3.05 in the nmr spectrum of the base may be attributed to the protons at C-6 and C-7.

The base is recovered unchanged after treatment with lithium aluminum hydride or acetic anhydride, and is



attacked only very slowly by potassium periodate in 2 N sulfuric acid. The examination of models of the structure XXXVIII and its C-5' diastereoisomer shows that in both structures attack from above the molecule at C-7 by a hydride ion (which gives an axial C-6 hydroxyl group in the product) is very severely hindered by the methyl or phenyl group at C-5'. Also, although the oxygen atom of the epoxide ring may be attacked by a solvated proton, completion of the reaction with the formation of a *trans*-diaxial 6,7-glycol is very severely hindered by the C-5' substituent. The stability of the base to the reagents cited above is thus explicable on the basis of the structure XXXVIII.

It may be assumed that the acid-catalyzed rearrangements of the codeines XXVII and XXXVI are complex processes leading to a variety of products, the aldehyde XXIX and the epoxide XXXVIII simply being the most easily crystallized reaction products in the two cases.

The dehydration of the alcohols I to the olefins II and rearrangement to the 14-alkenylcodeinones (V) results in a substantial decrease in analgesic potency, but further transformation into the analogs of flavone-penthone results in the production of bases of high potency. For example, the base XV (R = R' = Me) is about twice as potent and its methyl ether is about 15 times as potent as morphine.

Experimental Section

6,14-endo-Etheno-7 α -isopropenyltetrahydrothebaine (II, R¹ = R² = H) (Anhydro-19-methylthevinol). a. 6,14-endo-Etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (I, R = Me, 19-methylthevinol) (10 g) was boiled under reflux with 98–100% formic acid (25 ml) for 45 min. The mixture was diluted with ice-water (100 ml) and basified with ammonia, and the product was isolated by ether extraction. The dried extract was evaporated, and the residue was dissolved in benzene (250 ml) and passed down a column of grade 1 neutral alumina (75 g). A yellow band rapidly developed on the column, which was eluted with benzene until this band just reached the foot of the column. The eluate was concentrated and rechromatographed on alumina with elution again only of material running in front of the (narrow) yellow band. Evaporation of the eluate *in vacuo* gave a crystalline residue (3.8 g) which was recrystallized from methanol when the olefin was obtained as white irregular plates, mp 151°.

Anal. Calcd for C₂₄H₂₉NO₂: C, 76.0; H, 7.7. Found: C, 75.7; H, 7.5.

The hydrochloride, prepared in ethanol-ether had mp 198–200°. Elution of the yellow band on the alumina column with benzene containing 5% of chloroform gave 3.8 g of 14-(3-methylbut-2-enyl)codeinone (V, R = Me) (see below).

Methyltriphenylphosphonium bromide (3.6 g, 0.01 mole) led to a solution of butyllithium (0.01 mole) in hexane-ether in atmosphere of nitrogen, and the mixture was stirred at temperature for 4 hr. 7 α -Acetyl-6,14-*endo*-ethenotetrahebaïne (III, 3.8 g) in dry ether (100 ml) was added to the orange solution, and the mixture was then stirred at temperature overnight. Solid matter was removed from the mixture by filtration and washed well with ether; the filtrate and washings were then washed with water, dried, and evaporated. The residue was crystallized from petroleum ether (bp 40–60°), and the product was shown by thin layer chromatography to consist of approximately a 3:1 mixture of the olefin II ($R^1 = R^2 = H$) and ketone III. Chromatographic separation of the two was done in ether on a silica column, from which the olefin was first and was obtained on recrystallization from methanol as white prisms, mp 151°, alone or mixed with material prepared from alcohol I ($R = Me$) as in a above. Use of a 50% excess of ylide resulted in no improvement in the yield of olefin, and the ylide was generated with sodium hydride in dimethyl ether the yield of olefin was reduced, since base-catalyzed reversion of the ketone also took place.

Ozonolysis of Anhydro-19-methylthevinol (II, $R^1 = R^2 = H$). Ozonized oxygen, with an ozone delivery rate of 0.5 mmole of ozone/min, was passed into a solution of anhydro-19-methylthevinol (1 mmole) in 4 *N* acetic acid (50 ml) cooled in ice water. 2 min, when 2.1 mmoles of ozone had been absorbed, zinc dust was added to the solution, which was shaken for 5 min, filtered, and neutralized with sodium bicarbonate, and then warmed. All evolved gas was drawn through a solution of 2,4-dinitrophenylhydrazine in dilute sulfuric acid, in which a precipitate of phenylhydrazone-2,4-dinitrophenylhydrazone, mp and mmp (with an authentic specimen) 166°, was formed.

For the second ozonolysis ozone uptake was limited to 1 mmole per the neutralization with sodium bicarbonate the mixture was extracted with ether. The ether extract on evaporation afforded from which on chromatographic separation on silica the mp 151°, and 7 α -acetyl-6,14-*endo*-ethenotetrahydrothebaïne, 1°, were recovered. The aqueous phase after the ether extraction on treatment with dimedone gave the formaldehyde derivative, mp 186°, undepressed on mixing with an authentic specimen.

6,14-*endo*-Etheno-7 α -(1-phenylvinyl)tetrahydrothebaïne (Anhydro-19-phenylthevinol, II, $R^1 = R^2 = H$, $CH_2 = Ph$). 6,14-*endo*-Etheno-7 α -(1-(*R*)-hydroxy-1-phenylethyl)tetrahydrothebaïne (I, $R = Ph$) (10 g) was dissolved in boiling 98–100% formic acid (25 ml), and the solution was boiled for 1.5 min and then into ice-water. The solution was basified with ammonia; the product was isolated by ether extraction and was chromatographed on grade 1 neutral alumina in benzene solution. The product was eluted with benzene, and the eluate was collected until the UV band reached the foot of the column. Evaporation of the solvent *in vacuo* and recrystallization of the product from methanol gave the olefin (1.8 g) as pale fawn plates, mp 145–146°.

Anal. Calcd for $C_{29}H_{31}NO_2$: C, 79.0; H, 7.1. Found: C, 78.1; H, 7.1.

Elution of the yellow band from the alumina column with benzene containing 5% of chloroform afforded 5.3 g of 14-(3-phenylvinyl)codeinone, mp 168–169° (see below).

4-*endo*-Ethano-7 α -isopropenyltetrahydrothebaïne (Anhydro-19-methylthevinol, II, $R^1 = R^2 = H$, 6,14-*ethano*). 6,14-*endo*-Etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaïne (di-19-methylthevinol, 2.0 g) was boiled under reflux with 98–100% formic acid for 10 min. The mixture was diluted with water, basified with ammonia, and extracted with ether. The dried ether extract on evaporation gave a viscous residue which was chromatographed on alumina in benzene solution with elution with benzene containing 5% of ethyl acetate until the presence of a second base eluate was just detectable by thin layer chromatography. The eluate was then evaporated, and the residue was crystallized from petroleum ether (bp 40–60°), when the olefin was obtained as prisms, mp 127°.

Anal. Calcd for $C_{24}H_{31}NO_2 \cdot 0.5H_2O$: C, 73.9; H, 8.2. Found: C, 73.9; H, 8.2.

4-*endo*-Ethano-7 α -isopropyltetrahydrothebaïne (Dihydro-19-thevinan). 6,14-*endo*-Etheno-7 α -isopropylpenyltetrahydrothebaïne (anhydro-19-methylthevinol, 1.0 g) was shaken under reflux at 22° (760 mm) in the presence of 5% palladium on charcoal (250 mg) until absorption of hydrogen (130 ml, 2 mmole) ceased (3 hr). The solution was filtered from catalyst and concentrated, when the saturated base was obtained as an uncrystal-

lizable viscous gum characterized as the picrate, which was obtained as yellow needles, mp 194°, from 2-ethoxyethanol.

Anal. Calcd for $C_{24}H_{31}NO_2 \cdot C_6H_5N_3O_7$: C, 58.9; H, 5.9; N, 9.2. Found: C, 58.9; H, 5.9; N, 9.4.

6,14-*endo*-Etheno-7 α -(1-methylprop-1-enyl)tetrahydrothebaïne (Anhydro-19-ethylthevinol, II, $R^1 = H$, $R^2 = Me$). a. 6,14-*endo*-Etheno-7 α -(1-(*R*)-hydroxy-1-methylpropyl)tetrahydrothebaïne (19-ethylthevinol, I, $R = Et$) (1 g) was heated at 100° with 98–100% formic acid (10 ml) for 2 hr. The solution was diluted with ice-water and basified with ammonia. The product was isolated by ether extraction and crystallized and recrystallized from aqueous methanol when the olefin (II, $R^1 = H$, $R^2 = Me$) (0.6 g) was obtained as white irregular plates, mp 120–121°.

Anal. Calcd for $C_{25}H_{31}NO_2$: C, 76.4; H, 7.9. Found: C, 76.7; H, 8.0.

b. 6,14-*endo*-Etheno-7 α -(1-(*S*)-hydroxy-1-methylpropyl)tetrahydrothebaïne (I, $R = Me$; $Me = Et$) (1 g) was dehydrated in the same way and gave the same olefin, melting point and mixture melting point with material prepared as in part a, 120–121°.

6,14-*endo*-Etheno-7 α -(1-methylbut-1-enyl)tetrahydrothebaïne (Anhydro-9-propylthevinol, II, $R^1 = H$, $R^2 = Et$). 6,14-*endo*-Etheno-7 α -(1-hydroxy-1-methylbutyl)tetrahydrothebaïne (19-propylthevinol, I, $R = n-Pr$) (10 g) was boiled under reflux with 98–100% formic acid (50 ml) for 3 hr. The mixture was diluted with ice-water and basified with ammonia, and the product was isolated by ether extraction. On crystallization and recrystallization from aqueous methanol, the olefin II ($R^1 = H$, $R^2 = Et$) (6.8 g) was obtained as white plates, mp 110°.

Anal. Calcd for $C_{26}H_{31}NO_2$: C, 76.7; H, 8.2. Found: C, 76.7; H, 8.3.

The same olefin was obtained by the dehydration in the same way of 6,14-*endo*-etheno-7 α -(1-(*S*)-hydroxy-1-methylbutyl)tetrahydrothebaïne, which is the C-19 epimer of the alcohol I ($R = n-Pr$).

Ozonolysis of Anhydro-19-propylthevinol (II, $R^1 = H$, $R^2 = Et$). Ozonized oxygen, delivering 0.6 mmole of ozone/min, was passed into a solution of anhydro-19-propylthevinol (0.41 g, 1 mmole) in 4 *N* acetic acid (50 ml). The reaction was stopped when 2 mmole of ozone had been absorbed (8 min), and the reaction mixture was reduced with zinc dust, filtered, and neutralized with sodium bicarbonate. The neutralized solution was divided into two parts, one of which was warmed, and the evolved gas was passed through a solution of 2,4-dinitrophenylhydrazine in dilute sulfuric acid, when a 2,4-dinitrophenylhydrazone, mp 146°, was obtained. This depressed the melting point of pentan-2-one dinitrophenylhydrazone (mp 142°) but did not depress the melting point of propionaldehyde dinitrophenylhydrazone (mp 146°). The second portion of the neutralized reaction mixture was treated with dimedone, when the propionaldehyde derivative was obtained, mp 154° undepressed on mixing with an authentic specimen (mp 155°).

6,14-*endo*-Etheno-7 α -(1-methylbut-1-enyl)tetrahydrothebaïne (Anhydro-19-propyldihydrothevinol, II, $R^1 = H$, $R^2 = Et$, 6,14-*etheno*). a. 6,14-*endo*-Etheno-7 α -(1-(*R*)-hydroxy-1-methylbutyl)tetrahydrothebaïne (5 g) and 98–100% formic acid (100 ml) were boiled together under reflux for 20 min. The solution was diluted with ice-water and basified with ammonia, and the product was isolated by ether extraction and chromatographed on neutral alumina in benzene solution. Elution of the column with benzene:ethyl acetate, 95:5, gave the olefin (3 g) as white plates, mp 65–67°, from petroleum ether (bp 40–60°) characterized as the hydrochloride, mp 218–219°.

Anal. Calcd for $C_{26}H_{31}NO_2 \cdot HCl$: C, 70.0; H, 8.1; Cl, 7.95. Found: C, 69.6; H, 8.1; Cl, 8.3.

b. 6,14-*endo*-Etheno-7 α -(1-methylbut-1-enyl)tetrahydrothebaïne (1 g) was hydrogenated at 20° (760 mm) over 5% palladium on charcoal (0.25 g) in ethanol. Hydrogen (50 ml, 1 mole) was absorbed over 90 min. Evaporation of the solution afforded an oil giving a hydrochloride, mp 218–219°, identical in melting point, mixture melting point, and infrared absorption with that obtained as in part a above.

Other Olefins. The following olefins were prepared by the same process as the one described above for the preparation of 6,14-*endo*-etheno-7 α -(1-methylbut-1-enyl)tetrahydrothebaïne: 6,14-*endo*-etheno-7 α -(1-methylpent-1-enyl)tetrahydrothebaïne (anhydro-19-butylthevinol, II, $R^1 = H$, $R^2 = n-Pr$, white plates, mp 75°, from methanol. *Anal.* Calcd for $C_{27}H_{31}NO_2$: C, 77.0; H, 8.4. Found: C, 76.9; H, 8.4); 6,14-*endo*-etheno-7 α -(1-methylhex-1-enyl)tetrahydrothebaïne (anhydro-19-amylthevinol, II, $R^1 = H$, $R^2 = n-Bu$, white plates, mp 180°, from methanol. *Anal.* Calcd for $C_{28}H_{31}NO_2 \cdot 0.5H_2O$: C, 75.7; H, 8.6. Found: C, 75.6; H, 8.3); 6,14-*endo*-etheno-7 α -(1,4-dimethylpent-1-enyl)-

acid (8 ml) for 30 min. The base isolated in the usual way was recrystallized from aqueous 2-ethoxyethanol, when it was obtained as white prisms, mp 176–177°, ν_{\max} 1690 cm^{-1} .

Anal. Calcd for $\text{C}_{23}\text{H}_{31}\text{NO}_3$: C, 78.9; H, 7.0. Found: C, 78.3; H, 7.2.

6,14-endo-Etheno-7 α -(1-hydroxy-1-methylethyl)dihydrocodeine (VII, R = Me). a. 6,14-endo-Etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (I, R = Me) (20 g) was heated at 45° with 6 *N* hydrochloric acid (160 ml) for 6 hr. The mixture was diluted, and the base was precipitated with ammonia, collected, and recrystallized from ethanol, when the dihydrocodeine derivative (13.3 g) was obtained as white prisms, mp 265°.

Anal. Calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_4$: C, 72.0; H, 7.6; N, 3.7; OMe (1), 8.1. Found: C, 72.0; H, 7.6; N, 3.7; OMe, 8.0.

The hydrochloride was obtained as white prisms, mp 262°, from ethanol.

Anal. Calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_4 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 63.1; H, 7.4. Found: C, 62.6; H, 7.5.

b. 14-(3-Methylbut-2-enyl)codeinone (V, R = Me) (1 g) was heated at 45° with 6 *N* hydrochloric acid (10 ml) for 6 hr. The base recovered as above was obtained as white prisms, mp 262° alone or mixed with material prepared as in a. The bases prepared by both methods had identical infrared spectra.

6,14-endo-Etheno-7 α -(1-methoxy-1-methylethyl)tetrahydrothebaine (IX, R = Me). a. Perchloric acid (1.5 ml, 72%) was added dropwise to a stirred solution of 14-(3-methylbut-2-enyl)codeinone (V, R = Me) (500 mg) in methylene chloride (10 ml), methanol (10 ml), and trimethyl orthoformate (10 ml), and the mixture was kept at room temperature for 20 hr. Methylene chloride was added, and the mixture was washed with aqueous sodium bicarbonate and water and dried. Thin layer chromatography showed the product to consist of one major and one minor, less polar, component. The gum obtained by the removal of solvent was dissolved in *n*-hexane, and the solution was chromatographed on alumina (20 g, Woelm, activity II). Fractions of 10 ml were collected and examined by thin layer chromatography. The column was eluted first with 5% and then with 10% chloroform in *n*-hexane, when the less polar component was eluted. The material (12 mg, c 2.5%) was identical in melting point (143–145°) and infrared absorption with 6,14-endo-etheno-7 α -isopropenyltetrahydrothebaine (II, R¹ = R² = H) obtained by the dehydration of the alcohol (I, R = Me). Continued elution of the column gave a mixture of the two components followed by the more polar component. The column was then eluted with 25 and 50% methylene chloride in *n*-hexane. Evaporation of appropriate fractions gave a gum which was crystallized from aqueous methanol to give 6,14-endo-etheno-7 α -(1-methoxy-1-methylethyl)tetrahydrothebaine (130 mg), mp 97–99°. A further 90 mg was obtained from the mother liquors making a total yield of 39%. The compound showed no carbonyl absorption in the infrared and had nmr signals (in δ units) at 6.57 and 6.51 (C-1 H and C-2 H; doublets, $J_{1,2}$ = 9 cps), 5.72 and 5.37 (C-18 H and C-17 H; doublets, $J_{17,18}$ = 10 cps), 4.56 (C-5 H), 3.82 (C-3 OMe), 3.58 (C-6 OMe), 3.18 (C-19 OMe), 2.36 (NMe), 1.30 and 0.95 (C-19 methyls).

Anal. Calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_4$: C, 73.0; H, 8.1; N, 3.4. Found: C, 72.5; H, 7.9; N, 3.5.

b. 6,14-endo-Etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (19-methylthevinol, I, R = Me) (1 g) was added to a solution of potassium (from 0.2 g of potassium) in liquid ammonia (~100 ml), and the mixture was stirred for 15 min. Methyl iodide (1 ml) was then added and the mixture stirred for 10 min more and poured cautiously into water (200 ml). The precipitated product was isolated by ether extraction and shown by thin layer chromatography to consist of approximately 30% of starting material (I, R = Me) and 70% of a less polar compound. The mixture was dissolved in a 1:1 mixture of benzene and *n*-hexane and chromatographed on a column of alumina (Woelm, activity II). The column was eluted with benzene, and 25-ml samples were collected, the composition of these being followed by thin layer chromatography. The first material to be eluted from the column (500 mg) was obtained as a gum, which crystallized on keeping for several hours. On recrystallization from aqueous methanol it was obtained as white prisms, mp 96–98°, identical in infrared absorption with material prepared as in part a above.

5,14-Ethano-18-isopropylidenethebainone (XV, R = R¹ = Me). a. 6,14-endo-Etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (19-methylthevinol, I, R = Me) (50 g) was heated at 100° with 10 *N* hydrochloric acid (150 ml) for 45 min, during which time crystalline material separated. The mixture was diluted with water (150 ml) and cooled in ice, and the hydrochloride

(27 g) was collected. This was dissolved in aqueous methanol, and the base was precipitated with ammonia. It was recrystallized readily only from methanol, from which it separated as off-white solvated prisms, mp 138°, ν_{\max} 1690 cm^{-1} .

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_3 \cdot 0.5\text{CH}_3\text{OH}$: C, 73.0; H, 7.6. Found: C, 72.8; H, 7.8.

The hydrochloride was obtained as white prisms, mp 320°, from water.

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_3 \cdot \text{HCl}$: C, 68.7; H, 7.0. Found: C, 68.4; H, 7.2.

The picrate was obtained as yellow needles, mp 224°, from aqueous 2-ethoxyethanol.

Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_3 \cdot \text{C}_6\text{H}_5\text{N}_3\text{O}_7 \cdot 1.5\text{H}_2\text{O}$: C, 56.0; H, 5.2. Found: C, 55.8; H, 5.2.

b. The same base was obtained from 6,14-endo-etheno-7 α -(1-hydroxy-1-methylethyl)dihydrocodeine (VII, R = Me), from 6,14-endo-etheno-7 α -isopropenyltetrahydrothebaine (II, R¹ = R² = H), and from 14-(3-methylbut-2-enyl)codeinone (V, R = Me) by the same process as in a above, the yields being comparable with that in a in all cases.

The base was almost insoluble in aqueous alkalis but dissolved readily in aqueous methanolic potassium hydroxide to give an orange solution that readily coupled with diazotized sulfanilic acid to give a blood red solution. The alkaline solution was readily methylated and ethylated with methyl and ethyl sulfate, respectively.

The 4-O-methyl ether was prepared most conveniently from the hydrochloride obtained directly from the acid-catalyzed rearrangement of the alcohol (I, R = Me). The hydrochloride (20 g) was suspended in methyl sulfate (50 ml), and the mixture was cooled in ice. A solution of potassium hydroxide (40 g) in water (80 ml) was slowly added to the vigorously stirred suspension at a rate sufficient to keep the temperature of the mixture between 15 and 20°. When all of the alkali had been added, the mixture was stirred at 20° for 2 hr. Water (150 ml) was added, and the solid base was collected, washed, and recrystallized from methanol, when it was obtained as off-white prisms, mp 176–177°, ν_{\max} 1690 cm^{-1} .

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_3$: C, 76.0; H, 7.7. Found: C, 76.0; H, 7.8.

The 4-O-ethyl ether was obtained from aqueous methanol as white prisms, mp 126–127°, ν_{\max} 1690 cm^{-1} .

Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_3$: C, 76.4; H, 8.0. Found: C, 76.4; H, 7.9.

Ozonolysis of 5,14-Ethano-18-isopropylidenethebainone (XV, R = R¹ = Me). Ozonized oxygen, delivering 0.5 mmole of ozone/min was passed into a solution of 5,14-ethano-18-isopropylidenethebainone (0.365 g, 1 mmole) in 4 *N* acetic acid (50 ml). After 26 min, when 2 mmoles of ozone had been absorbed, the mixture was reduced with zinc dust, filtered, neutralized with sodium bicarbonate, and warmed. The evolved gas was passed through a solution of 2,4-dinitrophenylhydrazine in dilute sulfuric acid, when acetone 2,4-dinitrophenylhydrazone (0.192 g, 0.807 mmole) was obtained, mp 125° alone or mixed with an authentic specimen.

7,8-Dihydro-5,14-ethano-18-isopropylidenethebainone (XXIII, R = Me). a. 6,14-endo-Ethano-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (dihydro-19-methylthevinol, XXII, R = Me) (2 g) was heated with 10 *N* hydrochloric acid (20 ml) for 2 hr at 100°. The mixture was diluted with water, and the base was precipitated with ammonia, collected, and recrystallized from methanol, when it was obtained as white prisms, mp 142°, ν_{\max} 1715 cm^{-1} .

Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_3$: C, 75.2; H, 7.9. Found: C, 75.2; H, 7.8.

The hydrochloride formed prisms, mp 245°, from water.

Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_3 \cdot \text{HCl} \cdot 1.5\text{H}_2\text{O}$: C, 64.1; H, 7.7. Found: C, 64.1; H, 7.5.

b. Zinc dust (2 g) was added to a vigorously stirred boiling solution of 5,14-ethano-18-isopropylidenethebainone (V, R = R¹ = Me) in glacial acetic acid (25 ml) and water (2 ml). The mixture was stirred and heated under reflux for 2 hr, filtered, diluted with aqueous ammonium chloride, and basified with ammonia. The precipitated base was collected and recrystallized from methanol, when it was obtained as prisms identical in melting point, mixture melting point, and infrared absorption with material prepared as in part a above.

The 4-O-methyl ether, prepared by methylation of the phenol and by reduction of the corresponding thebainone methyl ether with zinc dust and acetic acid, was obtained as off-white prisms, mp 168–169°, ν_{\max} 1715 cm^{-1} .

Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_3$: C, 75.6; H, 8.1. Found: C, 75.8; H, 8.0.

N-Allyl-5,14-ethano-18-isopropylidenenorthebainone (XV, R = R¹ = Me, NMe = NCH₂CH=CH₂). N-Allyl-7,14-endo-etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydronorthebaine (1 g) was heated 100° with 10 N hydrochloric acid (10 ml) for 2 hr. The mixture was diluted with water; the hydrochloride (0.38 g) was collected and recrystallized from aqueous methanol, when it was obtained as white prisms, mp 186–188°, ν_{\max} 1690 cm⁻¹.

Anal. Calcd for C₂₅H₂₉NO₃·HCl: C, 70.1; H, 7.0. Found: C, 70.2; H, 7.2.

The base could not be crystallized.

The following hydrochlorides were prepared from the appropriate N-substituted 6,14-endo-etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydronorthebaines, and hot concentrated hydrochloric acid with isolation of the sparingly soluble salt: N-propargyl-5,14-ethano-18-isopropylidenenorthebainone (XV, R = Me, NMe = NCH₂C \equiv CH, prisms, mp 155°. *Anal.* Calcd for C₂₃H₂₇NO₃·HCl·H₂O: C, 67.6; H, 6.8. Found: C, 68.0; H, 6.7); N-(3,3-dimethylallyl)-5,14-ethano-18-isopropylidenenorthebainone (XV, R = Me, NMe = NCH₂CH=CMe₂, prisms, mp 196°. *Anal.* Calcd for C₂₇H₃₃NO₃·HCl·H₂O: C, 68.3; H, 7.6. Found: C, 68.3; H, 8.0); and N-cyclopropylmethyl-5,14-ethano-18-isopropylidenenorthebainone (XV, R = Me, NMe = N-cyclopropylmethyl, white prisms, mp 206°. *Anal.* Calcd for C₂₆H₃₁NO₃·HCl·H₂O: C, 67.9; H, 7.4. Found: C, 67.8; H, 7.4).

3-O-Desmethyl-5,14-ethano-18-isopropylidenethebainone (XV, R = R¹ = Me, OMe = OH). a. 5,14-Ethano-18-isopropylidenethebainone (5 g) was boiled under reflux with 48% hydrobromic acid (50 ml) for 1 hr. Solid material that separated was dissolved by the addition of water (10 ml) and methanol (50 ml), and the solution was then basified with ammonia and the solid collected and recrystallized from methanol, when it was obtained as prisms (3 g), mp 268°.

Anal. Calcd for C₂₂H₂₅NO₃: C, 75.2; H, 7.1. Found: C, 75.6; H, 7.0.

The hydrochloride was obtained as prisms, mp 342°, from aqueous methanol.

Anal. Calcd for C₂₂H₂₅NO₃·HCl: C, 68.1; H, 6.7. Found: C, 68.0; H, 6.8.

b. The same base (2 g, identical in melting point and infrared absorption with the above) was obtained by the direct rearrangement and demethylation of 6,14-endo-etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (5 g) with 48% hydrobromic acid (45 ml). The hydrobromide was separated and dissolved in aqueous ethanol, and the base was precipitated with ammonia.

N-Allyl-3-O-desmethyl-5,14-ethano-18-isopropylidenenorthebainone (XV, R = R¹ = Me, OMe = OH, NMe = NCH₂CH=CH₂). N-Allyl-6,14-endo-etheno-7-(1-hydroxy-1-methylethyl)tetrahydronororipavine (N-allyl-19-methylnororvinol) (6 g) was heated under reflux with 4 N hydrochloric acid (40 ml) for 3 hr. The solid hydrochloride was collected, dissolved in aqueous methanol, and converted to the base with ammonia, the base being obtained from methanol as white prisms, mp 260° dec.

Anal. Calcd for C₂₄H₂₇NO₃: C, 76.4; H, 7.3. Found: C, 76.2; H, 7.2.

5,14-Ethano-18-(methylbenzylidene)thebainone (XV, R = Me, R¹ = Ph, Methylflavonepenthone). 6,14-endo-Etheno-7 α -(1-(R)-hydroxy-1-phenylethyl)tetrahydrothebaine (I, R = Ph) (20 g) was heated with concentrated hydrochloric acid (75 ml) and ethanol (10 ml) at 100° for 30 min, during which time a crystalline hydrochloride separated. The mixture was diluted with water (100 ml) and thoroughly cooled in ice. The crystalline solid was collected. This consisted of the hydrochlorides of 7,8-dihydro-5'-phenylcyclohex-4'-eno[1',2':8,14]codeinone and the cyclohex-5'-eno isomer (see following paper), and a solution in aqueous methanolic sodium hydroxide gave only a pale pink color with diazotized sulfanilic acid.

The filtrate from the collection of this hydrochloride, which gave an intense diazo coupling reaction in alkaline solution, was basified with ammonia and the relatively small amount of gummy base produced was extracted rapidly with ether. The extract was shaken for 15 sec with magnesium sulfate and filtered. Rosettes of needles quickly separated from the ether solution and these were collected, washed well with ether, and recrystallized from aqueous 2-ethoxyethanol, when the thebainone derivative (320 mg) was obtained as off-white needles, mp 290°, ν_{\max} 1690 cm⁻¹.

Anal. Calcd for C₂₈H₂₉NO₃: C, 78.8; H, 6.8. Found: C, 78.7; H, 6.7.

The O-methyl ether was obtained as a crystalline precipitate on the addition of methyl sulfate (0.25 ml) to a solution of the phenol (100 mg) in methanol (3 ml), water (1 ml), and potassium hydroxide

(200 mg), and on recrystallization it was recovered, as almost white needles. *Anal.* Calcd for C₂₉H₃₁NO₃: C, 79.3; H, 7.0.

The O-ethyl ether, prepared in an analogous manner from the methyl sulfate, was obtained from aqueous 144°.

Anal. Calcd for C₃₀H₃₃NO₃: C, 79.3; H, 7.4.

6 α -Formyl-5',5'-dimethylcyclopentanil (Base A; XXIX). 14-(3-Methyl-5'-hydroxy-5'-methylcyclopentyl)-5,14-endo-etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydronorthebaine (5 g) was heated at 100° with acid (10 ml) for 45 min. The solution turned pink, and finally dark red brown. The solution was diluted with water (40 ml) and basified with ammonia. The suspension was washed three times with water with hot methanol (35 ml), when a white solid was obtained. The suspension was cooled, and the solid was washed with cold methanol, and recrystallized from ethanol when "base A" (1.5 g) was obtained as prisms, mp 200°, ν_{\max} 1730 cm⁻¹.

Anal. Calcd for C₂₂H₂₅NO₃: C, 75.8; H, 7.9.

The base was very sparingly soluble in ethanol in the presence of sodium hydroxide solution.

The perchlorate formed prisms, mp 144°, from ethanol.

Anal. Calcd for C₂₂H₂₅NO₃·HClO₄: C, 59.15; H, 6.4.

6-Formyl-5',5'-dimethylcyclopentanil-5-ene (Base B; XXX). Base A (1.5 g) in ethanol (10 ml) containing sodium hydroxide (0.5 g) was stirred for 1 hr. The solution was poured into an excess of water and the base was precipitated with water, and recrystallized from ethanol as white felted needles, mp 144°. *Anal.* Calcd for C₂₂H₂₅NO₃: C, 75.6; H, 7.9.

The same base was obtained, less colorless, from a solution of base A in sodium hydroxide. The base was readily soluble in ethanol and the solution gave a deep red color with diazotized sulfanilic acid.

Conversion of Base B (XXX) into Base A. Base B was dissolved in methanol (1 ml) and sodium hydroxide was added. The solution was warmed rapidly deposited a white solid, which was mixed with an authentic specimen.

Reduction of Base A with Sodium Borohydride. Base A (500 mg) and sodium borohydride (50 mg) were dissolved in cold ethanol (10 ml) until all the base was dissolved. The product was isolated by ether extraction, when 6-(1-cyclopentyl-1',2':8,14)-(–)-sinomenil was obtained as a viscous oil, characterized by its infrared spectrum, which was obtained as yellow needles, mp 144°. *Anal.* Calcd for C₂₀H₂₃N₂O₃: C, 64.3; H, 6.0; N, 7.8.

Reduction of Base A with Sodium Borohydride. Sodium borohydride (150 mg) and base A (XXIX) (1 g) in ethanolic sodium hydroxide and the mixture was warmed until the color disappeared. The almost colorless solution was poured into water and the product isolated by ether extraction, when 6-(1-cyclopentyl-1',2':8,14)-(–)-sinomenil-5-ene (XXXIII) (1 g) was obtained as a colorless glass, bp 190–200°/0.5 mm.

Anal. Calcd for C₂₂H₂₅NO₃: C, 74.7; H, 8.0.

6-Methylene-5',5'-dimethylcyclopentanil (XXXIV). 6-Hydroxymethyl-5',5'-dimethylcyclopentanil-5-ene [1',2':8,14]-(–)-dihydrosinomenil-5-ene (1 g) was boiled with concentrated hydrochloric acid. The mixture was diluted with water and the product, isolated by ether extraction, was recrystallized in part on trituration with ethanol so obtained dissolved readily in

in which the noncrystalline matter was virtually insoluble. Concentration of the petroleum solution afforded the olefin XXXIV (75 mg) as white elongated prisms, mp 107–108°.

Anal. Calcd for $C_{22}H_{28}NO_2$: C, 78.6; H, 8.3. Found: C, 78.2; H, 8.2.

Rearrangement of 14-(3-Phenylbut-2-enyl)codeine (XXXVI). 14-(3-Phenylbut-2-enyl)codeine (XXXVI) (2 g) was heated at 100° in the water bath with concentrated hydrochloric acid (20 ml) for 45 min. The pink solution was then diluted with 50% aqueous ethanol, cooled in ice, and basified under ether with ammonia. The ether extract was set aside overnight, and the crystalline matter that separated during that time was collected, washed with methanol, and recrystallized from 2-ethoxyethanol, when 8,14-dihydro-6,7 α -epoxy-5'-methyl-5'-phenylcyclopentano[1',2':8,14]deoxycodine-D (XXXVIII) was obtained as white prisms, mp 234° (0.3 g).

Anal. Calcd for $C_{28}H_{34}NO_2$: C, 78.3; H, 7.2. Found: C, 78.2; H, 7.2.

The ether solution after removal of this base was evaporated to leave a brown viscous gum, part of which was chromatographed

in ether solution on alumina plates. From the plates a nonphenolic α,β -unsaturated ketone XIII ($R = Me$, $R' = Ph$), a nonphenolic saturated ketone, and a nonphenolic aldehyde were obtained as well as a phenolic saturated ketone. Chromatographic separation of a further part of the same viscous gum on silica plates resulted in the separation of the material into a nonphenolic fraction and six nonphenolic bases which on recovery from the plate showed almost identical infrared absorption lacking any band attributable to a carbonyl group. The amounts of material recovered in this way were too small to permit further study.

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Novel Analgesics and Molecular Rearrangements in the Morphine-Thebaine Group. V.¹ Derivatives of 7,8-Dihydrocyclohexeno[1',2':8,14]codeinone

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Abstract: The acid-catalyzed rearrangement of alcohols of the 6,14-*endo*-ethenotetrahydrothebaine series of general structure I has been shown to proceed in most cases *via* the 14-alkenylcodeinones (II) to 7,8-dihydrocyclohex-4'-*eno*- and -cyclohex-5'-*eno*[1',2':8,14]codeinones of general structures X and XI. The structures of typical bases have been elucidated by nmr spectral studies and by chemical means. Analogous derivatives of dihydromorphinone and a series of nor bases and N-substituted nor bases have also been prepared. The mechanisms of the rearrangements are discussed.

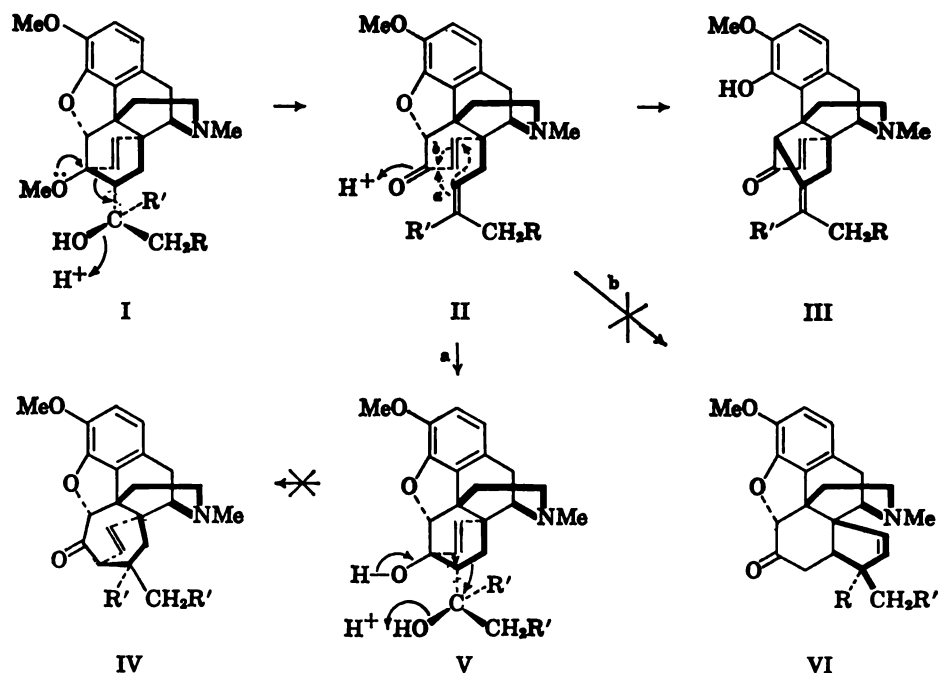
In the preceding paper it is shown that the alcohols of general structure I can be rearranged to 14-alkenylcodeinones (II), which may be further transformed by concentrated hydrochloric acid into 5,14-bridged thebainone derivatives III. The last of these transformations, however, competes with an alternative process, which in general represents the major reaction, the thebainone derivative III being the major product only in special cases. The alternative rearrangement of the codeinone II affords a nonphenolic nonconjugated ketone as the stable end product, which is, of course, obtained also by the complete rearrangement of the alcohol I under the same conditions, and from the olefin which is an intermediate in the conversion of the alcohol into the codeinone II (see preceding paper). As would be expected, since carbonium ion intermediates are clearly involved in the dehydration and rearrangement of the alcohol I to the codeinone II, di-

astereoisomeric pairs of alcohols afford the same ketonic end product, in all cases studied. The rearrangement of the alcohol I ($R = H$, $R' = Ph$) is a particularly rapid process; in cold concentrated hydrochloric acid the product is almost entirely the codeinone II ($R = H$, $R' = Ph$), and this is completely converted into stable end products after only 4-min boiling. The nonphenolic nonconjugated ketones obtained in this way are isomeric with the alkenylcodeinones II and the thebainone derivatives III prepared from the same alcohols.

One possible process by which the alkenylcodeinone II could be converted into a nonconjugated ketone involves the protonation of the enone system and non-Markovnikov addition of the resulting carbonium ion to the double bond in the side chain, followed by expulsion of a proton to give the ketone VI. However, the codeinone II ($R = H$, $R' = Me$) is known to suffer recyclization in acid solution, by a process involving Markovnikov addition to the isolated double bond, to give the alcohol V ($R = H$, $R' = Me$),¹ and the rearrangement of such a recycled base to the noncon-

(1) Part IV: K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89**, 3293 (1967).

(2) (a) Reckitt and Sons Ltd., Kingston-upon-Hull, England. (b) Lederle Laboratories, Pearl River, N. Y. (c) Central Research Laboratories, American Cyanamid Co., Stamford, Conn.



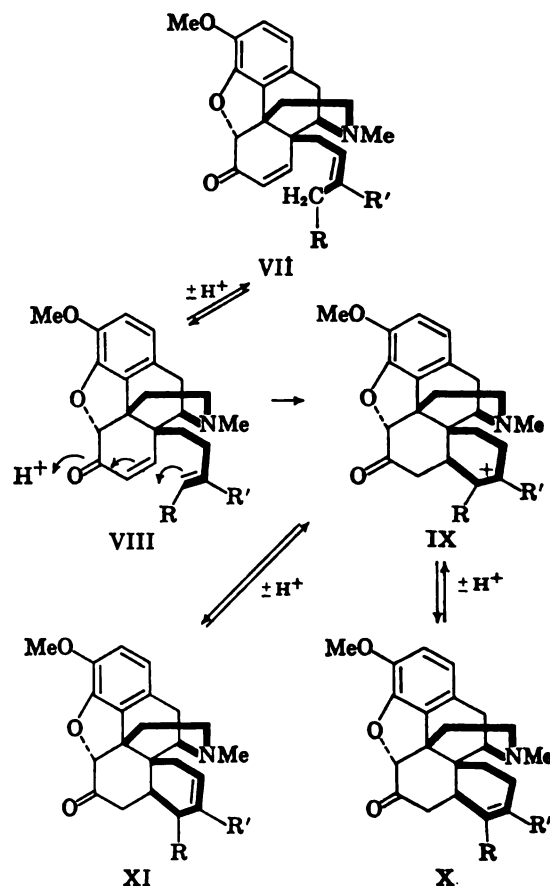
jugated ketone IV by the successive 1,2 shifts shown in formula V is also a plausible process, several variants of which can be envisaged.

The nmr spectra of three of these ketones, obtained by the acid-catalyzed rearrangement of the tertiary alcohols I ($R = H$, $R' = Ph$; $R' = Me$, $R = Me$; and $R' = Me$, $R = i-Bu$), however, showed no evidence of the presence in these three bases of the system $CH=CH$, signals due to which are clearly observed in the spectra of the parent alcohols I and the alkenyl-codeinone II ($R = H$, $R' = Ph$). Indeed only in the spectrum of the first of these ketones (from the alcohol I, $R = H$, $R' = Ph$) is the presence of even a single olefinic proton indicated. Further the spectrum of the first of these ketones shows no signal attributable to a C-methyl group, and the spectrum of the second ketone (from the alcohol I, $R' = Me$, $R = Me$) shows C-methyl signals only at δ 1.53 and 1.61, which evidently arise from groups in the system $C=CCH_3$. The spectrum of the third ketone (from the alcohol I, $R' = Me$, $R = i-Bu$) also shows a three-proton singlet at δ 1.62 ($C=CCH_3$) as well as a complex signal centered at δ 0.81, attributed to the system $CHMe_2$.

The spectra of all three ketones show signals attributable to two aromatic protons at C-1 and C-2, at about δ 6.68, and in addition the first of the three shows a five-proton complex signal at about δ 7.33 clearly due to the phenyl group. All three ketones show a one-proton singlet at δ 4.5–4.55, which is attributed to the proton at C-5 at the end of the cyclic ether bridge.

These spectra rule out of consideration the structures IV and VI for the three above-mentioned ketones, but do lead to the assignment of plausible structures to these and analogous compounds on the basis of a rational reaction mechanism for the acid-catalyzed rearrangements. The 14-alkenylcodeinone (II), which may be redrawn as VII, may very reasonably be expected to be in prototropic equilibrium in acid solution with the isomeric alkenylcodeinone VIII, which can then suffer protonation of the enone system and Markovnikov addition of the resulting carbonium ion to the double bond in the side chain to give the

carbonium ion IX, which can lose a proton in either two ways to give the ketones X and XI. The examination of models suggests that a similar cyclization of codeinone VII to give IV, in addition to requiring a Markovnikov addition to the double bond, is inhibited by the impossibility of arranging the double bond a position relative to the enone system suitable for cyclization. The examination of models of the isomeric system VIII, however, shows that in this double bond in the side chain can readily be positioned over C-8 in precisely the geometry required for p



pendicular attack of the enone system in the manner favored for Michael addition³ and the conjugated addition of Grignard reagents.⁴ Such a process would result in the formation from the alcohol I ($R' = \text{Me}$, $R = \text{Me}$) of the ketone X ($R = R' = \text{Me}$) which contains the system $\text{CH}_2\text{C}=\text{CCH}_3$ and no olefinic proton, and from the alcohol I ($R' = \text{Me}$, $R = i\text{-Bu}$) of the ketone X ($R' = \text{Me}$, $R = i\text{-Bu}$). In these cases hyperconjugation effects may be presumed to favor the formation of the olefin X rather than the isomeric olefin XI.

The application of this reaction mechanism to the rearrangement of the alcohol I ($R = \text{H}$, $R' = \text{Ph}$) would lead through the codeinones VII ($R = \text{H}$, $R' = \text{Ph}$) and VIII ($R = \text{H}$, $R' = \text{Ph}$) to the ketones X ($R = \text{H}$, $R' = \text{Ph}$) or XI ($R = \text{H}$, $R' = \text{Ph}$) or both. Both of these ketones are formulated with styrenoid chromophores, and indeed the product of the rearrangement does show styrenoid ultraviolet absorption. This rearrangement product has been separated into two isomeric ketones, the infrared and ultraviolet spectra of which are closely similar, and these can be formulated as the two isomers X ($R = \text{H}$, $R' = \text{Ph}$) and XI ($R = \text{H}$, $R' = \text{Ph}$). The nmr spectra of both isomers showed complex patterns for one olefinic proton, which made a distinction between structures X and XI very difficult without additional information. The identification of one isomer was possible, however, using spin-decoupling techniques. The spectrum of one of these ketones (mp 161–163°) (Figure 1) showed an olefinic proton as a multiplet (1 H) at about δ 6.1. Irradiation at about δ 2.1 collapsed this δ 6.1 multiplet into a doublet ($J \cong 7$ cps), indicating further coupling with another proton. That this proton is one absorbing at about δ 3.8 was shown by irradiation at this point, when the olefinic proton signal then appeared as a broad single peak. The proton pattern at δ 3.8 is a quartet, which collapsed to a doublet ($J = 18$ cps) when the olefinic proton was irradiated. The proton absorbing at δ 3.8 was also coupled with the one absorbing at about δ 2.1 ($J = 18$ cps), as shown by irradiation at about δ 2.1. The $J = 18$ cps can only be a *gem*-coupling constant. The proton giving the quartet at δ 3.8 must, therefore, be one-half of a methylene group adjacent to an olefinic proton.

Since the double bond is presumably the one present in the styrenoid system this ketone evidently contains the system $\text{CH}_2\text{CH}=\text{CPh}$, which is that present in the base XI ($R = \text{H}$, $R' = \text{Ph}$). The downfield shift of one of the methylene protons in this system to δ 3.8 is regarded as resulting from this proton being both allylic and near the unshared pair of electrons on the nitrogen atom^{5,6} as it is in a model of the ketone XI ($R = \text{H}$, $R' = \text{Ph}$). The other proton in this methylene group resonates at δ 2.17. Such large differences between halves of a methylene group are unusual, but not unprecedented.⁷

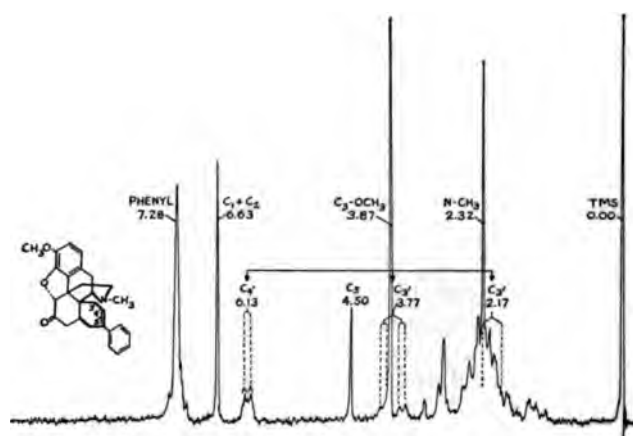
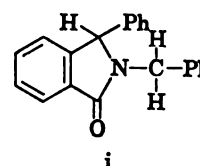


Figure 1. Nmr spectrum of 7,8-dihydro-5'-phenylcyclohex-4'-eno[1',2':8,14]codeinone (XI, $R = \text{H}$, $R' = \text{Ph}$). Arrows show spin system established by decoupling experiments.

It is clear, therefore, that the nmr spectrum of this ketone (mp 161–163°) is entirely consistent with the structure XI ($R = \text{H}$, $R' = \text{Ph}$). The isomeric ketone (mp 212–214°), which is the minor product of the acid-catalyzed rearrangement of the alcohol I ($R = \text{H}$, $R' = \text{Ph}$), gave an nmr spectrum substantially similar to that of the ketone (mp 161–163°). In this case, however, the complex olefinic proton signal at about δ 6.0 collapsed and appeared as a single peak, still showing residual coupling, on irradiation at about δ 2.4, thus establishing that the olefinic proton is coupled to a proton or protons absorbing at the latter point. Owing to the coincidence of other resonances in the δ 2.4 region, however, it was not possible to observe clear-cut changes in the spin-spin decoupling studies. Since this ketone is styrenoid and isomeric with one whose spectrum is consistent with the structure XI ($R = \text{H}$, $R' = \text{Ph}$) it may with confidence be assigned the structure X ($R = \text{H}$, $R' = \text{Ph}$). If these structural assignments are correct the two ketones represent the products of alternative modes of the loss of a proton from the carbonium ion IX ($R = \text{H}$, $R' = \text{Ph}$), through which they may be equilibrated in acid solution. This equilibration has been independently achieved, for each of the two pure ketones on treatment with *p*-toluenesulfonic acid in glacial acetic acid⁸ is converted into a mixture of approximately 80% of the ketone XI ($R = \text{H}$, $R' = \text{Ph}$) and 20% of the isomer X ($R = \text{H}$, $R' = \text{Ph}$), which is the composition of the crude product obtained in the rearrangement of the alcohol I ($R = \text{H}$, $R' = \text{Ph}$).

Although the spectra of the ketones discussed above are compatible with one or other of the structures X or XI for these bases, they do not provide any definitive information pertaining to the structure of the carbonyl-containing ring C, and, accordingly, chemical transformations have been carried out on two of these bases



(8) These conditions have been used for the equilibration of *cis*- and *trans*-2-phenyl-2-butene: D. J. Cram and M. V. R. Sahyun, *J. Am. Chem. Soc.*, **85**, 1257 (1963).

(3) E. L. Eliel, N. A. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 314–317.

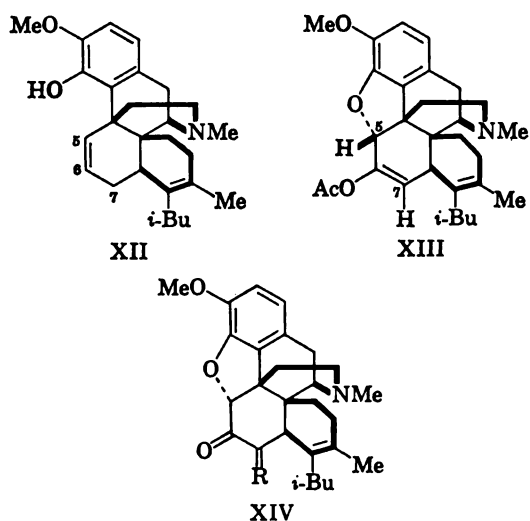
(4) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 360 (1963).

(5) S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull. (Tokyo)*, **11**, 1465 (1963).

(6) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *ibid.*, **12**, 104 (1964).

(7) For example, one of the benzylic methylene protons, shielded by the phenyl moiety in i, appears at δ 3.67 while the other methylene proton, deshielded by the carbonyl group, resonates at δ 5.42: A. H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Letters*, 1241 (1965).

to characterise this portion of the molecule. That the ketones still contain the 4,5-oxygen bridge intact may be inferred from their nonphenolic nature, and from the presence in their nmr spectra of the sharp singlet at about δ 4.5 attributed to the C-5 proton. The presence of the oxygen bridge and the relationship of this to the carbonyl group in the ketones are demonstrated by the behavior of two of the ketones on Huang-Minlon reduction. The reduction of derivatives of dihydrocodeinone by this process occurs with great ease, and involves fission of the 4,5-oxygen bridge and the production of derivatives of the phenolic dihydrodeoxycodines B and C.⁹ The hydrazones of the ketones XI ($R = H$, $R' = Ph$) and X ($R = i-Bu$, $R' = Me$) lose nitrogen at about 120° in alkaline solution and give phenolic products, which give positive tests with Gibb's reagent (dichloroquinone chlorimine) and with diazotized sulfanilic acid. The major product of reduction of the base X ($R = i-Bu$, $R' = Me$) shows nmr signals as doublets at δ 6.3 and 5.5 ($CH=CH$, $J_{A,B} = 9$ cps) and a singlet at δ 5.87 shifted to δ 7.95 in dimethyl sulfoxide, attributed to the phenolic hydroxyl proton. On mechanistic grounds this major product of the reaction is assigned the formula XII and the minor product may be the analogous derivative of dihydrodeoxycodine-C with a 6,7-double bond. This reaction can only be represented by a satisfactory mechanism if the carbonyl group in the ketones is located at C-6.



The ketones X ($R = i-Bu$, $R' = Me$) and XI ($R = H$, $R' = Ph$) are converted into enol acetates on heating with acetic anhydride and sodium acetate, and the enol esters are readily hydrolyzed to the parent ketones by hot hydrochloric acid. The examination of models shows that if the carbonyl group is contained in a five-, six-, or seven-membered ring enolization cannot involve the hydrogen atom at C-5 since the introduction of a 5,6 double bond would impose an unacceptable degree of strain on the oxygen-containing ring. Enolization must, therefore, involve C-7, and the nmr spectrum of the enol acetate XIII supports the assigned structure, showing signals (in δ units) at 6.7 (two aromatic H), 5.38 doublet (C-7, $J_{7,5} = 2$ cps), 4.91 doublet (C-5 H, $J_{5,7} = 2$ cps), 3.88 (aromatic OCH_3), 2.33 (NCH_3), 2.16 ($COCH_3$), 1.62 ($C=CCH_3$), and a complex six-proton peak at 0.82 ($CHMe_2$). C-Methylation

(9) T. D. Perrine and L. F. Small, *J. Org. Chem.*, **17**, 1540 (1952).

of the ketone X ($R = i-Bu$, $R' = Me$) can be accomplished with potassium *t*-butoxide and methyl iodide, and the nmr spectrum of the product XIV ($R = Me$) is very similar to that of the starting material except in the region δ 0.6–1.2 in which signals are found integrating for a total of 12 protons, indicating that two new methyl groups have been introduced at C-7. The dimethylated ketone, which bears no enolizable hydrogen atom, is recovered unchanged after heating with sodium acetate and acetic anhydride. These reactions clearly show that the parent ketones contain the system $OCHCOCH_2$ as in formulas X and XI.

The presence of this system in the ketone X ($R = i-Bu$, $R' = Me$) was confirmed by the conversion of the base into an α -oximino ketone XIV ($R = NOH$) by the action of sodium ethoxide and amyl nitrite. The base obtained in this way was soluble in alkalis and was precipitated from the solution by ammonium chloride or carbon dioxide. It also gave an insoluble stable copper chelate with methanolic cupric acetate, which was soluble in dilute acids and reprecipitated unchanged by ammonia. The α -oximino ketone was hydrolyzed by hot dilute sulfuric acid to a yellow α -diketone XIV ($R = O$), which gave a dark brown cupric complex and with ferric chloride gave a deep wine red solution that became intensely blue-green on the addition of a trace of ammonia. From this it may be concluded that the diketone is enolizable, and hence must contain the system $OCHCOCOCH$, which means that the original ketone X ($R = i-Bu$, $R' = Me$) must contain the system $OCHCOCH_2CH$. Further evidence for the presence of this system in the same ketone was obtained from the action on it of bromine and potassium carbonate in methanol, in an attempt to prepare the diketone XIV ($R = O$) by the method used in the dihydrocodeinone and sinomenine series.¹⁰ The reaction afforded a mixture of products from which a small quantity of an α,β -unsaturated ketone was isolated. Presumably this is formed from the α -bromo ketone by the loss of hydrogen bromide.

The chemical evidence given above indicates the nature of most of ring C in the rearranged bases, and, if the reasonable assumption is made that the dihydrocodeinone ring system remains intact, the complete structures of these bases must be made up by the addition of a new ring, which can only be added at positions 8 and 14. This new ring can only be five or six membered and must contain a double bond to satisfy the compositions of the bases, and the nmr spectra of the bases examined are only compatible with the arrangement of this ring as shown in formulas X and XI. The complete structures based on these general formulas can, therefore, be confidently assigned to the rearranged bases.

The position of the double bond in the end products of the rearrangement is determined by the nature of the substituents in the unsaturated ring. The major product of the rearrangement of the alcohol I ($R = H$, $R' = Ph$) is the ketone XI ($R = H$, $R' = Ph$), though some of the isomeric ketone X ($R = H$, $R' = Ph$) is also formed. The cyclohexenocodineone obtained in the rearrangement of the alcohol I ($R = H$, $R' = Me$) has also been identified as the Δ' ketone XI ($R = H$, $R' = Me$) [nmr signals (in δ units) at 6.64

(10) C. Schöpf, T. Pfeiffer, and H. Hirsch, *Ann.*, **492**, 213 (1932).

(C-1 and C-2 H), 5.38 (C-4' H; multiplet, $J_{3,4} = ca. 5.5$ cps, 1 H), 4.50 (C-5 H; singlet, 1 H), 3.88 (C-3 OCH₃), $ca. 3.45$ (C-3' H; diffuse double doublet, $J_{2,3'} = ca. 16.5$ cps, $J_{3,4'} = ca. 5.5$ cps), 2.33 (NCH₃), 1.65 (C-5' CH₃; singlet, 3 H)]. The base obtained by the rearrangement of the alcohol I (R = Me, R' = Ph) also belongs to the Δ' series, having the structure XI (R = Me, R' = Ph) and showing nmr signals (in δ units) at 7.35 (5 aromatic H), 6.72 (C-1 and C-2 H), 5.95 (diffuse multiplet, 1 olefinic H), 4.55 (C-5 H, singlet, 1 H), 3.95 (C-3 OCH₃), 2.41 (NCH₃), and 1.1 (CHCH₃; doublet, $J = ca. 10$ cps, 3 H). By contrast, the rearranged bases bearing alkyl substituents at C-5' and C-6' give nmr spectra showing no signal for olefinic hydrogen, and must belong to the Δ' series X.

Hyperconjugation effects may be expected to favor the Δ' form over the Δ form when alkyl groups are present at C-5' and C-6', and similar effects would be expected to favor the olefin VIII (R = R' = alkyl) over VII (R = R' = alkyl) at equilibrium in acid solution. Such effects would not, however, greatly favor the production of the olefin VIII (R = H, R' = Me) from the codeinone VII (R = H, R' = Me), and a considerable amount of the latter would be expected to be present at equilibrium in acid solution. As this latter base can rearrange irreversibly to the flavone-penthone analog III (R = H, R' = Me), a considerable quantity of the phenol is obtained in the rearrangement, which gives almost equal amounts of the phenol III (R = H, R' = Me) and the ketone XI (R = H, R' = Me). Since some of the phenol III is obtained in all of the acid-catalyzed rearrangements, the processes II \rightarrow III and VIII \rightarrow IX may be assumed to have similar rates, the composition of the initial rearrangement product being determined by the position of the equilibrium VII \rightleftharpoons VIII. Clearly, bases such as II (CH₂R = H, R' = Ph and also CH₂R = R' = Ph) which cannot be isomerized to olefins of structure VIII give only bases belonging to series III on rearrangement.

Although the olefin VIII is a necessary intermediate in the rearrangement of the alkenylcodeinone VII to the cyclized bases X and XI, no such olefin has been isolated from solutions of the bases VII (R = H, R' = Ph) and VII (R = H, R' = Me) in hydrochloric acid, presumably owing to the speed with which cyclization to the carbonium ion IX occurs.

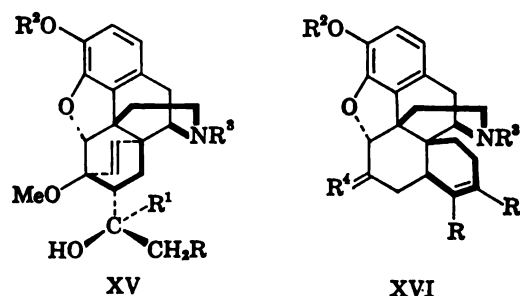
The cyclohexenodihydrocodeinones of general structures X and XI, being stable end products of acid-catalyzed reactions, are readily demethylated without further change on heating with 48% hydrobromic acid to give the corresponding derivatives of dihydromorphinone. These bases are also preparable by the rearrangement of the corresponding phenolic alcohols in the 6,14-*endo*-ethenotetrahydrooripavine series,¹¹ or by the combined rearrangement and demethylation of the alcohols in the 3-methoxy series I with 48% hydrobromic acid.

Bases in this series, bearing substituents other than a methyl group on the nitrogen atom, have been prepared by the rearrangement of the corresponding alcohols. In general, the acid-catalyzed rearrangement can be effected at any stage in the sequence of compounds represented by XV in which R³ = Me, CN, H, or other substituent.

(11) Part III: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3281 (1967).

pounds XV (R³ = CN) can be accomplished without hydrolysis of the NCN group in cold concentrated hydrochloric acid, the hydrolysis to the secondary base being subsequently accomplished in alkaline solution, since acid-catalyzed hydrolysis is generally slow and incomplete. Secondary bases in the cyclohexenodihydrocodeinone series are also preparable from the corresponding N-methyl compounds by treatment with methyl azodicarboxylate followed by acid hydrolysis, and by the combined hydrolysis and rearrangement of the N,N'-methylenebis alcohols (described in paper III of this series¹¹) by heating with concentrated hydrochloric acid, though this last is not a preferred process.

Reduction of the C-6 carbonyl group in these derivatives of dihydrocodeinone and dihydromorphinone is readily effected with sodium borohydride. By one or other of the processes set out above, the bases of general structure XVI listed in Table I have been prepared. In all cases rearrangement of the alcohols of



general structure XV results in a marked decrease in analgesic or morphine antagonizing potency. In general, however, the bases do still produce effects on the central nervous system, and the results of pharmacological appraisal will be published elsewhere.

The diversity of acid-catalyzed rearrangement products obtained from the *t*-carbinols I, as described in this series of papers, and their apparent interrelationships are summarized in Scheme I (partial structures).

Scheme I

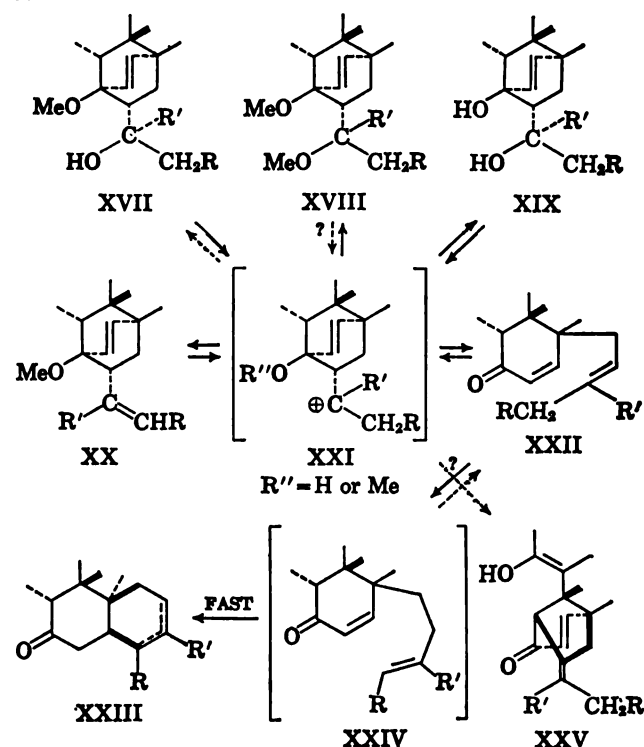


Table I. Bases of Structure XVI

R ²	R ³	R ¹	R	R ⁴	Mp, °C	Composition	Calcd, % C	H	Found, % C	H	Mp, °C, HCl
Me ^a	Me	Me	H	=C	112-114	C ₂₃ H ₂₇ NO ₃	75.6	7.45	76.0	7.4	
Me ^a	Me	Ph	H	=O	161-163	C ₂₈ H ₃₃ NO ₃	78.6	6.8	78.4	6.8	
Me	Me	Ph	H	=O	212-214	C ₂₈ H ₃₃ NO ₃	78.6	6.8	78.6	6.8	
Me ^a	Me	Ph	H	<H OH	191	C ₂₈ H ₃₁ NO ₃	78.4	7.3	78.1	7.4	
H ^a	Me	Ph	H	=O	235	C ₂₇ H ₂₇ NO ₃ ·H ₂ O	75.3	6.7	75.5	6.8	276-278
Me	Me	Me	Me	=O	199	C ₂₄ H ₂₉ NO ₃	72.2	8.3	76.1	7.9	284
Me	Me	Me	Me	<H OH	143	C ₂₄ H ₃₁ NO ₃ ·H ₂ O	72.2	8.3	72.0	8.4	
Me	CN	Me	Me	=O	265-272	C ₂₄ H ₂₅ N ₂ O ₃	73.8	6.7	73.4	6.7	
Me	CH ₂ -C-C ₂ H ₅	Me	Me	=O	137-140	C ₂₇ H ₃₃ NO ₃	77.3	8.0	77.7	8.0	
Me	Me	Me	Et	=O	229-230	C ₂₅ H ₃₁ NO ₃	76.4	8.0	76.3	8.0	282
Me	Me	Me	Et	<H OH	166	C ₂₅ H ₃₃ NO ₃	76.1	8.4	75.7	8.4	
Me	CN	Me	Et	=O	277-279	C ₂₅ H ₂₉ N ₂ O ₃	74.2	7.0	74.8	7.0	
Me	H	Me	Et	=O	210-215	C ₂₄ H ₂₉ NO ₃	76.0	7.7	76.5	7.8	
Me	CH ₂ CH=CH ₂	Me	Et	=O	131-133	C ₂₇ H ₃₃ NO ₃	77.3	7.9	77.3	8.0	
Me	CH ₂ CH=CH ₂	Me	Et	<H OH	45	C ₂₇ H ₃₅ NO ₃	76.9	8.4	76.5	8.4	
Me	CH ₂ CMe=CH ₂	Me	Et	=O	126-129	C ₂₈ H ₃₅ NO ₃	77.6	8.1	77.6	8.1	
Me	CH ₂ CH=CMe ₂	Me	Et	=O	109-113	C ₂₉ H ₃₇ NO ₃	77.8	8.3	77.7	8.4	
Me	<i>n</i> -Bu	Me	Et	=O	123-124	C ₂₈ H ₃₇ NO ₃	77.2	8.6	77.2	8.6	
Me	<i>n</i> -Hexyl	Me	Et	=O	129-131	C ₃₀ H ₄₁ NO ₃	77.7	8.9	77.5	9.0	
Me	<i>n</i> -Octyl	Me	Et	=O	103-104	C ₃₂ H ₄₅ NO ₃	78.2	9.2	78.3	9.3	
Me	CH ₂ -C-C ₄ H ₇	Me	Et	=O	146-147	C ₂₉ H ₃₇ NO ₃	77.8	8.3	77.5	8.1	
H	Me	Me	Et	=O	110-111	C ₂₄ H ₂₉ NO ₃ ·H ₂ O	72.6	8.3	73.0	8.0	
H	Me	Me	Et	<H OH	78	C ₂₄ H ₃₁ NO ₃	75.5	8.2	74.8	8.3	
H	CH ₂ -C-C ₃ H ₅	Me	Et	=O		C ₂₇ H ₃₃ NO ₃ ·HCl·H ₂ O	68.4	7.6	68.4	7.4	185-187
Me	Me	Me	<i>n</i> -Pr	=O	144	C ₂₆ H ₃₃ NO ₃	76.8	8.5	76.5	8.2	260
Me	CN	Me	<i>n</i> -Pr	=O	218-219	C ₂₆ H ₃₀ N ₂ O ₃	74.6	7.2	73.9	7.1	
Me	Et	Me	<i>n</i> -Pr	=O	50	C ₂₇ H ₃₅ NO ₃	76.9	8.4	76.8	8.5	142-145
Me	<i>n</i> -Pr	Me	<i>n</i> -Pr	=O	50	C ₂₈ H ₃₇ NO ₃	77.2	8.6	77.3	8.6	140-144
Me	CH ₂ CH=CH ₂	Me	<i>n</i> -Pr	=O	...	C ₂₉ H ₃₇ NO ₃	77.8	8.3	78.3	8.4	140-144
H	Me	Me	<i>n</i> -Pr	=O	114-115	C ₂₅ H ₃₁ NO ₃ ·H ₂ O	72.9	8.0	72.4	8.0	248-250
Me	Me	Me	<i>i</i> -Pr	=O	80	C ₂₆ H ₃₃ NO ₃ ·HCl	70.2	7.8	70.4	7.7	289
Me	CH ₂ CH=CH ₂	Me	<i>i</i> -Pr	=O	...	C ₂₈ H ₃₅ NO ₃ ·HCl	71.5	7.7	71.4	7.5	260
Me	Me	Me	<i>n</i> -Bu	=O	68	C ₂₇ H ₃₅ NO ₃ ·HCl	70.7	7.9	70.5	7.7	306
Me	CN	Me	<i>n</i> -Bu	=O	202-205	C ₂₇ H ₃₃ N ₂ O ₃	75.0	7.5	74.9	7.4	
Me	Me	Me	<i>i</i> -Bu	=O	195	C ₂₇ H ₃₅ NO ₃	76.7	8.2	76.5	8.3	254
Me	Me	Me	<i>i</i> -Bu	<H OH	184	C ₂₇ H ₃₇ NO ₃	76.3	8.7	76.5	8.9	
Me	CN	Me	<i>i</i> -Bu	=O	223-225	C ₂₇ H ₃₅ N ₂ O ₃	75.0	7.5	75.0	7.5	
Me	Et	Me	<i>i</i> -Bu	=O	65	C ₂₈ H ₃₇ NO ₃	77.2	8.5	76.6	8.6	
Me	CH ₂ CH=CH ₂	Me	<i>i</i> -Bu	=O		C ₂₉ H ₃₇ NO ₃	77.8	8.3	78.3	8.4	140-144
H	Me	Me	<i>i</i> -Bu	=O	128-129	C ₂₆ H ₃₃ NO ₃ ·H ₂ O	73.5	8.2	73.3	8.4	265-267
H	CH ₂ -C-C ₃ H ₅	Me	<i>i</i> -Bu	=O	263-265	C ₂₉ H ₃₇ NO ₃	77.8	8.3	77.6	8.4	289-290
Me	Me	Me	<i>n</i> -Am	=O	104	C ₂₈ H ₃₇ NO ₃	77.2	8.5	76.7	8.5	248
Me	Me	Me	CH ₂ Ph	=O	80	C ₃₀ H ₃₃ NO ₃ ·HCl·2H ₂ O	68.2	7.2	67.9	7.0	315
Me ^a	Me	Ph	Me	=O	224-226	C ₂₉ H ₃₁ NO ₃	78.8	7.0	78.6	6.9	
Me	Me	Et	Me	=O	198	C ₂₅ H ₃₁ NO ₃	76.4	8.0	76.2	8.1	

^a Δ' isomer.

Established reactions are indicated by solid arrows, and hypothetical reactions (which appear to be allowable by rational mechanistic considerations) are shown by dotted arrows.

The distribution of products formed depends on the reaction conditions (*i.e.*, the strength and concentration of acid and time of heating) and the substituents R and R'. For example, the transformations described in the upper two-thirds of Scheme I (XVII-XXII) are generally achieved with dilute hydrochloric acid at 25 to 50°, with 99% formic acid at 100°, or with perchloric acid in trimethyl orthoformate, methanol, and methylene chloride at 25°. Transformations of bases of structure XXII into those of structures XXIII and XXV, however, have required 6-12 *N* hydrochloric acid at 100°. The influence of substituents on the distribution

of final products is illustrated by the conversion of the base XVII (R' = Ph, R = H) into a mixture containing 95% of the base XXIII (R' = Ph, R = H; as the isomeric olefins) and 5% of the phenol XXV (R' = Ph, R = H), while treatment of the base XVII (R' = Me, R = H) under similar conditions gave 35% of the phenol XXV (R' = Me, R = H) and 36% of the ketone XXIII (isolated yields). Nepenthenone (XII, R' = Ph, RCH₂ = H) is, of course, incapable of isomerism to an olefin of structure XXIV and, therefore, yields flavone-penthenone (XXV, R' = Ph, RCH₂ = H). The observed recyclization reactions of the 14-alkenyl derivative XXII or XXIV (XXII → XXI → XIX, XXII → XXV, XXIV → XXIII) represent Markovnikov additions of an electrophilic center at C-5, C-6, or C-8 to the double bond, producing a five- or six-membered

ring. Products formed by anti-Markovnikov additions of these electrophilic centers or by Markovnikov additions to form four- or seven-membered rings have not been found. Similarly, products formed by 1,2 migration of the 7,8 or 6,7 bonds or by 1,3 migration of the 6,18 bond to the *t*-carbonium ion C-19 in XXI have not been observed.

Experimental Section

Rearrangement of 6,14-endo-Etheno-7 α -(1-(*R*)-hydroxy-1-phenylethyl)tetrahydrothebaine (19-Phenylthevinol, I, R' = Me, CH₂R = Ph). 6,14-endo-Etheno-7 α -(1-(*R*)-hydroxy-1-phenyl-1-ethyl)tetrahydrothebaine (5 g) was heated with concentrated hydrochloric acid (100 ml) and ethanol (15 ml) on the steam bath for 30 min during which time a sparingly soluble salt separated. This was collected, washed with cold water, and dissolved in hot 50% aqueous ethanol. The resulting solution was basified with ammonia, and the precipitated solid was collected and recrystallized from ethanol, when it was obtained as almost colorless plates, mp 149–151°, ν_{\max} 1730 cm⁻¹.

Anal. Calcd for C₂₈H₃₁NO₂: C, 78.6; H, 6.8. Found: C, 78.6; H, 7.8.

The same material was obtained when 6,14-endo-etheno-7 α -(1-(*S*)-hydroxy-1-phenylethyl)tetrahydrothebaine or 14-(3-phenylbut-2-enyl)codeinone (II, R = Me, R' = Ph) was rearranged in the same way with hot concentrated hydrochloric acid. Thin layer chromatographic studies showed this base to be a mixture of three components.

The base (0.363 g) was chromatographed on a column of Merck acid-washed alumina (60 g) and the chromatogram was developed with 200 ml of 1% ethyl acetate in benzene. Elution of the column with 2% (200 ml) and 5% (600 ml) ethyl acetate in benzene gave 29 20-ml fractions, each of which was examined by thin layer chromatography on alumina. Similar fractions were combined and concentrated. The first component eluted from the column (0.023 g) was 14-(3-phenylbut-2-enyl)codeinone (II, R = Me, R' = Ph) identical in infrared absorption and behavior on thin layer plates with an authentic specimen. The second component (0.204 g) was 7,8-dihydro-5'-phenylcyclohex-4'-eno[1',2':8,14]codeinone (XI, R = H, R' = Ph), mp 161–163° after two recrystallizations from methanol, ν_{\max} 1730 cm⁻¹, λ_{\max} 241 m μ (λ_{\max} 248 m μ (ϵ_{\max} 13,400) after subtraction of the benzenoid absorption of the base I, R = H, R' = Me).

Anal. Calcd for C₂₈H₃₁NO₂: C, 78.6; H, 6.8. Found: C, 78.3; H, 6.8.

The third component (0.020 g) was 7,8-dihydro-5'-phenylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = H, R' = Ph), mp 208–210°, raised to 212–214° when separated from a small amount of the Δ^4 isomer on five 0.3-mm thick 20 × 20 cm alumina plates, ν_{\max} 1730 cm⁻¹, λ_{\max} 241 m μ (λ_{\max} 252 m μ (ϵ_{\max} 12,200) after subtraction of the benzenoid absorption of the base I, R = H, R' = Me).

Anal. Calcd for C₂₈H₃₁NO₂: C, 78.6; H, 6.8. Found: C, 78.6; H, 6.8.

Equilibration of the Isomeric Olefins X (R = H, R' = Ph) and XI (R = H, R' = Ph). Solutions containing 2.5 mg each of 7,8-dihydro-5'-phenylcyclohex-4'-eno[1',2':8,14]codeinone (XI, R = H, R' = Ph) and 7,8-dihydro-5'-phenylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = H, R' = Ph) (the latter containing 16% of the Δ^4 isomer) in 0.10 ml of benzene were prepared. Each solution, after the withdrawal of 0.02 ml for standardization, was treated with 0.47 ml of 0.1 *M* *p*-toluenesulfonic acid in glacial acetic acid to make the solutions about 0.01 *M* in olefin and 0.09 *M* in toluenesulfonic acid. These solutions were heated at 95–100° and, after designated intervals, 0.14-ml aliquots were removed and added to a mixture of 0.2 ml of concentrated ammonium hydroxide and four drops of benzene. These mixtures were agitated and centrifuged, and the benzene layer was spotted along the bottom edge of a 5 × 20 cm silica gel G plate and developed with 2% triethylamine in benzene (occasionally redeveloped several times to obtain a satisfactory separation). The separated isomers were located with the aid of an ultraviolet lamp (250 m μ) and the respective zones were removed from the plates, extracted with methanol, and diluted to a known volume (5.0 to 25.0 ml, according to the size of the sample). The absorbances at 250 m μ were then measured for each solution, and the percentage composition of each aliquot removed from the reaction mixture was then calculated using the known $\epsilon_{250\text{m}\mu}^{\text{MeOH}}$ for the pure isomers. The results obtained are set out in Table II.

Table II

Time, hr	% Composition of mixture A		% Composition of mixture B	
	X	XI	X	XI
0	0	100	84	16
1	8	92	63	37
2	12	88	42	58
20	18	82	19	81

7,8-Dihydro-5'-phenylcyclohex-4'-eno[1',2':8,14]codeine (XI, R = H, R' = Ph, CO = CHO). The mixture of isomers XI (R = H, R' = Ph) and X (R = H, R' = Ph) (5 g) obtained from the rearrangement of 6,14-endo-etheno-7 α -(1-(*R*)-hydroxy-1-phenylethyl)tetrahydrothebaine (I, R' = Me, CH₂R = Ph) was reduced with sodium borohydride (0.5 g) in hot ethanol (200 ml). The resulting alcohol was precipitated from solution by the addition of water, collected (5 g), and recrystallized four times from ethanol, when it was obtained as white prisms, mp 191°, giving only one spot on thin layer chromatograms.

Anal. Calcd for C₂₈H₃₁NO₂: C, 78.4; H, 7.3. Found: C, 78.1; H, 7.4.

7,8-Dihydro-6'-methyl-5'-phenylcyclohex-4'-eno[1',2':8,14]codeinone (XI, R = Me, R' = Ph). 6,14-endo-Etheno-7 α -(1-(*S*)-hydroxy-1-phenylpropyl)tetrahydrothebaine (I, R' = Ph, R = Me) (2 g) was heated in the water bath for 1 hr with concentrated hydrochloric acid (50 ml). The mixture was diluted with water when a viscous hydrochloride separated. This was dissolved by the addition of ethanol, and the aqueous alcoholic solution was basified with ammonia. The precipitated noncrystalline base was collected, washed with water, and crystallized from 2-ethoxyethanol. On recrystallization from this solvent 7,8-dihydro-6'-methyl-5'-phenylcyclohex-4'-eno[1',2':8,14]codeinone was obtained as pale cream prisms, mp 224–226°, showing one spot only on thin layer chromatograms, ν_{\max} 1730 cm⁻¹.

Anal. Calcd for C₂₉H₃₁NO₂: C, 78.8; H, 7.0. Found: C, 78.6; H, 6.9.

The same base was obtained by the rearrangement of 14-(3-phenylpent-2-enyl)codeinone (II, R = Me, R' = Ph) in concentrated hydrochloric acid.

7,8-Dihydro-5'-methylcyclohex-4'-eno[1',2':8,14]codeinone (XI, R = H, R' = Me). 6,14-endo-Etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (I, R = H, R' = Me) (0.50 g) was heated in hydrochloric acid (2 ml, *d* 1.19) on the steam bath for 90 min, during which time crystals separated. Water (2 ml) was added, and the solid matter was collected, when 5,14-ethano-18-isopropylidenethebaine hydrochloride (III, R = H, R' = Me) (0.175 g), mp 310–315°, was obtained (see part IV of this series).

The combined filtrate and washings from the collection of this hydrochloride were neutralized with aqueous sodium bicarbonate and the resulting base was isolated by extraction with methylene chloride. The glass remaining after removal of the solvent was dissolved in methylene chloride and chromatographed on alumina (Woelm, activity II, 20 g). Continued elution of the column with methylene chloride afforded material that was crystallized from *n*-hexane, when 7,8-dihydro-5-methylcyclohex-4'-eno[1',2':8,14]codeinone (165 mg) was obtained as prisms, mp 112–114°, ν_{\max} 1725 cm⁻¹.

Anal. Calcd for C₂₈H₃₁NO₂: C, 75.6; H, 7.45. Found: C, 76.0; H, 7.4.

7,8-Dihydro-5',6'-dimethylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = R' = Me). 6,14-endo-Etheno-7 α -(1-(*R*)-hydroxy-1-methylpropyl)tetrahydrothebaine (I, R' = Me, R = Me) (5 g) was heated on the steam bath for 1 hr with concentrated hydrochloric acid (25 ml). The mixture was diluted with aqueous ethanol and made alkaline with ammonia. The resulting base was collected and recrystallized from ethanol, when it was obtained as white prisms, mp 199°, ν_{\max} 1730 cm⁻¹.

Anal. Calcd for C₃₀H₃₃NO₂: C, 76.0; H, 7.6. Found: C, 76.1; H, 7.9.

The same base was obtained by the rearrangement of 6,14-endo-etheno-7 α -(1-(*S*)-hydroxy-1-methylpropyl)tetrahydrothebaine (I, R' = Et, R = H) in the same way.

7,8-Dihydro-5'-ethyl-6'-methylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = Me, R' = Et). This base was obtained as above by heating 6,14-endo-etheno-7 α -(1-hydroxy-1-ethylpropyl)tetrahydrothebaine (1 g) with concentrated hydrochloric acid (5 ml) on the steam bath for 1 hr. It formed prisms, mp 198°, from ethanol, ν_{\max} 1730 cm⁻¹.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 76.4; H, 8.0. Found: C, 76.2; H, 8.1.

7,8-Dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = Et, R' = Me). The diastereoisomeric alcohols I (R = H, R' = *n*-Pr and also R = Et, R' = Me), on heating on the steam bath with concentrated hydrochloric acid for 1 hr, yielded the same base obtained as prisms, mp 229–230°, from ethanol, ν_{\max} 1730 cm^{-1} .

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 76.4; H, 8.0. Found: C, 76.3; H, 8.0.

7,8-Dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]morphinone (XVI, R² = H, R¹ = R³ = Me, R = Et, R⁴ = O). a. **7,8-Dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone** (X, R = Et, R' = Me) (5 g) was boiled under reflux for 1 hr with concentrated hydrobromic acid (48%) (100 ml). The mixture was cooled and diluted with aqueous ethanol, and the base was precipitated from the solution with ammonia. After collection and recrystallization from aqueous 2-ethoxyethanol the phenol (3.1 g) was obtained as cream plates, mp 110°, ν_{\max} 1730 cm^{-1} .

Anal. Calcd for $C_{24}H_{29}NO_3 \cdot H_2O$: C, 72.6; H, 8.3. Found: C, 73.0; H, 8.0.

b. **6,14-endo-Etheno-7 α -(1-(R)-hydroxy-1-methylbutyl)tetrahydrothebaine** (I, R' = Me, R = Et) (1 g) was boiled under reflux for 1 hr with concentrated (48%) hydrobromic acid (10 ml). The base was isolated as in a and was obtained as plates, mp 110°, identical in infrared absorption with material prepared by that process.

c. **6,14-endo-Etheno-7 α -(1-(R)-hydroxy-1-methylbutyl)tetrahydroorpavine** (XV, R² = H, R¹ = R³ = Me, R = Et) (1 g) was heated on the steam bath with concentrated hydrochloric acid (8 ml) for 1 hr. The dihydromorphinone was isolated as in a and was obtained as plates, mp 110°, identical in infrared absorption with material prepared as in a and b above.

N-Cyano-7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone (XVI, R¹ = R² = Me, R³ = CN, R = Et, R⁴ = O). **N-Cyano-6,14-endo-etheno-7 α -(1-(R)-hydroxy-1-methylbutyl)tetrahydrothebaine** (I, R' = Me, R = Et, NMe = NCN) (12.2 g) was dissolved in concentrated hydrochloric acid (85 ml) and the solution kept at the room temperature for 18 hr. The product was precipitated by the addition of water, collected, and washed with hot ethanol, when **N-cyano-7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone** (10.5 g) was obtained as white prisms, mp 277–279°.

Anal. Calcd for $C_{23}H_{29}N_2O_3$: C, 74.2; H, 7.0; N, 6.9. Found: C, 74.7; H, 7.0; N, 7.0.

7,8-Dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone (XVI, R¹ = R² = Me, R³ = H, R = Et, R⁴ = O). a. **N-Cyano-7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone** (37.5 g), water (1400 ml), 2-ethoxyethanol (600 ml), and potassium hydroxide (144 g) were boiled under reflux for 18 hr with vigorous stirring. The mixture was cooled and the solid matter (23.5 g) collected and recrystallized from aqueous ethanol, when the secondary base was obtained as white prisms, mp 210–212°, ν_{\max} 1730 cm^{-1} .

Anal. Calcd for $C_{24}H_{29}NO_3$: C, 76.0; H, 7.7; N, 3.7. Found: C, 76.5; H, 7.8; N, 3.7.

b. **6,14-endo-Etheno-7 α -(1-(R)-hydroxy-1-methylbutyl)tetrahydrothebaine** (I, R' = Me, R = Et, NMe = NH) (5 g) was heated at 100° with concentrated hydrochloric acid (50 ml) for 2 hr. The mixture was diluted with 40% aqueous ethanol (200 ml) and basified with aqueous ammonia. The precipitated base was collected, washed, and recrystallized from aqueous ethanol, when **7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone** (3.6 g) was obtained as white prisms, mp 210–212°, alone or mixed with a specimen prepared as in a.

Anal. Calcd for $C_{24}H_{29}NO_3$: C, 76.0; H, 7.7. Found: C, 75.8; H, 7.9.

N-Allyl-7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone (XVI, R¹ = R² = Me, R³ = $\text{CH}_2\text{CH}=\text{CH}_2$, R = Et, R⁴ = O). a. **7,8-Dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone** (XVI, R¹ = R² = Me, R³ = H, R = Et, R⁴ = O) (8 g), allyl bromide (4.8 g), anhydrous potassium carbonate (16 g), and acetone (250 ml) were heated together under reflux with stirring for 18 hr. The mixture was filtered, the filtrate evaporated to dryness, and the residue treated with ethereal hydrogen chloride. The solid hydrochloride was collected and converted into the base with aqueous ethanolic ammonia. The product was recrystallized from aqueous ethanol, when **N-allyl-7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone** (4.9 g) was obtained as white prisms, mp 131–133°, ν_{\max} 1730 cm^{-1} .

Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.3; H, 8.0; N, 3.3.

b. **N-Allyl-6,14-endo-etheno-7 α -(tetrahydrothebaine** (I, R' = Me, $\text{CH}=\text{CH}_2$) (3 g) was heated with conc ml) at 100° for 2 hr. The mixture was ethanol and basified with ammonia collected and recrystallized from allyl-7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]norcodeinone was obtained as prisms, mp

7,8-Dihydro-6'-isobutyl-5'-methylnorcodeinone (XVI, R¹ = R² = Me, a. **7,8-Dihydro-6'-isobutyl-5'-methylcodeinone** (X, R = *i*-Bu, R' = Me, boxylate (0.87 g) were heated together ml) for 45 min. The acetone was evaporated on the steam bath for 1 hr with 5 N) hydrochloric acid (5 N). The mixture was cooled with ether. The base was precipitated by ether extraction, when it was obtained (2.2 g).

Anal. Calcd for $C_{25}H_{33}NO_3$: C, 76.2; H, 8.4.

b. **N,N'-Methylenbis-6,14-endo-etheno-7 α -(1-(R)-hydroxy-1-methylbutyl)tetrahydrothebaine** (I, R' = Me, R = Et) (1 g) was heated on the steam bath with concentrated hydrochloric acid (8 ml) for 1 hr. The dihydromorphinone was isolated as in a and was obtained as plates, mp 110°, identical in infrared absorption with material prepared as in a and b above.

The secondary base prepared by boiling with methyl iodide, ethanol, and for 6 hr gave a good yield of **7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone** (R' = Me) identical with an authentic mixture melting point, and infrared at

Δ^4 -Dihydro-5'-phenylcyclohex-4-en-2-one (XII, R = H, R' = Ph) containing some **Δ^4 -Dihydro-5'-phenylcyclohex-4-en-2-one** (XII, R = H, R' = Ph), mp 149–151° (1 g), were heated in diethylene glycol (25 ml) at 100° for 2 hr. The temperature was reduced to 75° and poured, after which the temperature evolution began at 85° and proceeded to 140° it was almost stopped, and poured with stirring into 100 ml of water. The solid was collected and dried by ether extraction. On evaporation a crystallizable gum was obtained which was insoluble in all solvents except very sparingly soluble in all solvents except from 80% acetic acid, when it dissolved. **Δ^4 -Dihydro-5'-phenylcyclohex-4-en-2-one** (XII, R = H, R' = Ph) (1.5 g) and hydrazine hydrate (25 ml) was heated at 140–150° for 1 to 100° and potassium hydroxide (4 g) was slowly raised, and evolution began at 120°, became very rapid at 160–165 min at the latter temperature. The aqueous ammonium chloride, and was collected, washed thoroughly with

Anal. Calcd for $C_{22}H_{27}NO_3 \cdot \text{HCl}$: C, 74.0; H, 7.4.

Thin layer chromatography showed trace of impurity, presumably the Δ^4 could not be crystallized, in ethanolic diazotized sulfanilic acid to give a block.

Δ^4 -Dihydro-6'-isobutyl-5'-methyldeoxycodine (XII). A solution of **7,8-dihydro-6'-ethyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone** (XVI, R¹ = R² = Me, R³ = H, R = Et, R⁴ = O) (1.5 g) and hydrazine hydrate (25 ml) was heated at 140–150° for 1 to 100° and potassium hydroxide (4 g) was slowly raised, and evolution began at 120°, became very rapid at 160–165 min at the latter temperature. The aqueous ammonium chloride, and was collected, washed thoroughly with

from methanol, when the phenolic base XII was obtained (0.55 g) as white felted needles, mp 127–129°.

Anal. Calcd for $C_{27}H_{27}NO_3$: C, 79.5; H, 9.1. Found: C, 79.1; H, 9.3.

The infrared spectrum showed no carbonyl absorption, and the nmr spectrum showed signals (in δ units) at 6.61 (two aromatic H), 6.3 and 5.5 (doublets, $J_{AB} = 9$ cps, $CH=CH$), 5.85 (OH), 3.85 (OCH_3), 2.3 (NCH_3), 1.58 ($C=CCH_3$), and 0.80 (complex, $CHMe_2$). The signal due to the hydroxyl proton was moved to δ 7.93 in dimethyl sulfoxide.

The base was not readily soluble in aqueous alkalis but in ethanolic potassium hydroxide it coupled readily with diazotized sulfanilic acid to give a blood red solution.

The picrate was obtained as canary yellow needles, mp 186° from ethanol.

Anal. Calcd for $C_{27}H_{27}NO_3 \cdot C_6H_3N_3O_7$: C, 62.2; H, 6.3; N, 8.8. Found: C, 61.9; H, 6.5; N, 9.2.

The methanolic mother liquors from the recrystallization of the original reaction product on evaporation afforded a gum from which a second picrate (0.200 g) was obtained as dark yellow prisms, mp 190°.

Anal. Calcd for $C_{27}H_{27}NO_3 \cdot C_6H_3N_3O_7$: C, 62.2; H, 6.3; N, 8.8. Found: C, 61.9; H, 6.5; N, 9.1.

This is believed to be the picrate of the Δ^8 isomer of the base XII since the base recovered from the salt still gave a blood red color with diazotized sulfanilic acid in alcoholic potassium hydroxide solution.

6-Acetoxy-6'-isobutyl-5'-methylcyclohex-5'-eno[1',2':8,14]-deoxycodone-C (XIII). 7,8-Dihydro-6'-isobutyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = *i*-Bu, R' = Me) (1.5 g), acetic anhydride (7.5 ml), and anhydrous sodium acetate (0.25 g) were boiled together under reflux for 1.75 hr. The mixture was poured into water and the base was liberated with sodium carbonate and extracted with ether. The extracts yielded an orange gum that crystallized on standing. Recrystallization from methanol afforded the enol acetate (1.0 g) as white needles, mp 132°, ν_{max} 1750 cm^{-1} .

Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.2; H, 8.0. Found: C, 75.5; H, 8.2.

This enol acetate was heated with aqueous ethanolic hydrochloric acid on the water bath for 30 min, and the mixture was neutralized with ammonia to give 7,8-dihydro-6'-isobutyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = *i*-Bu, R' = Me), mp 196° alone or mixed with an authentic specimen, ν_{max} 1730 cm^{-1} .

7,8-Dihydro-6'-isobutyl-8,5'-trimethylcyclohex-5'-eno[1',2':8,14]codeinone (XIV, R = Me). A suspension of 7,8-dihydro-6'-isobutyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = *i*-Bu, R' = Me) (1 g) in dry *t*-butyl alcohol (10 ml) was added to a solution of potassium (0.5 g) in dry *t*-butyl alcohol (75 ml) and the mixture stirred for 10 min at 30°. Excess of methyl iodide (2 ml) was then added, and the mixture was stirred for 1 hr after which it was poured into water. The product was isolated by ether extraction and recrystallized from methanol when 7,8-dihydro-6'-isobutyl-8,5'-trimethylcyclohex-5'-eno[1',2':8,14]codeinone (0.4 g) was obtained as white plates, mp 169–170°, ν_{max} 1710 cm^{-1} .

Anal. Calcd for $C_{29}H_{33}NO_3$: C, 77.5; H, 8.75. Found: C, 77.2; H, 8.8.

The nmr spectrum was identical with that of the starting material except in the region δ 0.6–1.2 in which region signals integrate for 12 protons instead of 6. The base was recovered unchanged

after heating under reflux for 2 hr with acetic anhydride and anhydrous sodium acetate.

7,8-Dihydro-7-hydroxyimino-6'-isobutyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone (XIV, R = NOH). A solution of sodium (0.25 g) in ethanol (10 ml) was added to a suspension of 7,8-dihydro-6'-isobutyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone (X, R = *i*-Bu, R' = Me) (1 g) in ethanol (20 ml) and the mixture heated on the water bath for 5 min, then cooled to 60°. Isoamyl nitrite (0.4 g) in ethanol (1.5 ml) was then added and the resulting mixture, which rapidly became dark brown, set aside until a test portion gave only a slightly turbid solution when poured into excess of aqueous sodium hydroxide (about 15 min). The mixture was then poured into aqueous 2 *N* sodium hydroxide solution (50 ml) and insoluble matter was removed by ether extraction. The base was precipitated from the aqueous layer by the addition of ammonium chloride solution, collected, washed with water, and recrystallized from methanol, when the isonitroso ketone (0.8 g) was obtained as white prisms, mp 238–240°, ν_{max} 1700 cm^{-1} .

Anal. Calcd for $C_{28}H_{31}N_2O_4$: C, 72.0; H, 7.55. Found: C, 71.7; H, 7.5.

The base gave an immediate green-brown precipitate on treatment in methanol solution with methanolic cupric acetate. The precipitate dissolved readily to give an almost colorless solution in acids but was recovered unchanged on the addition of ammonia, no cupric tetraammine salt being obtained.

7,8-Dihydro-6'-isobutyl-5'-methyl-7-oxocyclohex-5'-eno[1',2':8,14]codeinone (XIV, R = O). A solution of 7,8-dihydro-7-hydroxyimino-6'-isobutyl-5'-methylcyclohex-5'-eno[1',2':8,14]codeinone (XIV, R = NOH) (0.5 g) in 2 *N* sulfuric acid (10 ml) was heated at 100° for 30 min, then basified with ammonia. The precipitated base was isolated by ether extraction and dissolved in hot petroleum ether (bp 60–80°). On cooling the solution deposited a green amorphous solid, which in petroleum ether suspension slowly became crystalline. The crystalline solid was collected, washed free of amorphous material with cold benzene, and recrystallized from benzene, when the α -diketone XIV (R = O) (0.28 g) was obtained as canary yellow prisms, mp 198–200°.

Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.5; H, 7.6. Found: C, 74.6; H, 7.8.

The base gave a deep wine red color with ethanolic ferric chloride, which became an intense blue green on the addition of a trace of ammonia.

The hydrochloride, prepared in ethanol and recrystallized from 2-ethoxyethanol containing 10% water, was obtained as light yellow prisms, mp 215–217°.

Anal. Calcd for $C_{27}H_{31}NO_4 \cdot HCl \cdot 1.5H_2O$: C, 64.8; H, 7.4. Found: C, 64.8; H, 7.6.

Acknowledgments. The authors wish to thank Dr. D. E. Webster of the University of Hull, England, and Dr. S. F. Dyke of the College of Science and Technology, Bristol, England, for the determination of some preliminary nmr spectra, and the following for experimental assistance: Dr. A. C. B. Smith, Mr. H. Fitton, Mr. J. Fulstow, Mr. M. J. Readhead, Mr. J. K. Saville, Mr. T. M. Sutton, Mrs. E. M. Walker, and the late Mr. S. R. Duff.

Novel Analgesics and Molecular Rearrangements in the Morphine-Thebaine Group. VI.¹ Base-Catalyzed Rearrangements in the 6,14-*endo*-Ethenotetrahydrothebaine Series

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Contribution from the Research Laboratories, Reckitt and Sons Ltd.,
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Abstract: The 7 α and 7 β ketones of the 6,14-*endo*-etheno- and -ethanotetrahydrothebaine series I suffer base-catalyzed rearrangement to isomeric bases VIII, though the reaction may be interrupted by other reagents at an intermediate stage II or V. The rearrangement of the esters and nitriles of this series does not proceed beyond the stage X or XII, corresponding to V. All of these products are unstable to acids which readily convert them into derivatives of 5,14-ethanothebainone III, VI, VII, and XII. The catalytic reduction of and the reaction of organometallic compounds with the ketone VIII have been studied. 18-Acetyl-5,14-ethanothebainone (VII, R' = H) has been shown to undergo base-catalyzed ketolization to the hexacyclic base XXV. The Hofmann degradation of the quaternary salts of certain of the rearranged bases has been shown to proceed normally.

The ketone nepenthone (I, CH₃ = Ph), which is the Diels-Alder adduct of thebaine and phenyl vinyl ketone, readily suffers base-catalyzed rearrangement to isonepenthone (VIII, CH₃ = Ph),² and similar rearrangements have been effected with certain other adducts of thebaine bearing electron-withdrawing substituents at C-7. The aldehyde I (CH₃ = H), the ketone I,^{2,3} the ester I (CH₃ = OEt),³ and the 7-nitrile I (COCH₃ = CN)^{2,3} have all been subjected to base-catalyzed rearrangement as have some of their 6,14-ethano analogs. The reaction is initiated by the removal of the C-7 proton, which is α to the activating group. Although the methyl ketone I is initially enolized by removal of a proton from the methyl group under kinetic control,³ under reversible conditions removal of the C-7 proton occurs with formation of an enolate ion in which C-7 is no longer asymmetric and both 7 α and 7 β forms of the reactive species give the same product after rearrangement.

Following the removal of the C-7 proton displacement of the 4,5-oxide bridge by the carbanion occurs to give the phenate ion IV, and the final fate of this ion then depends on the nature of C-7 substituent and on the conditions of the reaction. If no other reagent is present, and if the electron-accepting power of the C-7 substituent is great enough, *i.e.*, if this is a keto group, the cyclopropane ring may be opened under attack at C-5, which would lead to the starting material, or at C-6, which leads to the rearranged base VIII. The examination of models of the molecules of structures I and VIII shows that the ring system, and in particular the oxygen-containing ring, of the latter is appreciably the less strained of the two and, since the reactions are clearly reversible, excellent yields of the rearranged bases are obtained.

If methyl iodide is added to a solution in *t*-butyl alcohol of the phenate anion IV, obtainable from either of the ketones I and VIII, methylation occurs; the

cyclopropane ring is not affected, and the product is the base V (R' = Me). The rearrangement also occurs under the influence of Grignard reagents functioning as bases,⁴ and this process competes with the normal attack of the carbonyl group in the reaction of the ketone I and its 7 β epimer with these reagents. In this reaction the initially formed phenate anion IV reacts further with the Grignard reagent at the carbonyl group to give a tertiary alcohol, thus effectively blocking the route for opening of the cyclopropane ring; the product is the phenolic alcohol II (R' = H). This represents only a minor side reaction of the ketone I with Grignard reagents but frequently accounts for as much as 40% of the product of the reaction in the 6,14-ethano series.

Base-catalyzed rearrangements of the ester I (CH₃ = OEt) and the nitrile I (COCH₃ = CN) are also easily effected. The products of simple rearrangement are the ester X (R = Et, R' = H) and the nitrile XII (R' = H); the electron-accepting power of the C-7 substituent in these cases apparently is insufficient to effect the production of analogs of the ketone VIII. The ester I (CH₃ = OEt) reacts normally with methylmagnesium iodide to give a tertiary carbinol,⁴ but with other Grignard reagents the main products are the rearranged ester X (R = Et, R' = H) and the symmetrical tertiary carbinol II (R' = H, Me = R) resulting from the reaction of this ester with the reagent. The nitrile I (COCH₃ = CN) affords the rearranged base in excellent yield with aliphatic Grignard reagents, though with aromatic reagents some of the product of "normal" attack of the C \equiv N group is also obtained.³ The addition of alkyl or acyl halides during the rearrangement results in alkylation or acylation of the phenate ion, the products being the ethers or esters X (R' = Me) and XII (R' = Me, Et, Ac). The base-catalyzed rearrangement of the ester I (CH₃ = OEt) can also be combined with ester exchange processes; the products are esters of structure X (R' = H).

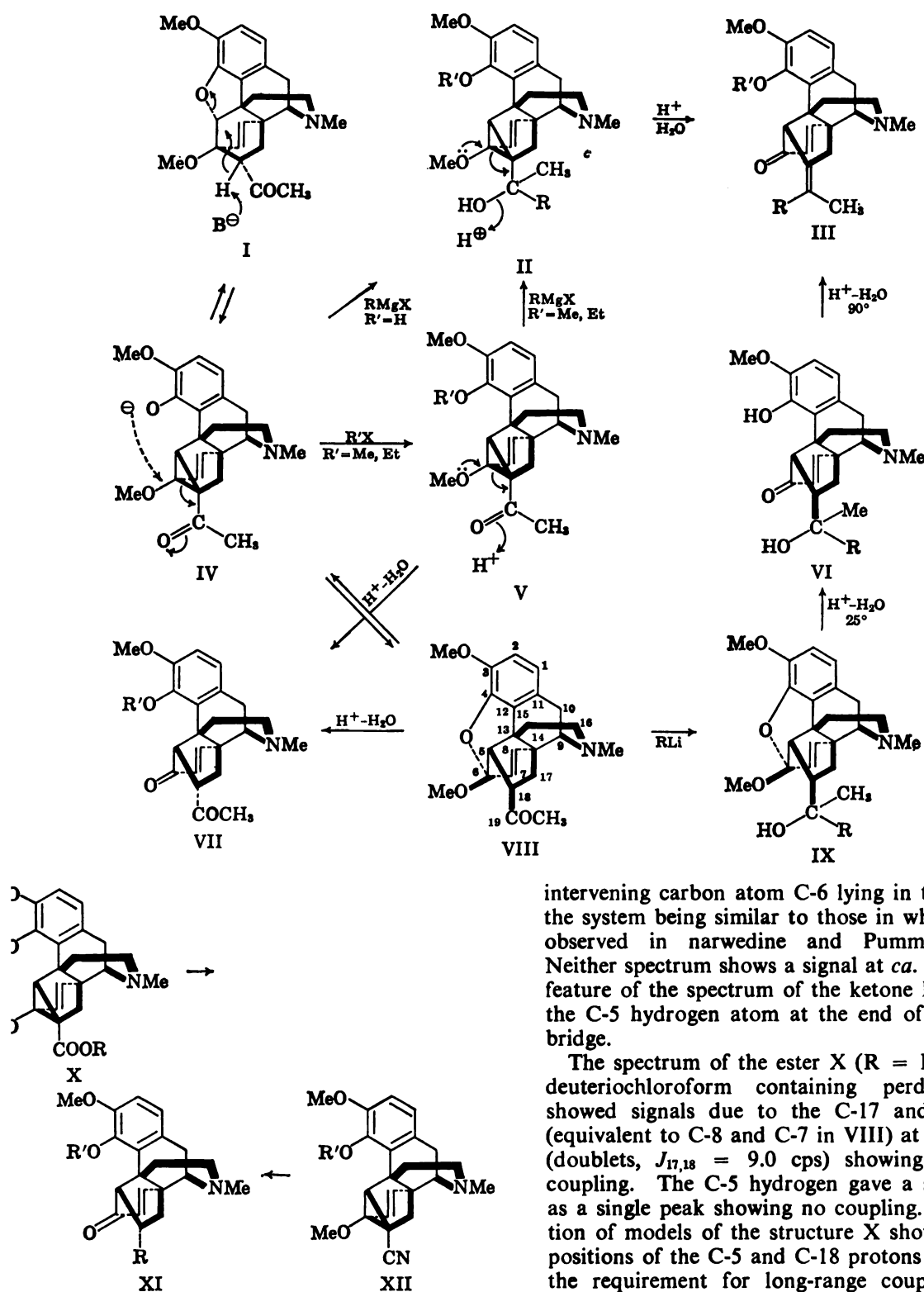
The nmr spectra of representative bases of the various groups are entirely in accord with the assigned structures. The spectrum of isonepenthone (VIII, CH₃ =

(1) Part V: K. W. Bentley, D. G. Hardy, C. F. Howell, W. Fulmor, J. E. Lancaster, J. J. Brown, G. O. Morton, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89**, 3303 (1967).

(2) K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1725 (1958).

(3) Part I: K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89**, 3267 (1967).

(4) Part II: K. W. Bentley, D. G. Hardy, and B. Meek, *ibid.*, **89**, 3273 (1967).



shows signals (in δ units) at 8.2–7.2 (complex, five aromatic H), 6.6 (two aromatic H), 6.0 (doublet, C-8 $J_{8,7} = 9$ cps), 5.15 (doublet, C-7 H, $J_{7,8} = 9$ cps, each k a doublet, $J_{7,5} = 2$ cps), 3.82 (C-3 OCH_3), 3.55 (5 OCH_3), and 2.30 (NCH_3). The spectrum of the one VIII is virtually identical with that of isonepenne except that it lacks the complex signals at δ 7.2 due to the phenyl group, and it shows instead signal at δ 2.22 due to $COCH_3$. The examination of iding models of these ketones shows that disposi- 1 of the C-5 and C-7 hydrogen atoms is such as to mit long-range coupling, the two protons and the

intervening carbon atom C-6 lying in the same plane, the system being similar to those in which coupling is observed in narwedine and Pummerer's ketone.⁶ Neither spectrum shows a signal at *ca.* δ 4.5 which is a feature of the spectrum of the ketone I,⁶ attributed to the C-5 hydrogen atom at the end of the 4,5-oxygen bridge.

The spectrum of the ester X ($R = Et$, $R' = H$) in deuteriochloroform containing perdeuteriopyridine⁷ showed signals due to the C-17 and C-18 protons (equivalent to C-8 and C-7 in VIII) at δ 5.93 and 5.72 (doublets, $J_{17,18} = 9.0$ cps) showing no additional coupling. The C-5 hydrogen gave a signal at δ 3.57 as a single peak showing no coupling. The examination of models of the structure X shows that the dispositions of the C-5 and C-18 protons no longer meet the requirement for long-range coupling. The C-8 αH pattern was found as a doublet, coupling occurring only with C-8 βH ($J_{8\alpha,8\beta} = 13.0$ cps) indicating the absence of a hydrogen atom at C-7. The phenolic hydroxyl proton was signalled at *ca.* δ 8.0 in the presence of deuteriopyridine, but in the absence of this agent the signal appeared partially superimposed upon one line of the C-17 proton doublet at δ 5.82. The other fea-

(5) G. W. Kirby and H. P. Tiwari, *J. Chem. Soc.*, 4655 (1964).

(6) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, 89, 3322 (1967).

(7) We are indebted to W. Fulmor, J. E. Lancaster, and G. O. Morton of Lederle Laboratories, Pearl River, N. Y., for the determination and interpretation of this spectrum.

tures of the spectrum of this ester were entirely consistent with the structure X ($R = \text{Et}$, $R' = \text{H}$).

The spectrum of the nitrile XII ($R = \text{H}$) was similar in essential features to that of the ester, showing signals due to C-17-C-18 at δ 6.1 and 5.7 (doublets, $J_{17,18} = 9.0$ cps) and C-8 αH at δ 1.13 ($J_{8\alpha,8\beta} = 13.0$ cps), as well as signals due to two aromatic H, two different methoxyls, and the N-methyl group. The phenolic hydroxyl group was located by a signal at δ 8.38 in dimethyl sulfoxide. The infrared spectrum of the nitrile, like that of the above ester, but unlike the spectra of the ketone VIII and isonepenthone, in solution showed hydroxyl absorption at 3545 cm^{-1} .

The nmr spectrum of the alcohol II ($R' = \text{H}$, $R = n\text{-Pr}$),⁷ isolated as a minor product from the products of the reaction of the ketone I with *n*-propylmagnesium halides, was also similar to that of the ester X ($R = \text{Et}$, $R' = \text{H}$) showing signals (in δ units) for the following: phenolic OH, 5.93 (exchangeable); C-18 H, C-17 H, 6.00 and 5.64 (doublets, $J_{17,18} = 9$ cps); alcohols OH 4.72 (exchangeable); C-5 H, 3.0; C-8 αH , 0.70 (doublet, $J_{8\alpha,8\beta} = 11$ cps), in addition to the expected signals for the other systems present in structure II ($R' = \text{H}$, $R = n\text{-Pr}$).

The products of the rearrangements set out above, *i.e.*, the bases of general structures II, V, VIII, X, and XII, are all unstable to acids and readily suffer hydrolysis. The ketones VIII and VIII ($\text{CH}_3 = \text{Ph}$), being both mixed ketals and allylic phenyl ethers, on treatment with acids under mild conditions are converted into the phenolic α,β -unsaturated ketones VII ($R' = \text{H}$) and VII ($R' = \text{H}$, $\text{CH}_3 = \text{Ph}$, *i.e.*, ψ -nepenthone). Both of the nonphenolic parent ketones, which are prepared under conditions of reversible enolization, may be assumed to be the stable isomers, which are shown by the examination of models to have the COCH_3 or COPh group disposed as shown in formula VIII. The examination of models of ψ -nepenthone (VII, $R' = \text{H}$, $\text{CH}_3 = \text{Ph}$), however, suggests that in this base there is little difference in stability between the two C-18 isomers. In support of this view it has been found that ψ -nepenthone produced by the mild acid hydrolysis of isonepenthone (VIII, $\text{CH}_3 = \text{Ph}$) is a single substance, presumably the 18β isomer, which can be equilibrated on standing in acid solution to an approximately 1:1 mixture of two bases⁸ which can be differentiated on alumina plates. The extraction of the separate zones on the alumina with methanol, however, results in re-equilibration of the isomers, and the C-18 epimer of ψ -nepenthone has not been isolated. The examination of models of the epimeric forms of the ketone VII ($R' = \text{H}$), however, suggests that the 18α isomer will be the more stable of the two, since in this form non-bonded interactions are minimal, whereas in the 18β ketone there is appreciable interaction between the methyl group in the side chain and one of the C-15 hydrogen atoms. The hydrolysis of the ketal VIII takes place without the separation of a hydrochloride, *i.e.*, under conditions similar to those required for the equilibration of ψ -nepenthone, and gives a single substance, which is assigned the 18α structure on the basis of its very ready cyclization to the base XXV (see below).

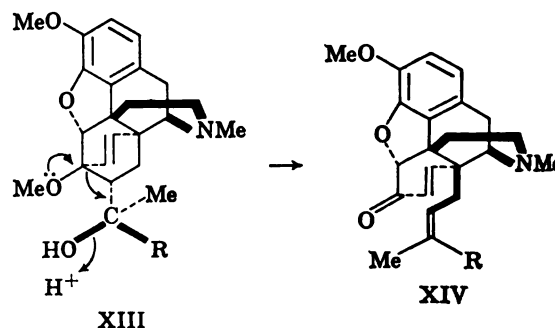
The ketone V ($R' = \text{Me}$) is an aldol methyl ether as well as a highly strained (cyclopropane) derivative, and

(8) This observation was made by Dr. J. W. Lewis and Mr. M. J. Readhead of this laboratory.

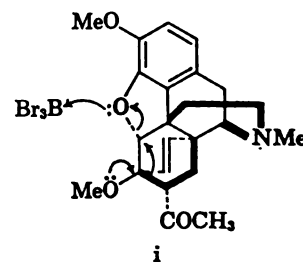
is readily hydrolyzed by acids under very mild conditions. Since this reaction must proceed through the enol form of the ketone, the product is the stable C-18 epimer, identical with the product of methylation of the phenol VII ($R' = \text{H}$).

The rearranged nitriles and esters of general structures XII and X are likewise very readily hydrolyzed with production of the corresponding α,β -unsaturated ketones XI ($R = \text{CN}$) or XI ($R = \text{COOR}$). The ease with which the hydrolysis of the bases V, X, and XII occurs contrasts markedly with the stability of the ketones I and also I ($\text{CH}_3 = \text{Ph}$) and the ester I ($\text{CH}_3 = \text{OEt}$) under acid conditions.⁹ This may be the result of strain in the cyclopropane ring, but it may be noted that a similar difference in stability has been observed in the enol ether systems of thebaine and dihydrothebaine, in which the 4,5-oxygen bridge is intact, which form stable hydrochlorides, and the phenolic bases dihydrothebaine- φ ,¹⁰ β -dihydrothebaine, thebainone-A enol methyl ether,¹⁰ and the Δ^5 - and Δ^6 -enol methyl ethers of dihydrothebainone,¹⁰ all of which are extremely rapidly hydrolyzed, even by cold acetic acid.

The ketone V ($R' = \text{Me}$), which is stable to bases, reacts normally with Grignard reagents, giving tertiary alcohols of general structure II ($R' = \text{Me}$), and these, like the corresponding phenols II ($R' = \text{H}$), on treatment with acid very readily suffer dehydration and hydrolysis to give the olefinic ketones III. This reaction is essentially the same as that involved in the conversion of alcohols of structure XIII into 14-alkenylcodeinones (XIV),¹¹ but occurs under much milder conditions. The bases III ($R = \text{Me}$, $R' = \text{H}$) and III ($R = R' = \text{Me}$), obtained in this way, are identical with the stable phenolic end product of acid-catalyzed rearrangement of the alcohol XIII ($R = \text{Me}$) or the alkenylcodeinone XIV ($R = \text{Me}$) and its methyl ether.¹¹



(9) This phenolic, α,β -unsaturated ketone VII ($R = \text{H}$) is the product of the action of boron tribromide on the ketone I at 5° . The reaction can be rationally represented by the mechanism set out in i, which involves no disturbance of stereochemistry at C-7 [becoming C-18 in the diketone VIII ($R = \text{H}$)], and is analogous to the flavothebaine rearrangement.



(10) L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939); K. W. Bentley, R. Robinson, and A. E. Wain, *J. Chem. Soc.*, **58**, 958 (1952).

(11) Part IV: K. W. Bentley, D. G. Hardy, and B. Meck, *J. Am. Chem. Soc.*, **89**, 3293 (1967).

nitrile XII ($R' = \text{Me}$), which contains no readily α proton, reacts normally with methylmagnesium and the initial product on hydrolysis yields the VII ($R' = \text{Me}$), identical with that prepared from the ketones V ($R' = \text{Me}$), and VIII. The (R = Et, $R' = \text{H}$) in part reacts further with other reagents, when generated by these from the (CH₃ = OEt), giving the tertiary carbinols II H, Me = R).

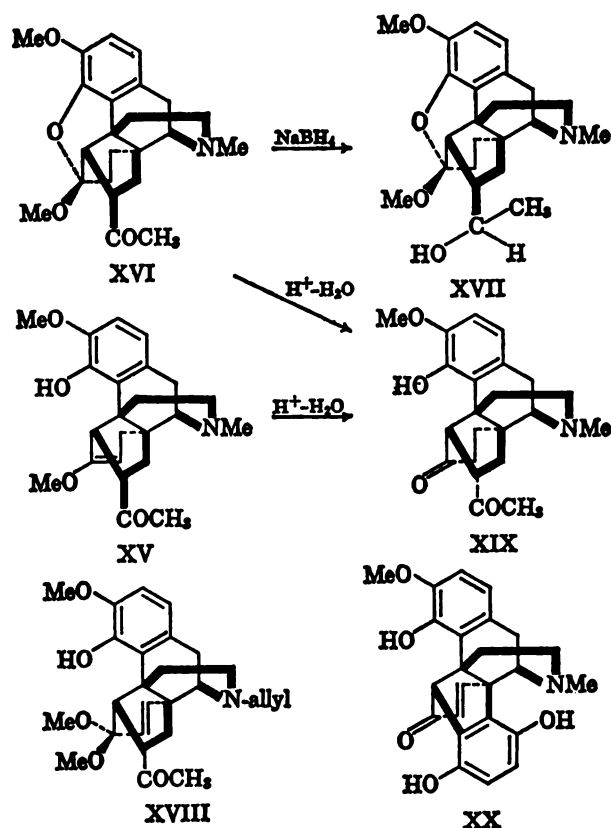
reaction of the ketones VIII and also VIII = Ph) with Grignard reagents is more complex, they contain more than one reactive system. As being ketones they are allylic phenyl ethers, and of this type in the morphine-thebaine group (dihydrothebaine,¹² dihydrocodeinone enol acetate,¹³ dehydrocodeine-C,¹⁴ ψ -codeine methyl ether¹⁵) readily undergo competing 1,2 and 1,4 addition of Grignard reagents to the allylic ether system to give nuclear substituted phenolic bases. In this event the ketone reacts vigorously with methylmagnesium iodide to give a nonketonic phenolic matter, together with unchanged starting material, both of which must be derived *via* the phenate ion IV.

reaction with methyllithium, however, afforded a good yield of the tertiary alcohol IX (R = Me), which is hydrolyzed by cold dilute hydrochloric acid to the secondary alcohol VI (R = Me) and by hot hydrochloric acid to the olefinic ketone III (R = Me, $R' = \text{H}$), along with the product of hydrolysis of the alcohol = Me, $R' = \text{H}$) and of rearrangement of the codeinone XIV (R = Me) and alcohol XIII (Me).¹¹ Other lithium alkyls, however, reacted only with the ketone VIII, and the process does not provide an attractive route to a series of alcohols of interest IX and VI. The ketone VIII is readily reduced with sodium borohydride to the secondary alcohol IX (R = H), which is hydrolyzed by acids to the VI (R = H), also obtainable by the reduction of the diketone VII ($R' = \text{H}$) with sodium borohydride, which process the hindered C-6 carbonyl group is unaffected.

Reductive reduction of the ketone VIII is not a simple process, and the composition of the product depends on the nature of the catalyst. The allylic ether system present in the ketone readily undergoes 1,4 addition of Grignard reagents to give the phenolic base XV. Simple saturation of the olefinic bond has also been observed, the product being the nonphenolic base XVI, which is also obtainable by the base-catalyzed rearrangement of the thebaine analog of the ketone I. The phenolic base is an enol ether and is very rapidly hydrolyzed by acids to the saturated diketone XIX, also accessible by hydrolysis of the base XVI and by the catalytic reduction of the unsaturated ketone VII ($R' = \text{H}$). Reduction of the ketone XVI with sodium borohydride yields the corresponding secondary alcohol which may be hydrolyzed to a saturated ketone, which is the dihydro derivative of the base VI (R =

Other analogs of the ketone VIII have been prepared by base-catalyzed rearrangement of the appropriate ketone I (NMe = NR). In one case in methanolic solution, L. F. Small, H. M. Fitch, and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 936 (1936). L. F. Small, S. G. Turnbull, and H. M. Fitch, *J. Org. Chem.*, **3**, 38 (1938). L. F. Small and K. C. Yuen, *J. Am. Chem. Soc.*, **58**, 192 (1936).

potassium hydroxide solution, two products were obtained: the expected ketone VIII (NMe = N-CH₂-CH=CH₂) and a phenolic base containing the elements

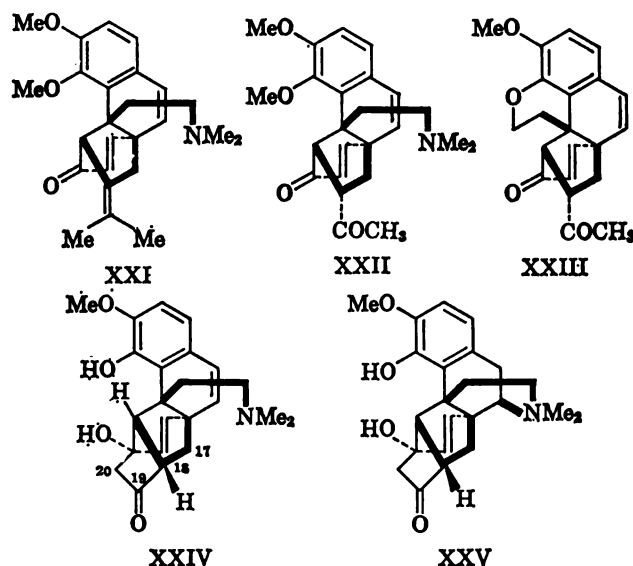


of added methanol. Since both bases yielded the same α,β -unsaturated ketone on hydrolysis with acids, and since each of the pure compounds was converted into an approximately 1:1 mixture of the two on heating with methanolic potassium hydroxide, the phenolic product, which is a ketone but not an enol ether (infrared spectrum), is assigned the structure XVIII. This base presumably arises through the phenate ion IV (NMe = N-allyl) by competitive opening of the cyclopropane ring by the phenate oxygen and by a methoxide ion. An analogous product has previously been isolated from the base-catalyzed rearrangement of nepeanthone (I, CH₃ = Ph).²

The 5,14-bridged thebainones of general structure III and VIII are quaternized more readily than the 6,14-*endo*-ethenotetrahydrothebaines I and XIII,^{3,4} but less easily than flavothebaine (XX), and this difference may be attributed to hindrance to approach of the quaternizing halide to the nitrogen by the C-17 β hydrogen. The methiodides of the bases III (R = R' = Me) and VII (R' = Me) readily suffer Hofmann degradation to the methine bases XXI and XXII. The last of these, subjected to further Hofmann degradation, afforded a very poor yield of a nitrogen-free product, containing CH₂ less than the simple Hofmann degradation product and showing no infrared absorption band characteristic of a vinyl group, and was assigned the structure XXIII.¹⁵ An attempt to confirm this assignment by the preparation of the ether XXIII by the exhaustive methylation of the phenol VII (R' = H) led in the first

(15) The tendency to form the thebenone cyclic ether system is so strong that a C-4 methoxyl group is split during Hofmann degradation: W. Bralley, Dissertation, University of Virginia, 1941, quoted by L. J. Sargent and L. F. Small, *J. Org. Chem.*, **16**, 1032 (1951).

Hofmann degradation to a base showing styrenoid ultraviolet absorption and carbonyl absorption in the infrared only at 1740 cm^{-1} .



The nmr spectrum of this base in deuteriochloroform showed signals (in δ units) at 6.70 (two aromatic H), 6.45 (doublet, C-9 CH=, $J_{9,10} = 9.0$ cps), 5.97 (doublet, C-10 CH=, $J_{9,10} = 9.0$ cps), 5.42 (two olefinic H), 3.92 (C-3 OCH₃), and 2.30 (2NCH₃). This spectrum, which clearly shows that the COCH₃ system of the phenol VII (R' = H) is no longer present in the new base, coupled with the infrared spectrum which shows the absence of an α,β -unsaturated ketone system, and the presence of a carbonyl group very probably in a five-membered ring, leads to the structure XXIV for the new base. Further examination of the nmr spectrum in deuteriochloroform containing deuteriobenzene⁷ resulted in resolution of the two aromatic proton signals and also of the signal at δ 5.42, which was resolved into a barely defined double doublet with centers at δ 5.63 and 5.40 ($J = ca. 9.0$ cps), attributed to the C-7 and C-8 protons. In this spectrum the C-5 proton was located as a doublet at δ 3.50 ($J_{5,18} = 9.0$ cps), and the C-20 protons were located as doublets at δ 2.95 and 2.58 ($J_{20,20} = 16$ cps). The base XXIV obviously results from the Hofmann degradation of the methiodide of the base VII (R' = H) and base-catalyzed ketolization of the COCH₃ and C-6 carbonyl groups.

A model of XXIV can be constructed without strain, and as the parent base containing an intact nitrogen-containing ring is also strain-free, the action of alkalis on the diketone VII (R' = H) was studied. This results in the production of the base XXV, Hofmann degradation of the methiodide of which yields the methine base XXIV. The ketolization can only occur with one arrangement of the COCH₃ group, and the stable ketone VII (R' = H) may confidently be assumed to be the 18α form shown. The phenol VII (R' = H) and its methyl ether VII (R' = Me) give deep orange solutions in alkalis and this color fades as the cyclization of the ketone VII (R' = H) proceeds. The color is, therefore, assumed to be that of the enolate ion, in which some interaction between the enone and enol systems must occur, and it may be noted that the color is similar to that of flavothebaine in alkaline solution.¹⁶

(16) K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, **22**, 418 (1957).

The methyl ether VII (R' = Me) of the phenol VII (R' = H) is recovered unchanged from alkaline solution, and methylation of the ketol XXV in alkali results in deketolization and the production of the diketone VII (R' = Me). The examination of a model of the base XXV shows that the hydroxyl groups at C-4 and C-6 are in very close proximity and the stability of the phenol in alkalis may be attributed to inhibition by the phenate anion of the removal of a proton from the C-6 hydroxyl group, which is an essential first step in the deketolization. Indeed, the proton of the C-6 hydroxyl may be expected to form a very firm hydrogen bond with the C-4 oxygen atom when the latter acquires a negative charge in alkaline solution. In the methyl ether of the phenol XXV, however, there will be no electrostatic inhibition of the removal of the proton of the C-6 hydroxyl group and deketolization can proceed.

Experimental Section

18-Acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebaine (VIII) (Isothevinone). a. 7 α -Acetyl-6,14-endo-ethenotetrahydrothebaine (50 g) was boiled under reflux with potassium hydroxide (50 g) in methanol (500 ml) and water (100 ml) for 1 hr, during which time crystalline material separated. The mixture was diluted with water (100 ml) and cooled, and the solid was collected, when isothevinone (VIII) (40 g) was obtained as pale cream prisms, mp 168° raised to 170° on recrystallization from ethanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for C₂₃H₃₇NO₄: C, 72.4; H, 7.1. Found: C, 72.3; H, 7.1.

The base was alkali insoluble and the alkaline suspension gave only a pale pink coloration with diazotized sulfanilic acid.

b. The same base was obtained in the same way by the rearrangement of 7 α -acetyl-6,14-endo-ethenotetrahydrothebaine.

7-Acetyl-5,7-dehydro-6,14-endo-etheno-4,6-O-dimethylthebaine (V, R' = Me). a. 7 α -Acetyl-6,14-endo-ethenotetrahydrothebaine (10 g) in dry *t*-butyl alcohol (20 ml) was added to a solution of potassium (1.1 g) in dry *t*-butyl alcohol (30 ml) and the mixture heated at 50° for 10 min. Methyl iodide (3.5 g, 0.95 mole) was then added and the mixture stirred for 15 min, after which it was poured into water and the product isolated by ether extraction. Evaporation of the dried extracts yielded a viscous yellow gum that crystallized on standing. Recrystallization of the product from petroleum ether (bp $80\text{--}100^\circ$) afforded the base V (R' = Me) as pale cream prisms, mp 116° , ν_{\max} 1690 cm^{-1} .

Anal. Calcd for C₂₄H₃₉NO₄: C, 73.0; H, 7.3. Found: C, 73.1; H, 7.3.

Acid hydrolysis of this base afforded 18-acetyl-5,14-ethano-4-O-methylthebaine (VII, R' = Me) (see below).

b. 18-Acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebaine (VIII) (32 g) (prepared by the alkaline rearrangement of 7 α -acetyl-6,14-endo-ethenotetrahydrothebaine) in *t*-butyl alcohol (100 ml) was added to a solution of potassium (12 g) in *t*-butyl alcohol (200 ml), and the mixture was stirred for 10 min at 50° . Methyl iodide (40 g) was added to the mixture which was stirred for 2 hr. The precipitated sodium iodide was removed by filtration, and the mixture was evaporated to dryness, the residue being thoroughly extracted with ether. The ether extract on evaporation afforded a viscous oil, which crystallized on standing. Recrystallization of the product from petroleum ether (bp $80\text{--}100^\circ$) afforded 7-acetyl-5,7-dehydro-6,14-endo-etheno-4,6-O-dimethylthebaine (V, R' = Me) as pale cream prisms, mp $115\text{--}116^\circ$, identical (mixture melting point and infrared spectrum) with material prepared as described above.

18-Acetyl-5,14-ethanothebaine (VII, R' = H) (ψ -Thevinone). 18-Acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebaine (isothevinone, VIII) (20 g) was dissolved in 2 *N* hydrochloric acid (100 ml) and the solution was basified with ammonia, when the diketone VII (R' = H) (18 g) was precipitated. The product was collected, washed, and recrystallized from methanol, when it was obtained as white prisms, mp 200° , ν_{\max} 1715 and 1690 cm^{-1} .

Anal. Calcd for C₂₃H₃₅NO₄: C, 71.9; H, 6.8. Found: C, 71.1; H, 6.9.

From aqueous 2-ethoxyethanol the hydrated base separated as prisms, mp $169\text{--}170^\circ$.

al. Calcd for $C_{22}H_{21}NO_4 \cdot H_2O$: C, 68.6; H, 7.0. Found: 7; H, 6.9.

is base was readily soluble in alkali to give a yellow solution which gave a blood red color with diazotized sulfanilic acid.

methiodide, prepared from the base, methyl iodide, and anol under reflux for 2 days, was precipitated with ether and utilized from methanol-ether and then from ethanol, when it obtained as white prisms, mp 202–205°.

al. Calcd for $C_{22}H_{21}NO_4 \cdot CH_3I \cdot H_2O$: C, 52.3; H, 5.7. d: C, 52.1; H, 6.0.

e oxime was obtained as prisms, mp 253–255°, from ethanol.

al. Calcd for $C_{22}H_{21}N_2O_4$: C, 69.1; H, 6.9; N, 7.2. Found: 6; H, 7.1; N, 7.2.

Acetyl-5,14-ethano-4-O-methylthebainone (VII, R' = Me). Methyl sulfate (40 g) was slowly added to a vigorously stirred solution of 18-acetyl-5,14-ethanotetrahydrothebainone (VII, R' = H) and potassium hydroxide (20 g) in water. The product was obtained as a cream solid (48 g) which was collected and recrystallized from aqueous 2-ethoxyethanol, when the methyl ether V (R = Me) (35 g) was obtained as white prisms, mp 183°, ν_{\max} 1690 cm^{-1} .

al. Calcd for $C_{22}H_{27}NO_4$: C, 72.4; H, 7.1. Found: C, 72.0; H, 7.6; N, 3.8.

e base was insoluble in alkali.

e methiodide was prepared by boiling the base in methyl iodide under reflux for 4 days, and was obtained from ethanol as prisms, mp 45°.

al. Calcd for $C_{22}H_{27}NO_4 \cdot CH_3I \cdot 0.5H_2O$: C, 54.1; H, 5.8. d: C, 54.0; H, 5.7.

e oxime was obtained as prisms, mp 247–248°, from ethanol.

al. Calcd for $C_{22}H_{27}N_2O_4$: C, 69.7; H, 7.1; N, 7.1. Found: 9; H, 7.4; N, 7.1.

7-Acetyl-5,7-dehydro-6,14-endo-etheno-4,6-O-dimethyldihydrothebainol (V, R' = Me) (1 g) was dissolved in 2 N hydrochloric acid (10 ml) and the solution basified with ammonia. The precipitated solid was collected and recrystallized from aqueous 2-ethoxyethanol, when 18-acetyl-5,14-ethano-4-O-methylthebainone (R' = Me), mp 183°, was obtained identical with material used as in the preceding paragraph (mixture melting point and infrared spectrum).

5,14-Ethano-4(O)-6-dehydro-18-(1-hydroxyethyl)-6-O-methylthebainol (IX, R = H) (Isothevinol). Sodium borohydride (0.5 g) was added to a solution of 18-acetyl-4(O)-6-dehydro-5,14-ethano-6-methylthebainol (VIII) (10 g) in 2-ethoxyethanol (20 ml), and the mixture was heated at 100° for 30 min. The resulting solution was cooled, and the solid (9 g) was collected and recrystallized from aqueous 2-ethoxyethanol, when the secondary alcohol IX (R = H) was obtained as white prisms, mp 215°.

al. Calcd for $C_{22}H_{29}NO_4 \cdot H_2O$: C, 68.8; H, 7.7. Found: 7; H, 7.8.

carbonyl absorption showed in the infrared. The base was insoluble, and the suspension in alkali gave no color with diazotized sulfanilic acid.

14-Ethano-18-(1-hydroxyethyl)thebainone (VI, R = H). 5,14-Ethano-4(O)-6-dehydro-18-(1-hydroxyethyl)-6-O-methylthebainol (IX, R = H) (10 g) was dissolved in 2 N hydrochloric acid (100 ml), and the resulting solution was basified with ammonia. The precipitated base was collected (9 g) and recrystallized from aqueous 2-ethoxyethanol, when the keto alcohol VI (R = H) was obtained as white prisms, mp 248°, ν_{\max} 1690 cm^{-1} .

al. Calcd for $C_{22}H_{27}NO_4 \cdot H_2O$: C, 68.3; H, 7.5. Found: 5; H, 7.3.

e base was readily soluble in alkali, and the solution gave a blood red color with diazotized sulfanilic acid.

Sodium borohydride (0.1 g) was added to a suspension of 18-acetyl-5,14-ethanotetrahydrothebainone (2 g) in ethanol (10 ml) and the solution stirred at 25° for 15 min. Water (50 ml) was added, and the mixture was stirred until crystallization was complete, and the crystals were then collected. Recrystallization of the product from aqueous ethanol afforded the secondary alcohol VI (R = H) identical with material prepared as above, mp and mmp 248°, ν_{\max} 1690 cm^{-1} .

5,14-Ethano-18-(1-hydroxyethyl)-4-O-methylthebainone. 18-Acetyl-5,14-ethano-4-O-methylthebainone (VII, R' = Me) (10 g) was reduced as above with sodium borohydride (0.5 g) in methanol. The product was recrystallized from methanol, when it obtained as white prisms, mp 271°, ν_{\max} 1690 cm^{-1} .

al. Calcd for $C_{22}H_{29}NO_4 \cdot 0.5H_2O$: C, 70.4; H, 7.7. Found: 7; H, 7.5.

The same base was obtained by the O-methylation of the phenol VI (R = H) in aqueous methanolic potassium hydroxide, with methyl sulfate, as an oil on removal of most of the methanol *in vacuo*.

Catalytic Reduction of 18-Acetyl-4(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII). a. A suspension of the ketone VIII (20 g) in 2-ethoxyethanol (200 ml, distilled from sodium) was shaken under hydrogen at 20° (55 psi) in the presence of 5% rhodium on alumina (1 g) for 3 hr. By the end of that time the base had dissolved and uptake of hydrogen had ceased. The solution was filtered and evaporated, and the residual solid was recrystallized from ethanol (100 ml), when 18-acetyl-4(O)-6-dehydro-5,14-ethano-6-O-methyldihydrothebainol (XVI) (14 g) was obtained as white prisms, mp 158–160°, ν_{\max} 1715 cm^{-1} .

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 72.0; H, 7.6; N, 3.7. Found: C, 72.0; H, 7.6; N, 3.8.

The base was insoluble in alkali and the suspension gave only a pale pink coloration with diazotized sulfanilic acid.

b. A suspension of the ketone VIII (10 g) in 2-ethoxyethanol (200 ml) was shaken under hydrogen at 20° (55 psi) in the presence of 10% palladized charcoal (0.5 g) for 2 hr after which time hydrogen absorption had ceased. Evaporation of the filtered solution gave an oil which was dissolved in ether (50 ml), when a crystalline solid separated (6.2 g). This was found to be a mixture of the dihydro compound XVI (see above) and 18-acetyl-5,14-ethanodihydrothebainon- Δ^4 -enol methyl ether (XV) from which the latter (3.4 g) was recovered by recrystallization from ethanol, rapid washing of the crystals with two 20-ml portions of ether, and further recrystallization from ethanol. In this way it was obtained as white prisms, mp 161–163°, ν_{\max} 1700 and 1675 cm^{-1} (C=O enol ether).

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 72.0; H, 7.6. Found: C, 72.1; H, 7.4.

An alkaline solution of the base gave a blood red color with diazotized sulfanilic acid.

Rearrangement of 7 α -Acetyl-6,14-endo-ethanotetrahydrothebaine (I, CH=CH=CH₂CH₂). Potassium hydroxide (8.8 g) was added to a hot solution of 7 α -acetyl-6,14-endo-ethanotetrahydrothebaine (8.8 g) in methanol (88 ml), and the mixture was boiled under reflux for 1 hr, evaporated to 45 ml, and poured into ice-water (350 ml). The precipitated solid (8.2 g) was collected and recrystallized from petroleum ether (bp 40–60°) to give 18-acetyl-4(O)-6-dehydro-5,14-methyldihydrothebainol (XVI) (4.5 g) as prisms, mp 155–157° raised to 158–160° on recrystallization from methanol. This base was identical in melting point, mixture melting point, and infrared absorption with that obtained by the catalytic reduction of 18-acetyl-4(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII) over rhodium on alumina.

18-Acetyl-5,14-ethanodihydrothebainone (XIX). a. 18-Acetyl-4(O)-6-dehydro-5,14-ethano-6-O-methyldihydrothebainol (XVI) (5 g) was dissolved in 1 N hydrochloric acid (100 ml) and after 1 hr crystalline 18-acetyl-5,14-ethanodihydrothebainone hydrochloride was collected, mp 197–198°.

Anal. Calcd for $C_{22}H_{27}NO_4 \cdot HCl \cdot H_2O$: C, 62.3; H, 7.1; Cl, 8.4; N, 3.3. Found: C, 61.7; H, 7.6; Cl, 8.0; N, 3.2.

The free base was recovered by treating the salt with sodium bicarbonate solution and extracting with chloroform. On recrystallization from ethanol it was obtained as white prisms, mp 205–207°, ν_{\max} 1720 and 1705 cm^{-1} .

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8. Found: C, 71.3; H, 7.5; N, 3.8.

b. The same base, mp 205–207°, undepressed on mixing with material prepared as in a, was obtained in the same way by the hydrolysis of 18-acetyl-5,14-ethanodihydrothebainone- Δ^4 -enol methyl ether (XV) with 1 N hydrochloric acid. It is most convenient to prepare the base by the hydrolysis of the mixture of bases XV and XVI obtained by the reduction of 18-acetyl-4(O)-6-dehydro-5,14-ethano-6-O-methylthebainol over palladized charcoal.

18-Acetyl-5,14-ethano-4-O-methyldihydrothebainone (XIX, OH = OMe). The mixture of bases (5 g) from the hydrogenation of the ketone VIII was dissolved in the minimum amount of 2 N hydrochloric acid, and the solution was diluted to 70 ml. Sodium hydroxide solution (2 N) was added until the precipitate redissolved followed by a further 50 ml. Dimethyl sulfate (5 ml) was then added and the mixture shaken for 1 hr, after which the solid was collected, washed with water, and recrystallized from ethanol, when the diketone XIX (OH = OMe) (2 g) was obtained as white prisms, mp 165–166°. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 72.0; H, 7.6; N, 3.7. Found: C, 71.8; H, 7.7; N, 3.7.

4-(O)-6-Dehydro-5,14-ethano-18-(1-hydroxyethyl)-6-O-methyl dihydrothebainol (XVII). Sodium borohydride (3 g) was added in portions over 15 min to a solution of 18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (XVI) (5 g) in 2-ethoxyethanol (50 ml) at 20°. The mixture was heated at 100° for 15 min, cooled, diluted with 2 *N* ammonia solution, and extracted with chloroform. The chloroform extract was evaporated and the residue recrystallized from ethanol, when the secondary alcohol XVII was obtained as white prisms, mp 165–166°.

Anal. Calcd for $C_{22}H_{31}NO_4$: C, 71.7; H, 8.1. Found: C, 71.8; H, 8.3.

5,14-Ethano-18-(1-hydroxyethyl)dihydrothebainone (VI, R = H, $CH=CH=CH_2CH_3$). 4-(O)-6-Dehydro-5,14-ethano-18-(1-hydroxyethyl)-6-O-methyldihydrothebainol (XVII) (0.5 g) was dissolved in 2 *N* hydrochloric acid (5 ml), and the solution was kept at room temperature for 30 min and in the refrigerator overnight. The solid was collected and recrystallized from water, when 5,14-ethano-18-(1-hydroxyethyl)dihydrothebainone hydrochloride was obtained as white prisms, mp 257° dec, ν_{max} 1720 cm^{-1} .

Anal. Calcd for $C_{22}H_{31}NO_4 \cdot HCl \cdot 3H_2O$: C, 57.2; H, 7.9. Found: C, 57.0; H, 8.0.

Rearrangement of N-Allyl-7 α -acetyl-6,14-endo-ethenotetrahydro-northebaine (I, NMe = $NCH_2CH=CH_2$) (N-Allylnorthevinone). A solution of potassium hydroxide (4.8 g) in methanol (50 ml) was added slowly to a boiling solution of N-allyl-7 α -acetyl-6,14-endo-ethenotetrahydro-northebaine hydrochloride (11 g) in methanol (50 ml) and the mixture then boiled under reflux for 1 hr. The solution was diluted with water and extracted with chloroform to give a mixture of two bases (11 g). The product (8 g) was crystallized from methanol to give N-allyl-18-acetyl-5,14-ethanonorthebainone dimethyl ketal (XVIII) (2.6 g) as prisms, mp 106–107°, ν_{max} 1715 cm^{-1} .

Anal. Calcd for $C_{24}H_{33}NO_5$: C, 71.0; H, 7.6; N, 3.2. Found: C, 70.6; H, 7.7; N, 3.5.

The mother liquor from this crystallization was diluted with water, and the precipitated solid was recrystallized from aqueous methanol, when N-allyl-18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylnorthebainol (VIII, NMe = $NCH_2CH=CH_2$) (1.1 g) was obtained as white prisms, mp 129–130°, ν_{max} 1715 cm^{-1} .

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 73.7; H, 7.2; N, 3.4. Found: C, 73.3; H, 7.0; N, 3.7.

N-Allyl-18-acetyl-5,14-ethanonorthebainone (VII, R' = H, NMe = $NCH_2CH=CH_2$). The above two bases XVIII (R = $CH_2CH=CH_2$) and VIII (NMe = $NCH_2CH=CH_2$) obtained by the rearrangement of the ketone I (NMe = $NCH_2CH=CH_2$), separately or together, on hydrolysis with 2 *N* hydrochloric acid followed by precipitation with ammonia and recrystallization of the product from ethanol, afforded the diketone VII (R' = H, NMe = $NCH_2CH=CH_2$) as prisms, mp 110–112°, ν_{max} 1715 and 1690 cm^{-1} .

Anal. Calcd for $C_{24}H_{33}NO_4 \cdot 0.5H_2O$: C, 71.4; H, 6.8; N, 3.6. Found: C, 71.6; H, 7.0; N, 3.5.

Rearrangement of N-Propargyl-7 α -acetyl-6,14-endo-ethenotetrahydro-northebaine (I, NMe = $NCH_2C\equiv CH$). The hydrochloride of the ketone I (NMe = $NCH_2C\equiv CH$) (10 g) was boiled with potassium hydroxide (4.8 g) in methanol (100 ml) for 1 hr. The product was isolated by chloroform extraction and crystallized from methanol, when N-propargyl-18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylnorthebainol (VIII, NMe = $NCH_2C\equiv CH$) was obtained as prisms, mp 177–179°.

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 74.0; H, 6.7. Found: C, 73.7; H, 6.7.

N-Propargyl-18-acetyl-5,14-ethanonorthebainone (VII, R' = H, NMe = $NCH_2C\equiv CH$). N-Propargyl-18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylnorthebainol (VIII, NMe = $NCH_2C\equiv CH$) (2 g) was dissolved in warm 2 *N* hydrochloric acid, and after 5 min the solution was basified with ammonia. The product was collected and recrystallized from methanol when the diketone VII (R' = H, NMe = $NCH_2C\equiv CH$) was obtained as prisms, mp 114°, ν_{max} 1715 and 1690 cm^{-1} .

Anal. Calcd for $C_{24}H_{31}NO_4 \cdot H_2O$: C, 70.4; H, 6.6; N, 3.4. Found: C, 70.4; H, 6.7; N, 3.9.

Base-Catalyzed Rearrangements Accompanying Normal Grignard Reactions with the Ketone I and Its 6,14-Ethano Analog. a. 7 β -Acetyl-6,14-endo-ethenotetrahydrothebaine (0.5 g) in anhydrous ether (100 ml) was added to a solution of methylmagnesium iodide (from 0.17 g of magnesium) in ether (25 ml), and the mixture was heated under reflux for 1 hr. The mixture was then poured into aqueous ammonium chloride, and the ether layer was separated, dried over magnesium sulfate, and evaporated, to leave a crude

product (0.5 g) shown by thin layer chromatography to consist of two components. These were separated on alumina plates using ether as developing solvent. The less polar material (125 mg) was recovered from the plate and obtained as white prisms, mp 215°, from methanol, ν_{max} 3545, 3490 cm^{-1} , and identified as 5,7-dehydro-6,14-endo-etheno-7-(1-hydroxy-1-methylethyl)-6-O-methyldihydrothebainol (II, R = Me, R' = H), by hydrolysis with cold 2 *N* hydrochloric acid to 5,14-ethano-18-isopropylidenethebainone (III, R = Me, R' = H), identical in melting point, mixture melting point, and infrared absorption with an authentic specimen.

b. The product of the reaction between 7 α -acetyl-6,14-endo-ethenotetrahydrothebaine (38 g) and *n*-propylmagnesium iodide was dissolved in methanol and cooled, and the crystalline 6,14-endo-etheno-7 α -(1-(*R*)-hydroxy-1-methylbutyl)tetrahydrothebaine (XIII, R = *n*-Pr)⁴ was collected. The mother liquors were concentrated to yield 11.1 g of a glass, a sample of which (1.08 g) was subjected to partition chromatography on Celite using a methanol–heptane system, with observation of the extinction of the eluate at 230 $m\mu$. Three main fractions were obtained, yielding 0.15 g (A), 0.25 g (B), and 0.65 g (C) of product on evaporation. Fraction A consisted of the tertiary alcohol XIII (R = *n*-Pr) and fraction C consisted of the secondary alcohol XIII (R = H), resulting from Grignard reduction of the ketone I.⁴

Fraction B was dissolved in benzene and rechromatographed on alumina (25 g) which was eluted successively with 100-ml portions of 1, 5, 20, 50, and 100% ethyl acetate in benzene. Fractions of 20 ml were collected and examined by thin layer chromatography, similar fractions being combined. Fractions 11–13 gave 96 mg of a mixture of 7 α - and 7 β -acetyl-6,14-endo-ethenotetrahydrothebaine and fractions 18–22 gave 176 mg of an oil, which on trituration with methanol gave 5,7-dehydro-6,14-endo-etheno-7-(1-hydroxy-1-methylbutyl)-6-O-methyldihydrothebainol (II, R = *n*-Pr, R' = H) (36 mg), mp 192–198°, raised to 202–203° on recrystallization from methanol.

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 73.4; H, 8.3; N, 3.3. Found: C, 73.1; H, 8.35; N, 3.8.

c. The crude product of the reaction between 7 α -acetyl-6,14-endo-ethanotetrahydrothebaine (I, 6,14- CH_2CH_3) (140 g) and isopropylmagnesium chloride (from 48.6 g of magnesium), in ether and benzene solution, which was noncrystalline, was triturated with cold methanol. The solid so formed was collected, and extracted with boiling ethanol (300 ml), and the undissolved matter was crystallized from chloroform. In this way 5,7-dehydro-6,14-endo-ethano-7-(1-hydroxy-1,2-dimethylpropyl)-6-O-methyldihydrothebainol (II, R = *i*-Pr, R' = H, 6,14- CH_2CH_3) was obtained as white prisms, mp 253–256°.

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 73.1; H, 8.7; N, 3.3. Found: C, 72.7; H, 8.3; N, 3.5.

d. In like manner to that described in part c above, the following were isolated from the products of reaction of 7 α -acetyl-6,14-endo-ethanotetrahydrothebaine and the appropriate Grignard reagent: 5,7-dehydro-6,14-endo-ethano-7-(1-hydroxy-1-methylpentyl)-6-O-methyldihydrothebainol (II, R = *n*-Bu, R' = H, 6,14- CH_2CH_3 , prisms, mp 169–170°. *Anal.* Calcd for $C_{27}H_{39}NO_4$: C, 73.4; H, 8.9; N, 3.2. Found: C, 72.9; H, 8.7; N, 3.3; 5,7-dehydro-6,14-endo-ethano-7-(1-hydroxy-1-methylpropyl)-6-O-methyldihydrothebainol (II, R = Et, R' = H, 6,14- CH_2CH_3 , white prisms, mp 215–216°. *Anal.* Calcd for $C_{27}H_{39}NO_4$: C, 72.6; H, 8.5; N, 3.4. Found: C, 72.8; H, 8.5; N, 3.4; and 5,7-dehydro-6,14-endo-ethano-7-(1-hydroxy-1,4-dimethylpentyl)-6-O-methyldihydrothebainol (II, R = *i*-Am, R' = H, 6,14- CH_2CH_3 , white prisms, mp 178–179°. *Anal.* Calcd for $C_{28}H_{41}NO_4$: C, 73.8; H, 9.1; N, 3.1. Found: C, 73.5; H, 8.9; N, 3.2).

5,14-Ethano-18-(3'-methylbut-2'-ylidene)dihydrothebainone (III, R = *i*-Pr, R' = H, 7,8-dihydro). 5,7-Dehydro-6,14-endo-ethano-7-(1-hydroxy-1,2-dimethylpropyl)-6-O-methyldihydrothebainol (II, R = *i*-Pr, R' = H, 6,14- CH_2CH_3) (0.1 g) was dissolved in 1.5 *N* hydrochloric acid (2.5 ml), and the solution was heated on the water bath for 10 min. A crystalline hydrochloride separated and was collected and recrystallized from water, when it was obtained as white prisms, mp 199–201°, ν_{max} 1690 cm^{-1} .

Anal. Calcd for $C_{24}H_{33}NO_4 \cdot HCl \cdot 3H_2O$: C, 61.7; H, 8.3. Found: C, 61.2; H, 8.3.

4-(O)-6-Dehydro-5,14-ethano-18-(1-hydroxy-1-methylethyl)-6-O-methylthebainol (IX, R = Me) (Methylisothervinol). A solution of methylolithium (4 g) in ether (125 ml) was slowly added to a vigorously stirred solution of 18-acetyl-4-(O)-6-dehydro-5,14-ethano-6-O-methylthebainol (VIII) (35 g) in ether (200 ml), under nitro-

rate sufficient to maintain boiling. The mixture was finally ed under reflux for 30 min and then diluted cautiously with τ (250 ml). The ether layer on evaporation afforded 34.9 g solid matter, still containing some ketone (infrared spectrum), this was treated under the same conditions with a further 4 g methyl lithium. Evaporation of the ether layer then gave non-nic material from which the tertiary alcohol IX ($R = Me$) (27.8 as recovered on recrystallization from ethanol as white prisms, 117–218°.

anal. Calcd for $C_{14}H_{21}NO_4$: C, 72.5; H, 7.9; N, 3.5. Found: 2.2; H, 8.1; N, 3.4.

hydrolysis of 4-(O)-6-Dehydro-5,14-ethano-18-(1-hydroxy-1-ylethyl)-6-O-methylthebainol (Methylisothevinol, IX, $R = Me$). The tertiary alcohol IX ($R = Me$) (3 g) was dissolved in 1 *N* ochloric acid (100 ml), and the solution was kept at 25° for nin. Neutralization of the solution with sodium bicarbonate isolation of the product by ether extraction gave 5,14-ethano-1-hydroxy-1-methylethyl)thebainone (VI, $R = Me$) (2.2 g), h was obtained from aqueous ethanol as rosettes of white les, mp 129–132°, ν_{max} (CCl_4 solution) 3615 (free tertiary OH), (phenolic OH), 3450 (bonded OH), and 1670 cm^{-1} (α,β -aturated carbonyl).

anal. Calcd for $C_{23}H_{37}NO_4 \cdot H_2O$: C, 68.8; H, 7.8. Found: 1.9; H, 7.7.

The tertiary carbinol IX ($R = Me$) (1.5 g) was boiled under τ for 30 min with 5 *N* hydrochloric acid (25 ml), and the mixture cooled and diluted with water (25 ml). The crystalline solid btained was collected (1.4 g) and recrystallized from water, 5,14-ethano-18-isopropylidenethebainone (III, $R = Me$, $R' = H$) hydrochloride was obtained as white prisms, mp 320°.

anal. Calcd for $C_{23}H_{37}NO_4 \cdot HCl$: C, 68.7; H, 7.0; Cl, 8.8. d: C, 68.4; H, 7.0; Cl, 8.7.

ie free base crystallized readily only from methanol, when it obtained as solvated prisms, mp 138–139°, ν_{max} (CCl_4 solution) (methanol), 3532 (phenolic OH), and 1690 cm^{-1} (α,β -un-ated carbonyl). The base coupled with diazotized sulfanilic in alkalis. The base and its hydrochloride were identical frared absorption and in behavior on thin layer chromatog-y with 5,14-ethano-18-isopropylidenethebainone and its hydro-ide prepared by the acid-catalyzed rearrangement of 6,14-etheno-7 α -(1-hydroxy-1-methylethyl)tetrahydrothebaine (XIII, Me).¹¹

hydration of 5,14-Ethano-18-(1-hydroxy-1-methylethyl)thebainol (VI, $R = Me$). The tertiary alcohol VI ($R = Me$) (120 mg) boiled under reflux with 5 *N* hydrochloric acid (5 ml) for 30

The solution was cooled; the crystalline solid was collected shaken with sodium bicarbonate solution and ether. Evap-on of the ether and crystallization of the product from meth-gave 5,14-ethano-18-isopropylidenethebainone (III, $R = R' = H$), identical in infrared absorption with material pre-l by the acid-catalyzed rearrangement of the tertiary alcohol ($R = Me$).¹¹

5,7-Dehydro-6,14-endo-etheno-7-(1-hydroxy-1-methylethyl)-4,6-methyldihydrothebainol (II, $R = R' = Me$). A solution 7-acetyl-5,7-dehydro-6,14-endo-etheno-4,6-O-dimethyldihydro-ol (V, $R' = Me$) (3.79 g) in dry ether (50 ml) was d to a vigorously stirred boiling solution of methylmagnesium e (from 0.96 g of magnesium and 5.64 g of methyl iodide) in (150 ml). The mixture was heated under reflux for 3 hr, ured into saturated ammonium chloride solution. The ether was separated, dried, and evaporated, to leave a viscous (3.8 g) that crystallized on standing. Recrystallization of the from methanol afforded the tertiary alcohol II ($R = R' =$ is white prisms, mp 140°.

anal. Calcd for $C_{24}H_{33}NO_4$: C, 73.0; H, 8.0. Found: C, H, 7.8.

5,14-Ethano-18-isopropylidene-4-O-methylthebainone (III, $R = R' = Me$). 5,7-Dehydro-6,14-endo-etheno-7-(1-hydroxy-1-ylethyl)-4,6-O-dimethyldihydrothebainol (II, $R = R' = Me$) was dissolved in 2 *N* hydrochloric acid (10 ml) and after 5 min lution was basified with ammonia, and the precipitated solid collected. After recrystallization from methanol the un-ated ketone III ($R = R' = Me$) was obtained as off-white s, mp 178°, ν_{max} 1690 cm^{-1} , identical in melting point, mixture ng point, and infrared absorption with the 4-O-methyl ether : base III ($R = Me$, $R' = H$) obtained by the acid-catalyzed ngement of the alcohol XIII ($R = Me$).¹¹

anal. Calcd for $C_{24}H_{33}NO_4$: C, 75.9; H, 7.7. Found: C, H, 8.1.

5,14-Ethano-4-O-methyl-18-pent-2'-ylidenethebainone (III, $R = n-Pr$, $R' = Me$). 7-Acetyl-5,7-dehydro-6,14-endo-etheno-4,6-O-dimethyldihydrothebainol (V, $R' = Me$) (3.8 g) was treated with *n*-propylmagnesium chloride, and the noncrystalline reaction product was dissolved in 2 *N* hydrochloric acid. Basification of the acid solution with ammonia, isolation of the product by ether extraction, and crystallization from aqueous methanol afforded the unsaturated ketone III ($R = n-Pr$, $R' = Me$) as prisms, mp 70°, ν_{max} 1690 cm^{-1} .

Anal. Calcd for $C_{25}H_{33}NO_4 \cdot 0.5H_2O$: C, 75.0; H, 8.2. Found: C, 74.9; H, 8.1.

5,14-Ethano-4-O-methyl-18-(1'-methyl-2'-phenylethylidene)thebainone (III, $R = CH_2Ph$, $R' = Me$). This was prepared by the acid hydrolysis of the noncrystalline reaction product of the action of benzylmagnesium bromide on the ketone V ($R' = Me$), and was obtained as white prisms, mp 142°, ν_{max} 1690 cm^{-1} , from 70% ethanol.

Anal. Calcd for $C_{28}H_{33}NO_4 \cdot H_2O$: C, 76.1; H, 7.4. Found: C, 76.3; H, 7.6.

5,14-Ethano-18-(1'-cyclohexylethylidene)-4-O-methylthebainone (III, $R = cyclohexyl$, $R' = Me$). This was obtained by the acid hydrolysis of the noncrystalline product of the reaction between cyclohexylmagnesium chloride and the ketone V ($R' = Me$), and was recovered as white prisms, mp 98°, ν_{max} 1690 cm^{-1} , from ethanol.

Anal. Calcd for $C_{28}H_{37}NO_4$: C, 77.8; H, 8.3. Found: C, 77.4; H, 8.0.

5,14-Ethano-18-isopropylidene-4-O-methylthebainone Methine (XXI). 5,14-Ethano-18-isopropylidene-4-O-methylthebainone (9 g) and methyl iodide (60 ml) were boiled together under reflux for 3 days with stirring. The solid matter (12 g) was collected, when the methiodide was obtained as almost colorless prisms, mp 236°, from ethanol.

Anal. Calcd for $C_{24}H_{33}NO_4 \cdot CH_3I$: C, 57.6; H, 6.2. Found: C, 57.4; H, 6.4.

The methiodide (12 g) in water (100 ml) was boiled with potassium hydroxide (15 g) for 10 min. The mixture was cooled and the solid was collected (8.7 g) and recrystallized from benzene-petroleum ether (bp 60–80°), when the methine base was obtained as elongated white prisms, mp 152°, ν_{max} 1690 cm^{-1} , λ_{max} 272 and 305 μ , ϵ_{max} 12,600 and 47,200.

Anal. Calcd for $C_{24}H_{31}NO_4$: C, 76.3; H, 7.9. Found: C, 76.8; H, 8.1.

The methine methiodide formed rapidly from the base and methyl iodide in benzene, and was obtained from methanol as white prisms, mp 180°.

Anal. Calcd for $C_{24}H_{31}NO_4 \cdot CH_3I$: C, 58.3; H, 6.4. Found: C, 58.4; H, 6.4.

This methiodide resisted Hofmann degradation in aqueous solution, and pyrolysis of the methohydroxide resulted in the loss of methanol and the production of the methine base in very high yield. Only a trace of uncharacterized neutral matter was obtained.

18-Acetyl-5,14-ethano-4-O-methylthebainone Methine (XXII). 18-Acetyl-5,14-ethano-4-O-methylthebainone methiodide (see above) (4.0 g) was boiled with water (100 ml) and potassium hydroxide (15 g) for 10 min. The precipitated oil was isolated by ether extraction, and the uncrystallizable product was converted into its hydrochloride, which was obtained as white prisms, mp 210°, from ethanol-ether; ν_{max} 1690 cm^{-1} ; λ_{max} 272, 298, and 308 μ ; ϵ_{max} 10,000, 4800, and 4000.

Anal. Calcd for $C_{24}H_{33}NO_4 \cdot HCl \cdot H_2O$: C, 64.2; H, 7.2. Found: C, 64.2; H, 7.4.

The methine methiodide, prepared from the methine base in benzene, was obtained from ethanol as white prisms, mp 283°.

Anal. Calcd for $C_{24}H_{33}NO_4 \cdot CH_3I$: C, 55.9; H, 6.0. Found: C, 55.5; H, 6.0.

18-Acetyl-5,14-ethano-7,8,9,10-tetrahydrothebenone (XXIII). 18-Acetyl-5,14-ethano-4-O-methylthebainone methine methiodide (0.20 g) in water (10 ml) was boiled under reflux with potassium hydroxide (1.5 g) for 6 hr. The insoluble brown product (0.031 g) was dissolved in benzene, and the solution was passed through a short column of alumina, which removed a trace of a violet impurity. The almost colorless solid recovered from the eluate (one spot on thin layer chromatography) was recrystallized from petroleum ether (bp 60–80°), when the ketone XXIII was obtained as white prisms, mp 167–168°, ν_{max} 1690 cm^{-1} .

Anal. Calcd for $C_{24}H_{35}O_4$: C, 75.0; H, 6.0. Found: C, 74.7; H, 6.3.

5,14-Ethano-6,18-(2'-oxoethano)thebainol (XXV). Potassium hydroxide (1 g) in water (10 ml) was added to a solution of 18-acetyl-5,14-ethanothebainone (VII, $R' = H$) (5 g) in 2-ethoxyethanol (80

ml), and the solution was heated in the boiling water bath for 5 min. Water was then added (100 ml), and a pale yellow solution was obtained. The addition of saturated ammonium chloride solution (20 ml) discharged the yellow color. Almost immediately a crystalline solid began to separate, and the separation was complete after 10 min. The solid was collected, washed with water, and recrystallized from 2-ethoxyethanol, when the base XXV was obtained as white prisms, mp 275–276°, ν_{\max} 1740 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{31}\text{NO}_4$: C, 71.9; H, 6.8. Found: C, 71.8; H, 6.8.

The same base was obtained on warming the diketone VII ($\text{R}' = \text{H}$) in aqueous potassium hydroxide containing sufficient ethanol to prevent the separation of the potassium salt. Dilution of the solution with water and addition of ammonium chloride gave an immediate precipitate which, on collection and recrystallization from aqueous 2-ethoxyethanol, afforded the base XXV as prisms, mp 275–276°, ν_{\max} 1740 cm^{-1} .

The methiodide, prepared from the base and methyl iodide in 2-ethoxyethanol solution under reflux for 5 hr, was obtained as elongated prisms, mp 268–270°, from water.

Anal. Calcd for $\text{C}_{22}\text{H}_{31}\text{NO}_4 \cdot \text{CH}_3\text{I} \cdot \text{H}_2\text{O}$: C, 52.3; H, 5.7. Found: C, 52.0; H, 5.9.

5,14-Ethano-6,18-(2'-oxoethano)thebainol Methine (XXIV). a. 18-Acetyl-5,14-ethanothebainone methiodide (4.5 g) was boiled with water (60 ml) and potassium hydroxide (15 g) for 30 min. The solution was cooled and the liquid decanted from the glassy solid, which was dissolved in water, and the solution was acidified with dilute hydrochloric acid. On basification of the solution with ammonia, no precipitate was obtained, and the base was isolated by extraction with chloroform, when it was obtained as a yellow solid. On recrystallization from methanol it was recovered as white prisms, mp 204°, ν_{\max} 1740 cm^{-1} .

Anal. Calcd for $\text{C}_{22}\text{H}_{31}\text{NO}_4$: C, 72.4; H, 7.1. Found: C, 72.6; H, 7.4.

b. The same base was obtained in the same way from 5,14-ethano-6,18-(2'-oxoethano)thebainol methiodide.

5,7-Dehydro-6,14-endo-etheno-7-ethoxycarbonyl-6-O-methyl-dihydrothebainol (X, R = Et, R' = H). 6,14-endo-Etheno-7-ethoxycarbonyltetrahydrothebaine (I, $\text{CH}_2 = \text{OEt}$) (15 g) in dry *t*-butyl alcohol (100 ml) was added to a solution of potassium (6 g) in *t*-butyl alcohol (150 ml), and the mixture was boiled under reflux for 15 min. The resulting solution was cooled and poured into an excess of saturated aqueous ammonium chloride, and the organic layer was separated, concentrated under reduced pressure, and kept in the refrigerator overnight. The crystalline ester that separated was collected (14 g) and recrystallized from methanol, when it was obtained as white prisms, mp 186°, ν_{\max} 1715 cm^{-1} .

Anal. Calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_6 \cdot \text{H}_2\text{O}$: C, 67.2; H, 7.2. Found: C, 67.1; H, 7.0.

The same base was obtained during the reaction of 6,14-endo-etheno-7-ethoxycarbonyltetrahydrothebaine with Grignard reagents other than methylmagnesium iodide. Being phenolic it was readily separated by virtue of its solubility in aqueous alkalis from the tertiary carbinols resulting from normal Grignard attack of the ester. The phenolic material so obtained, however, contained some tertiary alcohol II ($\text{CH}_2 = \text{R}$), which was removed by acid-catalyzed hydrolysis in cold 2 *N* hydrochloric acid (in which the ester is stable) to the sparingly soluble hydrochloride of the related ketone III ($\text{CH}_2 = \text{R}$). In this way the ester X ($\text{R} = \text{Et}$, $\text{R}' = \text{H}$) was obtained from the reaction of the ester I ($\text{CH}_2 = \text{OEt}$) and ethylmagnesium bromide and *n*-propylmagnesium chloride, together with the hydrochlorides of 5,14-ethano-18-pent-3'-ylidenethebainone (III, $\text{R}' = \text{H}$, $\text{CH}_2 = \text{R} = \text{Et}$), mp 285–287°, ν_{\max} 1690 cm^{-1} (Anal. Calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_5 \cdot \text{HCl}$: C, 69.8; H, 7.4. Found: C, 70.0; H, 7.3) and 5,14-ethano-18-hept-4'-ylidenethebainone (III, $\text{R}' = \text{H}$, $\text{CH}_2 = \text{R} = n\text{-Pr}$), mp 291°, ν_{\max} 1690 cm^{-1} (Anal. Calcd for $\text{C}_{27}\text{H}_{38}\text{NO}_5 \cdot \text{HCl}$: C, 70.8; H, 7.9. Found: C, 70.6; H, 8.0).

5,7-Dehydro-6,14-endo-etheno-7-ethoxycarbonyl-4,6-O-dimethyl-dihydrothebainol (X, R = Et, R' = Me). 6,14-endo-Etheno-7-ethoxycarbonyltetrahydrothebaine (I, $\text{CH}_2 = \text{OEt}$) (10 g) was heated with a solution of potassium (4 g) in dry *t*-butyl alcohol (150 ml) under reflux for 15 min, and methyl iodide (8 ml) in *t*-butyl alcohol (20 ml) was then added slowly with vigorous stirring. The mixture was filtered from precipitated potassium iodide and evaporated, leaving a semisolid residue, which was extracted thoroughly with ether. Evaporation of the ether extract afforded a viscous gum, which was crystallized with difficulty from aqueous methanol, when the ester X ($\text{R} = \text{Et}$, $\text{R}' = \text{Me}$) was obtained as white prisms, mp 100°, ν_{\max} 1715 cm^{-1} .

Anal. Calcd for $\text{C}_{31}\text{H}_{41}\text{NO}_6$: C, 70.6; H, 7.3. Found: C, 70.2; H, 7.1.

5,7-Dehydro-6,14-endo-etheno-7-isopropoxycarbonyl-4-O-methyl-dihydrothebainol (X, R = *i*-Pr, R' = H). A solution of 6,14-endo-etheno-7-ethoxycarbonyltetrahydrothebaine (10 g) in dry benzene was added to one of sodium (1 g) in 2-propanol (10 ml). The resulting mixture was boiled under reflux for 3 hr, with a Whitmore-Lux variable take-off head so adjusted that one drop in 12 of the refluxing liquid was removed. The resulting mixture was poured into an excess of ice-cold 2 *N* hydrochloric acid; the aqueous layer was removed and made alkaline with ammonia. The base precipitated in this way was collected and recrystallized from aqueous 2-ethoxyethanol, when the isopropyl ester was obtained as white prisms, mp 177–178°, ν_{\max} 1715 cm^{-1} .

Anal. Calcd for $\text{C}_{31}\text{H}_{41}\text{NO}_6$: C, 70.6; H, 7.3. Found: C, 70.5; H, 7.3.

The ester was soluble in alkalis and the solution coupled readily with diazotized sulfanilic acid to give a blood red solution.

The following esters were prepared by base-catalyzed rearrangement of the ester I ($\text{CH}_2 = \text{OEt}$), with simultaneous base-catalyzed ester exchange: 5,7-dehydro-6,14-endo-etheno-6-O-methyl-7-propoxycarbonyl dihydrothebainol (X, R = *n*-Pr, R' = H, white prisms, mp 137°, from methanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_6$: C, 70.6; H, 7.3. Found: C, 70.5; H, 7.3); 5,7-dehydro-6,14-endo-etheno-7-isobutoxycarbonyl-6-O-methyl-dihydrothebainol (X, R = *i*-Bu, R' = H, white prisms, mp 84°, from aqueous methanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{29}\text{H}_{41}\text{NO}_6 \cdot 0.5\text{H}_2\text{O}$: C, 69.6; H, 7.6. Found: C, 69.2; H, 7.8); 7-butoxycarbonyl-5,7-dehydro-6,14-endo-etheno-6-O-methyl-dihydrothebainol (X, R = *n*-Bu, R' = H, white prisms, mp 138°, from aqueous methanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{30}\text{H}_{43}\text{NO}_6$: C, 71.0; H, 7.5. Found: C, 70.5; H, 7.3); 5,7-dehydro-6,14-endo-etheno-6-O-methyl-7-pentyloxycarbonyldihydrothebainol (X, R = *n*-Am, R' = H, white prisms, mp 146°, from methanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{31}\text{H}_{45}\text{NO}_6$: C, 71.5; H, 7.7. Found: C, 71.0; H, 7.9); 5,7-dehydro-6,14-endo-etheno-7-furfuryloxycarbonyl-6-O-methyl-dihydrothebainol (X, R = furfuryl, R' = H, white prisms, mp 211°, from ethanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{27}\text{H}_{35}\text{NO}_6$: C, 70.0; H, 6.3. Found: C, 69.6; H, 6.2); 5,7-dehydro-6,14-endo-etheno-6-O-methyl-7-tetrahydrofurfuryloxycarbonyldihydrothebainol (X, R = tetrahydrofurfuryl, R' = H, noncrystalline, hydrochloride white prisms, mp 236°, from ethanol. Anal. Calcd for $\text{C}_{28}\text{H}_{37}\text{NO}_6 \cdot \text{HCl}$: C, 64.1; H, 6.8. Found: C, 63.6; H, 7.1); 7-cyclohexyloxycarbonyl-5,7-dehydro-6,14-endo-6-O-methyl-dihydrothebainol (X, R = cyclohexyl, R' = H, white prisms, mp 200°, from ethanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_6$: C, 72.3; H, 7.5. Found: C, 72.6; H, 7.3); 5,7-dehydro-7-(2'-diethylaminoethoxycarbonyl)-6,14-endo-etheno-6-O-methyl-dihydrothebainol (X, R = $\text{CH}_2\text{CH}_2\text{NEt}_2$, R' = H, noncrystalline, dihydrochloride, mp 238°, from ethanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{28}\text{H}_{41}\text{N}_2\text{O}_6 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$: C, 58.6; H, 7.3. Found: C, 58.8; H, 7.3). 5,7-Dehydro-6,14-endo-etheno-6-O-methyl-7-(2'-morpholinoethoxycarbonyl)dihydrothebainol (X, R = morpholinoethyl, R' = H, noncrystalline, dihydrochloride, white prisms, mp 221°, from ethanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_6 \cdot 2\text{HCl} \cdot 4\text{H}_2\text{O}$: C, 52.3; H, 7.1. Found: C, 52.0; H, 6.8); and 5,7-dehydro-6,14-endo-etheno-7-(2'-ethoxyethoxycarbonyl)-6-O-methyl-dihydrothebainol (X, R = $\text{CH}_2\text{CH}_2\text{OEt}$, R' = H, noncrystalline, hydrochloride white prisms, mp 270°, from ethanol, ν_{\max} 1715 cm^{-1} . Anal. Calcd for $\text{C}_{31}\text{H}_{43}\text{NO}_6 \cdot \text{HCl}$: C, 63.3; H, 7.0. Found: C, 63.6; H, 7.3).

5,14-Ethano-18-ethoxycarbonylthebainone (XI, R = COOEt, R' = H). 5,7-Dehydro-6,14-endo-etheno-7-ethoxycarbonyl-6-O-methyl-dihydrothebainol (X, R = Et, R' = H) (2 g) was heated with 2 *N* hydrochloric acid (20 ml) at 100° for 5 min. The solution was basified with ammonia, and the precipitated base was isolated by ether extraction and crystallized from methanol, when the ester XI (R = COOEt, R' = H) (1.7 g) was obtained as white prisms, mp 168°, ν_{\max} 1735 and 1690 cm^{-1} .

Anal. Calcd for $\text{C}_{28}\text{H}_{37}\text{NO}_6$: C, 69.5; H, 6.8. Found: C, 69.6; H, 6.7.

5,14-Ethano-18-ethoxycarbonyl-4-O-methylthebainone (XI, R = COOEt, R' = Me). Hydrolysis of the ester X (R = Et, R' = H) with 2 *N* hydrochloric acid at 100° for 5 min, followed by basification of the solution with ammonia, afforded the ester XI (R = COOEt, R' = Me), which was isolated by ether extraction and obtained from aqueous methanol with difficulty as white prisms, mp 78°, ν_{\max} 1735 and 1690 cm^{-1} .

Anal. Calcd for $C_{14}H_{22}NO_3$: C, 70.0; H, 7.1. Found: C, 69.5; H, 7.0.

5,14-Ethano-18-(2'-ethoxyethoxycarbonyl)thebaine (XI, R = COOCH₂CH₂OEt, R' = H) was obtained as above by the hydrolysis of the ester X (R = CH₂CH₂OEt, R' = H) with 2 *N* hydrochloric acid at 100° for 5 min. The base could not be crystallized, but the hydrochloride was obtained from ethanol-ether as white prisms, mp 254–256°, ν_{\max} 1735 and 1690 cm⁻¹.

Anal. Calcd for $C_{28}H_{44}NO_6 \cdot HCl$: C, 62.7; H, 6.9. Found: C, 62.6; H, 6.8.

7-Cyano-5,7-dehydro-6,14-endo-etheno-6-O-methyldihydrothebaine (XII, R' = H). 7-Cyano-6,14-endo-ethenotetrahydrothebaine (10 g, mixture of 7 α and 7 β isomers obtained directly from the Diels-Alder addition of acrylonitrile to thebaine⁹) in ether (200 ml) was added to a boiling solution of methylmagnesium iodide (from 2.52 g of magnesium and 15.4 g of methyl iodide) in ether (100 ml), and the mixture was heated and stirred under reflux for 4 hr, and then poured into aqueous ammonium chloride. The ether layer was separated, dried, and evaporated, and the crystalline residue (9.3 g) was recrystallized from methanol, when the nitrile XII (R' = H) was obtained as almost white prisms, mp 234°, ν_{\max} 2250 cm⁻¹, readily soluble in aqueous potassium hydroxide and coupling in solution with diazotized sulfanilic acid to give a red dye.

Anal. Calcd for $C_{22}H_{34}N_2O_2$: C, 72.5; H, 6.7. Found: C, 72.8; H, 6.8.

The same base was obtained when 7-cyano-6,14-endo-ethenotetrahydrothebaine (10 g) was added to a solution of potassium (5 g) in *t*-butyl alcohol (200 ml), the solution being maintained at 65° for 15 min after which it was poured into saturated aqueous ammonium chloride, and the product was isolated by ether extraction. It was obtained also by either process starting from the pure 7 α and 7 β nitriles.

7-Cyano-5,7-dehydro-6,14-endo-etheno-4,6-O-dimethyldihydrothebaine (XII, R' = Me). 7-Cyano-6,14-endo-ethenotetrahydrothebaine (6 g, mixture of 7 α and 7 β forms) was added to a solution of potassium (2.4 g) in *t*-butyl alcohol (40 ml) and methyl iodide (6 ml) was added to the resulting red solution. The mixture was stirred at ca. 65° for 1 hr and poured into aqueous ammonium chloride, and the organic layer was separated. The aqueous layer was extracted once with ether, and the combined organic solutions were evaporated to dryness. The residue (6 g) was recrystallized from methanol, when the O-methyl ether XII (R' = Me) (5 g) was obtained as prisms, mp 187°, ν_{\max} 2250 cm⁻¹.

Anal. Calcd for $C_{24}H_{36}N_2O_2$: C, 73.0; H, 6.9. Found: C, 72.6; H, 6.9.

7-Cyano-5,7-dehydro-6,14-endo-etheno-4-O-ethyl-6-O-methyldihydrothebaine (XII, R = Et). 7-Cyano-6,14-endo-ethenotetrahydrothebaine (3 g) in a solution of potassium (1.2 g) in *t*-butyl alcohol (20 ml) at 60° was ethylated by the addition of ethyl bromide (3 ml). Isolation of the product in the manner described above gave the 4-O-ethyl ether XII (R' = Et) as white needles, mp 120°, from aqueous methanol.

Anal. Calcd for $C_{26}H_{38}N_2O_2$: C, 73.5; H, 7.15. Found: C, 73.0; H, 7.3.

4-O-Acetyl-7-cyano-5,7-dehydro-6,14-endo-etheno-6-O-methyldihydrothebaine (XII, R¹ = COCH₃). Acetyl chloride (3 ml) was added to a solution of 7-cyano-6,14-endo-ethenotetrahydrothebaine (3 g) in one of potassium (1.2 g) in *t*-butyl alcohol (30 ml). After 15 min at room temperature the mixture was poured into ammonium chloride solution containing ammonia. The product

was isolated by ether extraction and recrystallized from methanol, when the acetylated nitrile XII (R' = COCH₃) was obtained as elongated plates, mp 217°, ν_{\max} 2250 and 1720 cm⁻¹.

Anal. Calcd for $C_{24}H_{36}N_2O_4$: C, 70.9; H, 6.4. Found: C, 70.9; H, 6.4.

18-Cyano-5,14-ethanothebaine (XI, R = CN, R' = H). 7-Cyano-5,7-dehydro-6,14-endo-etheno-6-O-methyldihydrothebaine (XII, R' = H) (5 g) was heated for 5 min at 100° with 2 *N* hydrochloric acid (20 ml). The ketone was precipitated with ammonia and recrystallized from methanol, when it was obtained as white prisms, mp 200°, ν_{\max} 2250 and 1690 cm⁻¹.

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 72.0; H, 6.3. Found: C, 72.1; H, 6.2.

18-Cyano-5,14-ethano-4-O-methylthebaine (XI, R = CN, R' = Me). Prepared as above by the hydrolysis of the methylated nitrile XII (R' = Me), this ketone was obtained as prisms, mp 284°, ν_{\max} 2250 and 1690 cm⁻¹, from ethanol.

Anal. Calcd for $C_{23}H_{34}N_2O_2$: C, 72.5; H, 6.7. Found: C, 72.1; H, 6.3.

18-Cyano-5,14-ethano-4-O-ethyl-6-O-methylthebaine (XI, R' = Et) was obtained by the hydrolysis of the nitrile XII (R' = Et) with 2 *N* hydrochloric acid at 100° as above, and was recovered from aqueous methanol as prisms, mp 200°, ν_{\max} 2250 and 1690 cm⁻¹.

Anal. Calcd for $C_{23}H_{36}N_2O_2 \cdot H_2O$: C, 69.7; H, 7.1. Found: C, 69.9; H, 6.7.

Reaction of the Nitrile XII (R' = Me) with Methylmagnesium Iodide. 7-Cyano-5,7-dehydro-6,14-endo-etheno-4,6-O-dimethyldihydrothebaine (XII, R' = Me) (6.1 g) in tetrahydrofuran (200 ml) was added to a boiling stirred solution of methylmagnesium iodide (from 2 g of magnesium and 4.6 ml of methyl iodide) in tetrahydrofuran (100 ml). The resulting mixture was stirred and heated under reflux for 5 hr, and poured into saturated ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted once with ether. Evaporation of the combined organic solutions afforded a viscous material, which was warmed on the water bath for 30 min with 2 *N* hydrochloric acid (25 ml). Basification of the solution with ammonia and isolation of the product by ether extraction afforded a solid (4 g). On crystallization from ethanol this gave 18-acetyl-5,14-ethano-4-O-methylthebaine (VII, R' = Me), mp 186°, identical in melting point, mixture melting point, and infrared absorption with the base obtained by the methylation of the phenol VII (R¹ = H).

Action of Boron Tribromide on the Ketone I. 7 α -Acetyl-6,14-endo-ethenotetrahydrothebaine (5 g) in methylene chloride (30 ml) was treated with boron tribromide (3.2 g) at 5° for 1 hr. Aqueous ammonium chloride containing ammonia was added to the solution, and the organic layer was separated, dried, and evaporated, when 18-acetyl-5,14-ethanothebaine, mp 199–200°, alone or mixed with an authentic specimen was obtained.

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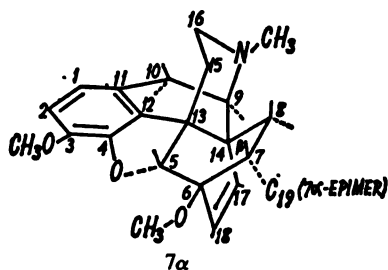
Nuclear Magnetic Resonance Studies in the 6,14-*endo*-Ethenotetrahydrothebaine Series

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Abstract: Nuclear magnetic spectroscopy, including homonuclear field-sweep spin-decoupling techniques, has been used to determine the stereochemistry of the epimers and the configuration of some of the diastereomers formed by the Diels–Alder addition of electrophilic olefins to thebaine, followed by further transformations. Analyses of the nmr spectra include the comparisons of computed spectra with the observed spectra for the various spin-spin systems. Differences in chemical shift between similar protons in the various compounds have been explained in terms of the anisotropy of a phenyl substituent or the shielding parameters of the cyclic tertiary nitrogen atom and the bicyclo[2.2.2]octene double bond present in these structures.

The preceding papers² describe the preparation and chemical transformations of a variety of 6,14-*endo*-ethenotetrahydrothebaine derivatives containing the bicyclo[2.2.2]octene system, obtained by Diels–Alder addition of electrophilic olefins to thebaine followed by further transformations. This paper describes the application of nuclear magnetic resonance (nmr) spectroscopy, including homonuclear field-sweep spin-decoupling techniques, to the elucidation of the absolute configuration of asymmetric centers formed during these transformations. Included specifically are stereochemical assignments of epimers (at C-7) produced by the Diels–Alder reactions^{2a} (and generally maintained during subsequent transformations) and a study of diastereomeric alcohols (at C-19) formed by stereoselective transformations of the Diels–Alder adducts.^{2b} The structure below is a stereochemical representation



Ia	CN	H
Ib	H	CN
IIa	COCH ₃	H
IIb	H	COCH ₃
IIIa	C(CH ₃) ₂ OH	H
IIIb	H	C(CH ₃) ₂ OH
IV	COC ₂ H ₅	H
V	C(=NOH)CH ₃	H
VI	C(=CH ₂)CH ₃	H
VII	C(=CH ₂)C ₆ H ₅	H
VIII	C(CH ₃) ₂ OCH ₃	H
IX	C(CH ₃) ₂ OH (nor-IIIa NCN)	H
X	CH ₂ OH	H

of the 6,14-*endo*-ethenotetrahydrothebaine system and illustrates the numbering and designations for C-7 epimers used throughout these papers.³

Compounds Epimeric at C-7

A mixture of 7-cyano epimers (Ia and Ib) was obtained by repeating the synthesis of Bentley and Ball,⁴ and these isomers were separated and isolated in approximately equal amounts by a combination of fractional crystallization and partition chromatography.^{2a} At the outset, chemical data did not permit unequivocal assignment of the C-7 epimer configuration. However, the nmr data, including the results of spin decoupling, demonstrated that the more polar isomer, mp 183–184°, had the 7α-nitrile configuration (Ia) with the 6,14-etheno bridge disposed in the *endo* position “inside” the tetrahydrothebaine skeleton. The nmr spectrum of this epimer is shown in Figure 1 (with arrows indicating the spin systems established by decoupling experiments). Irradiation of the olefinic H-18 (δ 5.93) established that it was part of a four-spin system. Spin coupling was found between H-18 and H-17 (δ 5.61), $J_{17,18} = 9.0$ cps (a typical AB pattern). Additionally, H-18 was coupled to both H-5β (δ 4.50), $J_{5β,18} = ca. 2$ cps, and to H-7β (δ 2.85), $J_{7β,18} < 1.0$ cps. Examination of a Dreiding model of Ia showed that both H-5β and H-7β, together with H-18 and the intervening carbon atoms, approximate a plane in which the connecting bonds resemble a “W”;⁵ both protons would therefore be expected to couple with H-18.⁶ These couplings are summarized in Figure 1. Decoupling experiments were also performed on the four-line pattern of the upfield proton (δ 1.50). This absorption, eventually assigned to H-8α, was established as part of a *three-spin system* involving H-7β and H-8β. Inspection of the H-8α pattern at δ 1.50 established that $J_{8α,8β} = 12.0$ cps (geminal coupling) and $J_{7β,8α} = 4.5$ cps (vicinal coupling, transoid). By using spin decoupling and observing the

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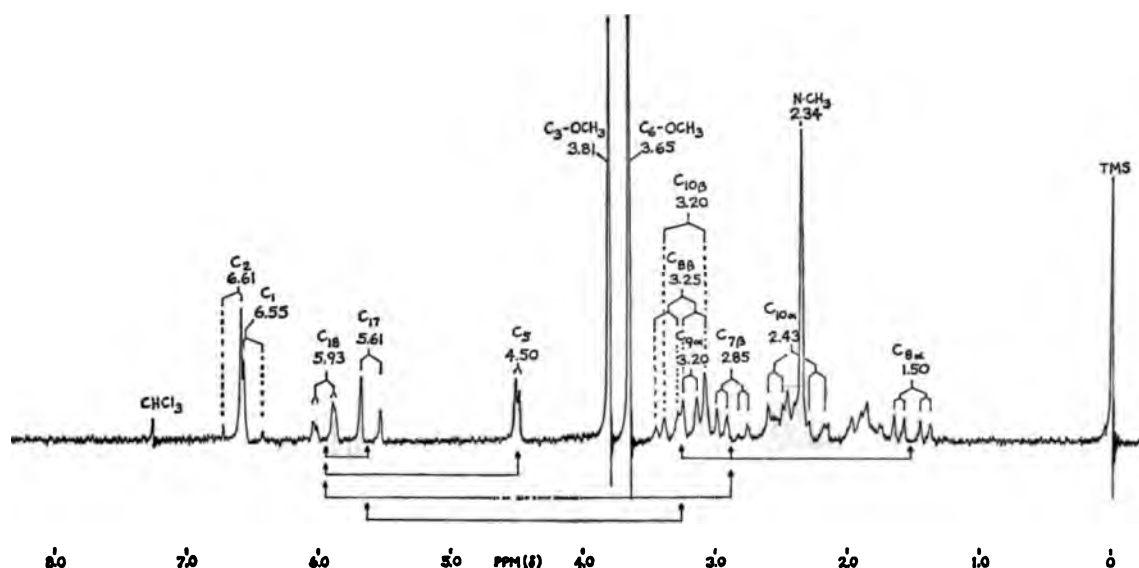


Figure 1. Proton nmr spectrum of the 7 α -cyano epimer Ia.

perturbations of the four-line H-8 α pattern, it was possible to locate both of the H-7 β and H-8 β multiplets in the region δ 2.5–3.5. However, owing to resonances from other protons in this region (H-9 α and H-10 β), identification of the individual resonance lines from these protons was difficult. Careful examination of the δ 2.8 region revealed a pair of doublets which had the same 4.5-cps vicinal splitting, but separated by 9.5 cps ($J_{7\beta,8\beta}$) in which the intensities of each component varied considerably. Careful spin decoupling then clearly indicated that the 4.5-cps doublets of H-8 α were collapsed by irradiating these doublets at δ 2.8, and, moreover, it appeared that the upfield doublet of H-8 α was collapsed by irradiating the *low-field* doublet of the pair at δ 2.8, and *vice versa*. This indicated that the two couplings, $J = 12.0$ cps and $J = 9.5$ cps, had opposite signs. This finding was consistent with the assigned arrangement of these protons, for it is known that the sign of J_{HH} (geminal) is negative while that for J_{HH} (vicinal) is positive.⁷ Accordingly, the δ 2.8 doublets belonged to H-7 β , and the H-8 β pattern appeared partly hidden near δ 3.2.

To confirm the observed intensities of the H-7 β doublets and to help locate the H-8 β pattern, the expected spectrum was calculated using estimated chemical shifts (which approximated the true values) and the following J values: $J_{8\alpha,8\beta} = -12.0$ cps, $J_{7\beta,8\beta} = +9.5$ cps, and $J_{7\beta,8\alpha} = +4.5$ cps. The three spins were treated as an ABC system, following established mathematical procedures.^{8,9} The line positions and intensities were calculated with the aid of a program written for a Burroughs 205 computer. The excellent agreement between the calculated and experimental spectra is shown in Figure 2, where the calculated H-8 β set of lines fits under the observed lines. Two of the H-8 β lines can be seen in the spectrum, while the other two are obscured. The three combination lines which result from an ABC treatment are omitted, as their

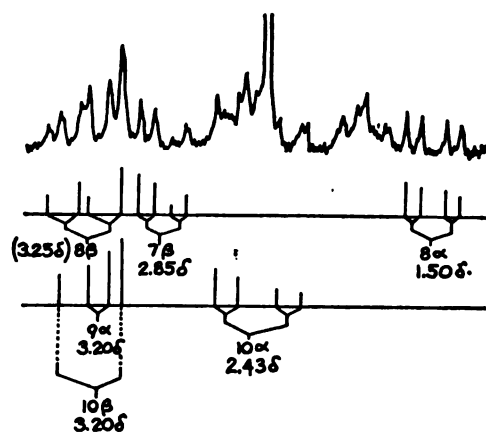


Figure 2. Calculated and experimental spectra (nmr) for the C-7 β , C-8 α , C-8 β , C-9 α , C-10 α , and C-10 β protons in the 7 α -cyano epimer Ia.

intensities were near zero. The patterns for the H-9 α and H-10 β protons were also found in this region (δ 2.5–3.5) which integrates for four protons (H-7 β , δ 2.8 and H-8 β , δ 3.2 are also present). Using estimated chemical shifts for H-9 α (δ 3.20), H-10 β (δ 3.20), and H-10 α (δ 2.43) with the observed coupling constants ($J_{9\alpha,10\alpha} = +6.2$ cps, $J_{10\alpha,10\beta} = -18.0$ cps, and $J_{9\alpha,10\beta} = ca. 0.0$ cps, which are in agreement with Rüll and Gagnaire¹⁰) the line positions and intensities of these proton patterns were calculated, and the agreement between these calculated and observed spectra is also shown in Figure 2. Thus, spin decoupling, together with the excellent agreement between the computed and observed spectra, confirmed the chemical shifts assigned for H-7 β (δ 2.85) and H-8 β (δ 3.25), as indicated in Figures 1 and 2, even though the complex patterns resulting from H-9 α and H-10 β resonance lines also appeared in this region.

Very small (<0.2 cps) long-range coupling between H-8 β (δ 3.25) and H-17 (δ 5.61) was also detected by spin decoupling. These protons are sterically related to each other in the same sense that H-7 β is related to

(7) C. N. Banwell and N. Sheppard, *Discussions Faraday Soc.*, **34**, 115 (1962).

(8) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959.

(9) C. N. Banwell and N. Sheppard, *Mol. Phys.*, **3**, 351 (1960).

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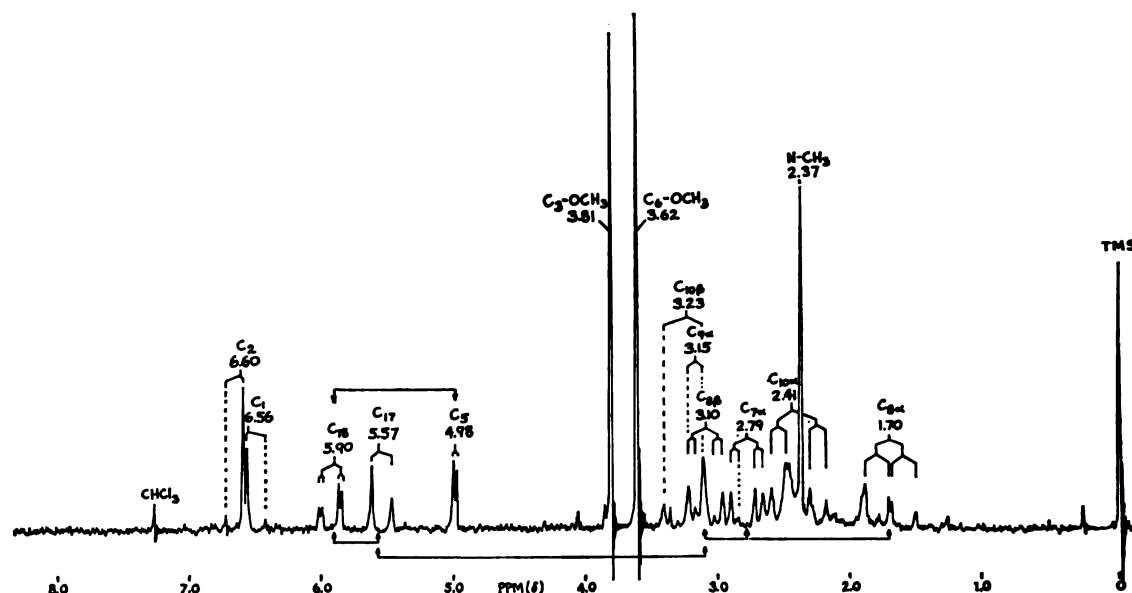


Figure 3. Proton nmr spectrum of the 7 β -cyano epimer Ib.

H-18 (see structures I–X). The downfield chemical shift of H-8 β (δ 3.25) compared with that of H-8 α (δ 1.50) was somewhat surprising, since the corresponding protons in bicyclo[2.2.2]octene resonate at δ 1.50 and 1.27, respectively.^{8c} The large difference in chemical shifts of the geminal protons H-8 α and H-8 β may be understandable upon consideration of the shielding (or the free electron pair) of the tertiary nitrogen atom held in proximity to H-8 β (*ca.* 2.9 Å)¹¹ by the rigid ring system (see structures I–X). The chemical shift of H-8 β is similar to that observed for the *syn*-methylene bridge proton of sparteine,¹² which is also held in the proximity of a nitrogen atom (*ca.* 2.3 Å away). Additional discussion of this point is included in the latter part of this paper, as this marked downfield shift for H-8 β is evident in virtually all of the compounds examined in this series.

Assignment of the other isomer, mp 195–196°, as the 7 β -cyano epimer (Ib) was based on equivalent decoupling experiments; this nmr spectrum is shown in Figure 3. In contrast to Ia, spin decoupling established that H-18 in this epimer was part of a *three-spin system*. Again, H-18 (δ 5.90) and H-17 (δ 5.57) formed a typical AB coupling pattern ($J_{17,18}$ = 9.0 cps), and the H-5 β (δ 4.98), H-18 coupling ($J_{5\beta,18}$ = *ca.* 2 cps) was also similar to that found previously. However, no coupling was found between H-18 and any upfield proton in the area δ 2.8–3.1, where H-7 α and H-8 β were subsequently located by irradiation of H-8 α (the upfield proton; δ 1.70 in this epimer). The absence of spin coupling between H-18 and H-7 α in this isomer is as expected since the 7 β position is now occupied by the nitrile group, and H-7 α is not oriented correctly⁵ for long-range coupling with H-18. The downfield shift of H-5 β from δ 4.50 for the 7 α -nitrile (Ia) to δ 4.98 for this epimer (Ib) was especially noteworthy. The chemical shifts for H-5 β in virtually all of the related compounds (including II–XIV) appear to be diagnostic for assigning the configuration at C-7, and these ranges for both series of C-7 epimers are summarized in Table I. In-

deed, mixtures of C-7 epimers (including Ia and Ib) were frequently recognized by examination of their nmr spectra (even of relatively crude products), as resonances from other protons (except for exchangeable hydroxyl protons) were generally not found in the δ 4.3–5.2 region. Confirmation of the C-7 epimer assignment based on the readily observed chemical shift for H-5 β could then be established by spin decoupling.

Table I. Protons Diagnostic for C-7 Substituents

Proton	No. of examples	Average chemical shift, δ	Exceptions
			7 α Substituted
H-5 β	21	4.57 ± 0.05	XIIIa (4.47), b (4.47), c (4.37)
			7 β Substituted
H-5 β	3	5.07 ± 0.12	
			7 α or 7 β Substituted (Ia–IX)
H-8 α	8	1.35 ± 0.15	IIIa (0.79), b (?), VIII (1.18), IX (0.93)
			7 α -C-19 Carbinols
H-8 α	11	0.78 ± 0.05	XIb (1.20), XIIa (1.22), IIIb (?)

Close examination of the spectra and equivalent spin-decoupling experiments on the H-8 α four-line pattern (δ 1.70) of Ib established that this proton was still part of a *three-spin system*. The high-field H-8 α lines now showed nearly equal splittings of 11.2 cps (vicinal) and 12.2 cps (geminal). This increase in vicinal coupling would be expected for the *cis* relationship between H-7 α and H-8 α . Some of the H-7 α and H-8 β lines (in the δ 2.5–3.5 region) of this 7 β epimer (see Figure 3) were more obvious than the corresponding lines in the spectrum of the 7 α epimer (see Figure 1). This ABC system (H-8 β , H-7 α , H-8 α) may be approximated by an ABX pattern where the AB part consists of two AB subspectra. One of these slightly perturbed AB subspectra was visible near δ 2.9 (Figure 3). The location of the other AB subspectrum followed from the couplings already determined; three of the four lines were identified near δ 3.1. The third coupling (3.6

(11) Estimated from Dreiding models.

(12) F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Letters*, 2705 (1965).

Table II. Protons in Spin-Decoupled Systems^{a,b}

Compd	Proton, chem shifts, δ					Coupling constants, J (cps)		
	H-5 β	H-7 α	H-7 β	H-8 α	H-8 β			
Ia	4.49	...	2.85	1.50	3.26	5.60	5.93	5 β ,18 (<2.0), 7 β ,8 α (+4.5), 8 α ,8 β (-12.0), 7 β ,8 β (+9.5), 17,18 (9.0), 7 β ,18 (<1.0), 8 β ,17 (<0.2)
Ib	4.99	2.79	...	1.70	3.10	5.57	5.90	5 β ,18 (<2.0), 7 α ,8 α (+11.2), 8 α ,8 β (-12.2), 7 α ,8 β (+3.6), 17,18 (9.0), 8 β ,17 (<0.2)
IIa	4.53	...	2.90	1.34	2.91	5.54	5.85	5 β ,18 (<2.0), 7 β ,8 α (+6.5), 8 α ,8 β (-12.6), 7 β ,8 β (+9.7), 17,18 (10.0), 7 β ,18 and 8 β ,17 (<0.2)
IIb	4.98	2.69	...	1.40	3.04	5.48	6.04	5 β ,18 (<2.0), 7 α ,8 α (+13.9), 8 α ,8 β (-15.6), 7 α ,8 β (+5.0), 17,18 (9.0)

^a General characteristics are in Table III. ^b These values are included in the averages in Table I.

ps) was evident by the splitting of the outer lines of each AB pattern. Using these chemical shifts and coupling constants and a negative value for the geminal coupling constant (-12.2 cps), the complete spectrum was calculated as before. By analogy with the 7 α epimer (Ia), the four lines belonging to the upfield halves of each AB spectrum were assigned to H-7 α (δ 2.79), and the low-field halves to H-8 β (δ 3.10). The agreement with the observed spectrum is shown in Figure 4 together with equivalent results for the H-9 α , H-10 α , and H-10 β patterns. The very small long-range coupling (J = 0.2 ps) between H-17 and H-8 β was also detected in this epimer by spin decoupling (analogous to that observed in Ia).

These nmr data pertaining to Ia and b, including the experimentally observed spin systems and coupling constants, and consideration of the anisotropic effects of the *t*-nitrogen on the C-8 protons independently confirm the conclusions of Bentley and co-workers^{2a,4} that neither Ia nor Ib could be an 8-cyano derivative. They also confirm the assignment of the *endo* disposition of the 6,14-etheno bridge "inside" the tetrahydrothiabaine system.¹⁸ These conclusions, based upon nmr data, can generally be extended to other analogous Diels-Alder adducts (e.g., IIa and IIb below), although our investigations of spin-spin couplings by double irradiation techniques (see Table II) and computed spectra produced the most definitive results with Ia and b of the several pairs of epimers studied. Other characteristic proton patterns recognized in the nmr spectra of Ia and b (and of II-XIV) are summarized in Table III.

The epimeric methyl ketones IIa and IIb¹⁴ were similarly studied. The general characteristics of these nmr spectra were similar to those of the nitriles Ia and b (Table III). Detailed spin-decoupling experiments were also carried out to establish the appropriate spin systems for H-5 β , H-7 α , H-7 β , H-8 α , H-8 β , H-17, and H-18, as before; these chemical shifts and coupling constants are included in Table II. However, additional difficulties in spin decoupling were encountered

(13) In both 8-cyano epimers, H-18 would always be expected to be part of a *four-spin* system including H-7 β which would have a geminal coupling constant as well. This was not observed in any compound examined. The possibility that Ib might be a 6,14-*exo*-etheno derivative may be dismissed because of the similarity of the H-17 and H-18 olefinic proton patterns to those of Ia, which had been assigned the *endo*-etheno configuration^{2a,4} on the basis of chemical data.

(14) These epimers were obtained by repeating the synthesis of Bentley and coworkers;^{2a,4} IIa, mp 115–118° (pure by nmr and tlc), was obtained in 80% yield (first crop), and IIb, mp 198–201°, was isolated in 8% yield by partition chromatography of the mother liquors.

owing to the greater overlap of resonance patterns (e.g., in IIa). Of particular interest was the pattern for H-8 α in the spectrum of IIa. This was clearly seen between δ 1.1 and 1.6 (centered at δ 1.34), but it did not resemble the four-line pattern observed for H-8 α in the spectra of Ia, Ib, and IIb. Instead, a five-line pattern was observed. Four of the five lines were narrow and symmetrically arranged, with the inner lines

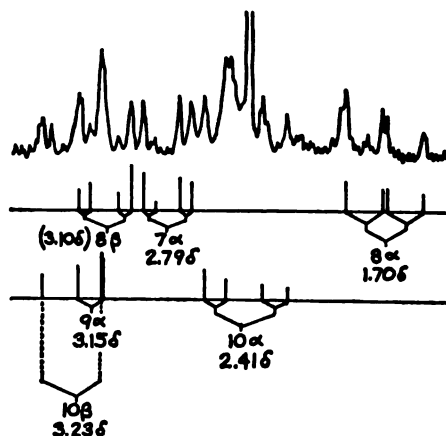


Figure 4. Calculated and experimental spectra (nmr) for the C-7 α , C-8 α , C-8 β , C-9 α , C-10 α , and C-10 β protons in the 7 β -cyano epimer Ib.

being stronger than the outer ones; the fifth line was somewhat broader and appeared in the center (see Figure 5). The two combination lines in the X pattern

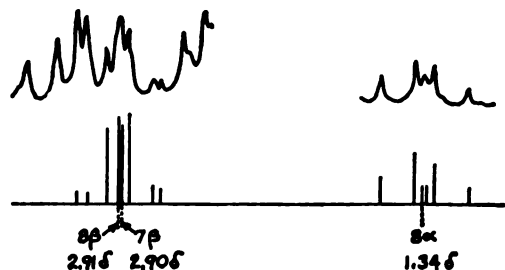


Figure 5. Calculated and experimental spectra (nmr) for the C-7 β , C-8 α , and C-8 β protons in the 7 α -methyl ketone epimer IIa.

of an ABX system can become quite strong and appear in the center of the X pattern when the chemical shift of A is very close to that of B.¹⁵ Indeed, decoupling

(15) J. I. Musher and E. J. Corey, *Tetrahedron*, 18, 791 (1962).

Table III. General Characteristics of Compounds Studied*

Proton	No. of examples	Av chem shift, δ	Coupling constant, J (cps)	Exceptions
H-1	27	6.54 ± 0.03	$1,2 (8 \pm 0.5)$	(1) IX (2.67), (2) known only for the compounds in Table II
H-8 β	16	$2.9 \pm 0.15 (1)$	$8\beta,8\alpha (2) (12 \pm 2)$	
			$8\beta,7\beta (2) (8 \pm 0.5)$	XIa (2.94), IX (3.93), XIIIa (2.70), XIIIb (2.62), c (2.63), IIa·HCl (4.20)
			$8\beta,7\alpha (2) (4.3 \pm 0.7)$	
H-9 α	22	3.13 ± 0.04	$9\alpha,10\alpha (6.5 \pm 0.5)$	
H-10 α	23	~ 2.4	$10\alpha,10\beta (18 \pm 1)$	IX (3.1)
H-10 β	28	3.15 ± 0.05	...	IIa·HCl (?)
H-17	22	5.48 ± 0.06	$17,18 (8.5 \pm 0.5)$	XIa (4.88), XIg (5.69), VIII (5.37), IIa·HCl (5.78)
H-18	21	5.91 ± 0.08	$18,5\beta (\leq 2)$	IIIb (6.15), XIIa (5.04), IIa·HCl (5.61)
3-OCH ₃	25	3.81 ± 0.02		XIa (2.17), IIa·HCl (3.05)
6-OCH ₃	27	3.65 ± 0.10	...	
N-CH ₃	26	2.43 ± 0.02	...	
C-19 CH ₃	21	1.1 ± 0.1	...	

* The nmr spectra were run on a Varian A-60 spectrometer equipped with a variable-temperature probe. Solutions were 20% (w/v) in deuteriochloroform except where noted otherwise. Tetramethylsilane was used as an internal reference, and the accuracy of the measurements is within δ 0.03 for the chemical shifts and 0.5 cps for the coupling constants. The spin-decoupling work was done on a Varian DP-60 equipped with a Varian integrator-decoupler.

experiments made while observing H-8 α (δ 1.34) indicated that H-7 β and H-8 β were both near δ 2.9. With the values $J_{8\alpha,8\beta} = -12.0$ cps, $J_{8\alpha,7\beta} = +4.5$ cps, and $J_{8\beta,7\beta} = +9.5$ cps, obtained from the analogous isomer (Ia), trial three-spin spectra were computed. From these, an assignment of transitions could be made to the H-8 α lines and four clearly visible lines assignable to H-7 β and H-8 β . The entire energy-level scheme could then be drawn up and the unobserved lines filled in. An exact Castellano-Waugh¹⁶ calculation was carried out using the measured shift values. The spectrum was then exactly reproduced with the following parameters: H-8 α , δ 1.34; H-7 β , δ 2.90; H-8 β , δ 2.91; $J_{8\alpha,8\beta} = -12.6$ cps; $J_{8\alpha,7\beta} = +6.5$ cps; $J_{8\beta,7\beta} = +9.7$ cps. The two combination lines in the H-8 α pattern appeared at its center, separated by about 0.01 ppm, and could easily account for the central broad line (as shown in Figure 5).

Spin decoupling of the 7 β -acetyl epimer IIb was similar to that of the 7 β -nitrile Ib (see Tables I and III). The spin systems determined from the spectra of both IIa and IIb also confirmed the prior C-7 assignments of Bentley, *et al.*^{2a,4} These assignments are: the configuration at C-7, that neither isomer could be an eight-substituted derivative, and that the 6,14-etheno bridge was in an *endo* disposition.

The epimeric tertiary carbinols IIIa¹⁷ and IIIb,¹⁸ synthesized from IIa and IIb, respectively, were also thoroughly investigated. In the 7 α epimer IIIa, double-irradiation methods readily established that H-7 β had moved upfield to δ 2.1 with respect to H-7 β at δ 2.8 in its precursor, IIa. This upfield shift of the H-7 β lines is as expected with the removal of the inductive and/or anisotropic effects of the 7 α -cyano or -acetyl group.

Observation of the spectrum showed that H-8 α was also upfield at δ 0.79 (δ 1.32 in IIa) with the typical four-line pattern of an ABX system. Spin-decoupling experiments on this epimer gave completely analogous results to those obtained previously with Ia and IIa. The H-5 β doublet ($J_{5\beta,18} = ca. 2.0$ cps) was found at δ 4.50, as expected for a 7 α epimer, and H-18 was part of a *four-spin system*: H-5 β (δ 4.50), H-7 β (δ 2.10), H-17 (δ 5.43), and H-18 (δ 5.92). H-8 α was part of a *three-spin system*: H-8 α (δ 0.79), H-8 β (δ 2.88), and H-7 β (δ 2.10). One additional spin-decoupling experiment on IIIa established that H-1 (δ 6.50) was coupled to at least one proton (probably H-10 β) in the δ 3.0 region. This coupling ($J = <0.2$ cps) was apparent in the increased line width and lowered intensity of H-1, relative to H-2 in all compounds examined.

Spin-decoupling experiments on the epimeric 7 β -carbinol IIIb were not successful. The 8 α proton was not found in the region around δ 0.8 as in IIIa. This pattern was probably under the C-19-methyl resonances at *ca.* δ 1.25. Because of overlapping lines from other protons and lacking the H-8 α handle, it was not possible to determine the chemical shifts and coupling patterns as in the spin systems previously investigated. The 5 β proton was observed at δ 5.26 (a peak at δ 4.58 was assigned to the C-19 OH by exchange with D₂O). This was in accord with other 7 β -substituted derivatives (Table I). Thus, although one might argue for the paramagnetic effects of the 7 β -cyano¹⁹ and -acetyl²⁰ moieties being responsible for the downfield shifts of H-5 β in Ib and IIb (compared with Ia and IIa), these effects cannot be present in the 7 β -carbinol IIIb, which showed an even larger downfield shift for H-5 β . Probably steric compression is a better explanation.²¹ It

(16) S. Castellano and J. S. Waugh, *J. Chem. Phys.*, **34**, 295 (1961).

(17) This compound was synthesized by Grignard addition of methylmagnesium bromide to IIa as described by Bentley and co-workers.^{1b}

(18) Obtained from the Reckitt and Sons Ltd., Laboratories through the courtesy of Dr. K. W. Bentley.

(19) A. D. Cross and I. T. Harrison, *J. Am. Chem. Soc.*, **85**, 3223 (1963).

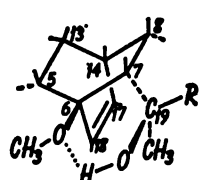
(20) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 112 ff.

so of interest to note that the H-8 α lines (δ 1.2) in had apparently moved downfield compared with position (δ 0.79) in the spectrum of IIIa even though IIIa and IIIb were C-19 tertiary carbinols (see Table I). Again, any rationale which invokes removal of the anisotropic effects of 7 α -cyano or -acetyl groups to account for the marked upfield shift of H-8 α to 79 in the 7 α -*t*-carbinol IIIa (compared with δ 1.50 in IIa, and δ 1.32 in IIb) apparently does not apply in equivalent changes (IIb and IIc to IIIb) for 7 β substituents. Other factors must be involved (see Additional Studies of the C-8 Protons below).

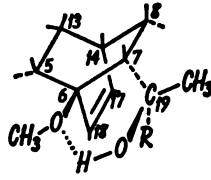
Compounds IV–X²³ are additional examples of C-7 diastereomers whose nmr spectra were entirely analogous to those just discussed in detail (Ia–IIIb). Chemical shift data from these spectra (all 7 α epimers) are included in the summary data in Tables I and III. Of particular interest is the fact that the nmr spectrum (δ 4.60) of nepenthone (IV; the precursor for the diastereomer XIIa) confirmed its previous assignment as a 7 α epimer.^{23,4} Compounds V, VI, and VII are additional derivatives in which C-19 bears an unsaturated moiety; these spectra were similar to those of Ia and IIa. Compounds VIII, IX, and X are derivatives in which C-19 is a saturated carbon bearing a hydroxyl or ether moiety; their spectra were analogous to that of IIIa.

Compounds Diastereomeric at C-19

In the course of our investigations, it became apparent that spectral data (nmr and infrared) might provide a basis for assigning the configuration for the asymmetric carbon at C-19 in the appropriate derivatives. This expectation was realized in our study of the diastereomeric phenylmethyl tertiary carbinols XIa and XIIa. Two other pairs of diastereomers (XIb and XIc; XIIc and XIIe) were also studied, but their spectra did not provide such definitive conclusions.



XIa, R = C₆H₅
 b, R = H
 c, R = *n*-C₄H₉
 d, R = *n*-C₄H₉ (3-OH)
 e, R = *i*-C₄H₉
 f, R = cyclohexyl
 g, R = CH₂CH₂C₆H₅ (3-OH)



XIIa, R = C₆H₅
 b, R = H
 c, R = *n*-C₄H₉

The first pair of C-19 diastereomers studied in detail were XIa, obtained from the 7 α -acetyl derivative IIa by addition of phenylmagnesium bromide,²³ and XIIa, obtained from the 7 α -benzoyl derivative IV (nepenthone) by addition of methylolithium.²⁴ The nmr spectra of

XIa and XIIa showed a number of general features consistent with those previously described (Table III), and the chemical shifts for H-5 β in both of these C-19 diastereomers (Table I) indicated they were 7 α epimers; the C-7 configuration had not been affected during their synthesis. However, in XIIa the upfield shift of both olefinic protons, H-17 (δ 4.88; $\Delta\delta$ = 0.55 ppm) and H-18 (δ 5.04; $\Delta\delta$ = 0.91 ppm), was striking and somewhat unexpected when compared with these chemical shifts in XIa and in virtually all analogous compounds (see Table III). These upfield shifts in XIIa are understandable if the phenyl moiety (R) in this diastereomer is held in a "down under" position in close proximity to the C-17 and C-18 protons of the *endo*-etheno bridge (as illustrated in XI and XII), thereby producing a shielding effect. Examination of models indicated this was possible, and the greater upfield shift of H-18 over that of H-17 was consistent with the closer proximity of H-18 to the phenyl group. There appeared to be considerable restriction of free rotation about the C-19 to C-7 bonds in both diastereomers (XIa and XIIa), and high-temperature nmr experiments provided experimental data consistent with these observations. In perdeuteriodimethyl sulfoxide the C-19-hydroxyl resonance of XIa was observed at δ 4.9 at ambient temperature and moved upfield to δ 4.7 at 180°. In XIIa, this hydroxyl absorption was found at δ 4.6 at ambient temperature, at δ 4.4 at 140°, and at 180° it was too diffuse to locate. There were no significant changes (more than δ 0.05) from the ambient temperature spectra for any other protons.

Intramolecular hydrogen bonding²⁵ of the C-19-*t*-hydroxyl proton was evident from the infrared spectra of both diastereomers XIa and XIIa (OH, 2.92 μ ; not concentration dependent). This must involve the 6-methoxyl groups as indicated by the conformations shown in XI and XII. Hydroxyl resonances at δ 5.26 and 5.8 in the deuteriochloroform spectra of XIa and XIIa, respectively, also agreed with these hydrogen-bonded conformations.²⁶ The conformation shown for XIIa with the *t*-hydroxyl near the 6-methoxyl group and the phenyl group near the *endo*-etheno bridge thus fixed the configuration of this C-19 asymmetric center as 7 α -(α -(R)- α -hydroxy- α -methylbenzyl).²⁷ The isomer XIa then had to have the opposite 7 α -(α -(S)- α -hydroxy- α -methylbenzyl) configuration as shown. These assignments for the C-19 diastereomer configurations in XIa and XIIa, obtained solely from spectral data, are entirely consistent with conclusions suggested by chemical data, including the high degree of stereoselectivity observed during the synthesis of a variety of C-19 diastereomeric alcohols.^{2b}

Close inspection of the nmr spectra of XIa and XIIa revealed other relationships which appeared to be consistent with the assigned conformations of these diastereomers although they are probably less definitive. Models of XIIa indicated that the edge of the phenyl moiety is directed toward H-8 α . Thus, a deshielding effect from the phenyl group may be responsible for the

tlc indicated a trace amount of XIa. Purification by partition chromatography then gave crystalline material which was free from the diastereomer XIa (by nmr and tlc).

(25) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, p 89, gives 2.8–2.9 μ for intramolecularly hydrogen-bonded hydroxyl stretching.

(26) Reference 8, p 400.

(27) R. S. Cahn, *J. Chem. Educ.*, **41**, 116 (1964).

) W. Nagata, T. Terasawa, and K. Tori, *J. Am. Chem. Soc.*, **86**, (1964); D. R. Arnold, D. J. Trecker, and E. B. Whipple, *ibid.*, **87**, (1965).

) Compounds VI and VII were obtained through the courtesy of C. W. Bentley; the others were obtained by repeating the syntheses indicated by Bentley and co-workers as indicated: IV,⁴ V,²³ VIII,^{2d} X.²

) This compound, mp 210–212°, was synthesized by the Grignard reaction of phenylmagnesium bromide to IIa. The crude product (mp 107°, 86%) had traces of the other diastereomer XIb (by tlc), and purified by partition chromatography.

) This compound, mp 148–150°, was synthesized by the addition of methylolithium to IV. It was initially obtained as a glass (90% yield) and

downfield position (δ 1.22) of this 8α proton in XIIa as compared with H- 8α (δ 0.60) in XIa. There were other differences such as the C-19-methyl singlet in XIa which appeared at δ 1.42 compared with δ 1.52 in XIIa. In XIa, the H- 8β pattern had apparently shifted slightly upfield (δ < 2.7), since the δ 2.7–3.5 region integrated for only two protons, which were assigned as H- 9α and H- 10β . In the spectrum of XIIa and most other *carbinols*, this δ 2.7–3.5 region integrated for three protons, one of which was H- 8β in addition to H- 9α and H- 10β . Another difference between the spectra of XIa and XIIa was found in the chemical shifts of the N-methyl groups. In the spectrum of XIIa, the N-methyl singlet (δ 2.36) appeared at a position consistent with the other compounds studied (see Table III). In contrast stood the upfield shift of the N-methyl singlet (δ 2.17) in the spectrum of XIa; a satisfactory explanation of these phenomena is not readily apparent.²⁸

The second pair of C-19 diastereomers studied in detail (both nmr and infrared) were the secondary alcohols XIb²⁹ and XIIb,¹⁸ obtained from the 7 α -acetyl derivative IIa.^{2b} These nmr spectra had general features in agreement with the values in Table I and Table III. The nmr spectrum of XIIb showed the C-19-hydroxyl proton resonance at δ 4.92, suggesting hydrogen bonding (with the 6-methoxyl) as discussed with the previous diastereomers XIa and XIIa. Infrared studies also indicated an intramolecular hydrogen bond in XIIb (2.90 μ , not concentration dependent) equivalent to the previous findings. In contrast, the C-19-hydroxyl resonance in the nmr spectrum of XIb was found at *ca.* δ 2.2. Parallel infrared studies with XIb showed maxima at both 2.78 and 2.86 μ (neither of which was concentration dependent) suggesting that this C-19 hydroxyl exists in two conformers, one with a weak hydrogen bond (2.86 μ) and one with a "free" hydroxyl (2.78 μ).³⁰ In addition to these indications of weaker hydrogen bonding, the H- 8α lines were found at δ 1.20 in the nmr spectrum of XIb, while in its diastereomer XIIb, H- 8α was observed at δ 0.69. In the previous pair of diastereomers XIa and XIIa (see above), the difference in chemical shifts for the H- 8α protons could be ascribed to the deshielding edge of the "down under" phenyl group in XIIa directed toward H- 8α and held rather firmly by steric constraints to rotation. An explanation for the opposite chemical shifts for H- 8α in XIb and XIIb is not readily apparent. Comparative data were also obtained with the primary alcohol X in which the C-19 hydroxyl did not appear to be hydrogen bonded (infrared, 2.86 μ , not concentration dependent; nmr, δ 2.6). The location of H- 8α (δ 0.52) in X, however, was similar to that of H- 8α in the hydrogen-bonded secondary carbinol diastereomer XIIb. Thus, satisfactory interpretation of the range of chemical shifts (*ca.* δ 1.2–0.5) observed for H- 8α in these very closely related structures was difficult (see below).

(28) The upfield shift of the N-methyl singlet and the apparent upfield shift of H- 8β in this diastereomer are unique among all of the spectra examined, and may be due to the C-19 phenyl group held in an "up" position. However, any interpretation of these factors which may be related appears to be speculative in the absence of additional examples.

(29) This compound, XIb, mp 73–75°, was obtained as a Grignard reduction by-product from the reaction of IIa with propylmagnesium iodide as described by Bentley and coworkers;^{2b} it was isolated by chromatography of the mother liquors after separation of XIc.

(30) Bentley and co-workers^{2b} have attributed the band at 2.78 μ to a conformation with the C-19 hydroxyl bonded to the C-17–C-18 double bond.

Although these detailed interesting differences between binol diastereomers XIb and XIIb preclude definitive conclusions concerning configuration at C-19. Assignments (shown in XIb and XIIb) are based on chemical data.^{2b}

The third diastereomer pair methyl tertiary carbinols XIc from the 7 α -acetyl (IIa) and XIIc, respectively. The nmr spectra were completely in accord with those listed in Table III, and the H- 8α in XIc; δ 4.55 in XIIc were consistent with the configuration. The C-19 hydroxyl in both diastereomers (δ 4.8) as in XIa and XIIa. Thus, the diastereomers were virtually indistinguishable and provided no assignment of the absolute configuration. These were assigned by analogy, assuming similar stereochemistry^{2b} (XIa–g, all obtained by crystallographic analysis of the crystals) confirmed the configuration of XI and XII, bonded conformation of the C-19 hydroxyl.

Compounds XIId–g,³¹ including diastereomers whose nmr spectra and chemical shift data are included in the Tables I and III. These data were consistent with the assignments and did not permit conclusions concerning diastereomeric configurations. chemical analogy.^{2b} Compound XIId of particular interest as it is a very pure derivative whose biological activity has been intensively studied;³⁴ its nmr spectrum was identical with that of XIc but lacked the 3-methoxyl singlet in XIc; this indicated that no reaction had taken place during its synthesis (alkaline hydrolysis).^{2b}

Additional Studies of the C-8 Protons

As these nmr studies of the C-19 diastereomers progressed, the C-8 protons became increasingly important by the sometimes unexpected shifts. The proximity of the nitrogen atom has already been noted (of H- 8β). Both C-8 protons are affected by the C-17–C-18 part of the bicyclo[2.2.2]octane system; the *endo*- and *exo*-proton shifts may well apply to our compounds.

(31) This compound was synthesized by propylmagnesium iodide to IIa as described by Bentley and coworkers.^{2b}

(32) Private communication from J. Bentley, to be published.

(33) Compound XIId was obtained by hydrolysis in diethylene glycol at 200°C by co-workers.³⁰ Compounds XIe–g, in Reckitt and Sons Ltd., Laboratories at Bentley.

(34) (a) R. E. Lister, *J. Pharm. Pharmacol.* 1967, 18, 100; (b) Harthoorn, *J. S. African Vet. Med. Assoc.* 1967, 38, 100.

Table IV. Chemical Shift of Protonated Species^a

Compd	Changes ($\Delta\delta$, ppm) observed vs. the bases			
	H-8 α	H-8 β	H-9 α	N-Methyl ^f
Ia·HCl	-0.34		-1.1	-0.7
IIa (CF ₃ COOH) ^{b,c}	-0.21		-1.0	-0.7
I (CF ₃ COOH) ^e	-0.31	Ca. +0.4	-1.0	-0.7
IIb (CF ₃ COOH) ^e	-0.10	?	-1.0	-0.7
IIIb (CF ₃ COOH) ^e	Ca. -0.3	?	-1.0	-0.7
II ^e	-0.14	+0.21	-0.81	...

In none of the experiments (CF₃COOH-CDCl₃) did additional experiments of acid move either the H-9 α or N-methyl lines farther upfield (indicating complete protonation of the *t*-nitrogen). In the experiment on IIIa, the acid was added to the CDCl₃ solution and small increments and both the H-8 α and N-methyl absorptions were observed moving downfield simultaneously as the acidity increased. ^c In each case, after recording the protonated spectra, acid was neutralized with dilute NaOD-D₂O until the spectra showed the original bases were recovered (establishing the absence of composition). ^d In these spectra, the H-8 β lines could not be located because of overlap with other proton lines, presumably 5 α and H-16 β . ^e The N-cyano derivative (not protonated) included for comparison. ^f The N-methyl absorption was a broadened singlet in all cases studied.

tions in our C-7 epimers and C-19 diastereomers are primarily influenced both by the nature of and the stereochemical orientations of the C-7 substituents. This section describes further studies of these apparently unique chemical shifts directed toward a better correlation of the observed chemical shifts with structural and environmental factors responsible for them.

The N-cyano derivative IX, obtained from IIIa, and intermediate for N-substituted derivatives,^{2c} is a compound in which the basicity of the nitrogen is diminished by the nitrile moiety. Although anisotropic effects of the nitrile group might distort some chemical shifts, spin-decoupling techniques were used to locate the H-8 α , H-8 β , H-7 β spin system in IX (as in Ia-IIIa). The lines for H-8 β in the spectrum of IX were located centered at δ 2.67, slightly upfield ($\Delta\delta = +0.21$ ppm) from this pattern in IIIa, probably because of the reduced basicity of the ring nitrogen. The H-8 α lines at δ 0.93, the upfield "handle" for the spin decoupling, were slightly downfield ($\Delta\delta = -0.14$ ppm) from those in the precursor (IIIa). Both of these changes can be ascribed to the effects of the diminished nitrogen availability on the ring nitrogen. The third proton in this spin system, H-7 β , was found at δ 2.04, shifted slightly upfield ($\Delta\delta = +0.06$ ppm) from its position in the spectrum of IIIa. Interestingly, the H-8 α lines moved downfield ($\Delta\delta = -0.7$ ppm) to about δ 3.1 and overlapped with the lines from H-10 β (1.6) which did not change from their position in the spectrum of IIIa. The H-9 α absorption (δ 3.93) moved upfield ($\Delta\delta = -0.81$ ppm from IIIa) as expected. Other proton absorptions maintained their positions (0.05 ppm) compared with IIIa.

Since the nmr spectrum of IX (ring nitrogen with diminished electron density) indicated that the H-8 α and H-8 β lines had moved toward each other, further studies were undertaken with a number of protonated derivatives. These were carried out with an isolated hydrochloride or by the addition of trifluoroacetic acid to deuteriochloroform solutions of the free bases. The results are summarized in Table IV ($\Delta\delta$ shifts for H-8 α , H-8 β , H-9 α , N-Me). In the spectrum of the hydrochloride of IIa (the 7 α -acetyl epimer), H-8 α had moved

downfield about 0.3 ppm, but, unfortunately, the H-8 β lines could not be observed because of overlap with other lines (H-16 α and H-16 β would be expected to shift downfield upon protonation of the ring nitrogen). H-1 and H-2 moved slightly downfield ($\Delta\delta = -0.15$ and -0.14 ppm, respectively), as did H-17 ($\Delta\delta = -0.24$ ppm). Both H-9 α and the N-methyl resonance lines showed the expected downfield shifts (Table IV) and the N-methyl absorption was a broadened singlet in all cases. No other proton absorptions which could be identified by observation had moved, compared with the spectrum of the base.

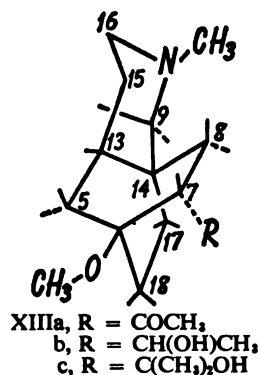
The nmr spectrum of the primary alcohol X as the conjugate with trifluoroacetic acid showed similar shifts. The H-8 α lines moved downfield by ca. 0.3 ppm (to δ 0.83) and the H-8 β lines were tentatively identified at δ 2.5, an upfield shift of ca. +0.4 ppm compared with the base. In this case, then, the difference between the chemical shifts of the geminal pair, H-8 α and H-8 β , was reduced from ca. 2.4 to ca. 1.7 ppm upon protonation of the ring nitrogen.

Spectra of protonated conjugates of the following compounds were also studied: the dimethyl tertiary carbinol IIIa and the diastereomeric secondary carbinols XIb and XIIb. The results of these experiments were similar to those just described (with IIa and X). All of these protonation experiments (Table IV) indicated a downfield shift for H-8 α which varied somewhat with different C-7 substituents. There is a possible progression for the tertiary carbinol IIIa, the secondary carbinol XIIb, and the primary carbinol X. In their nmr spectra, the H-8 α lines were found at δ 0.79, 0.69, and 0.52, respectively. In the presence of CF₃COOH and in the same order, the H-8 α lines were observed at δ 1.0, ca. 1.0, and 0.83, respectively. In the two cases where H-8 β could be located, the lines for these protons were found to have shifted upfield. The constancy of the downfield shifts for H-9 α and the N-methyl protons was also apparent (Table IV). These experiments clearly indicated that at least part of the large difference between the H-8 α and H-8 β chemical shifts is due to shielding by the ring nitrogen, rigidly held by the fused ring system. This effect is analogous to that found by Winstein and co-workers³⁵ for the hydroxyl group in half-cage hydrocarbons, but smaller in magnitude.

High- and low-temperature nmr experiments were performed on the tertiary carbinol IIIa, the secondary carbinol XIIb, and the primary carbinol X, and a low-temperature experiment only on XIb. The purpose was to investigate any observable effects on the H-8 α chemical shifts by possibly inducing more rotation about the C-19 to C-7 bond, or the effects of any additional conformers. The high-temperature experiments were run using *o*-dichlorobenzene as the solvent. The probe temperature was raised to $180 \pm 2^\circ$ without any diagnostic changes occurring from the observed ambient temperature spectra (essentially the same as deuteriochloroform spectra). In each case, of course, the hydroxyl absorption moved upfield and usually became too diffuse to locate. In the low-temperature experiments, deuteriochloroform was used as the solvent, and the probe temperature was lowered to -50

(35) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5247 (1965).

$\pm 2^\circ$. It is probable that additional conformers were present as evidenced by line broadening, but in no case was a conformer obtained that was markedly different from that present in the ambient temperature spectrum, nor was there any diagnostic shift in any of the proton resonance lines.



Three 17,18-dihydro (6,14-*endo*-ethano) derivatives XIIIa, b, and c,³⁶ formed by reduction of the C-17-C-18 double bond (or transformation of a reduced derivative) from IIa, XIIb, and IIIa, respectively,^{2a,b} provided insight to a deshielding effect on H-9 α . The lines for H-9 α , normally found around δ 3.13 (Table III) in the unsaturated compounds, had moved upfield about 0.5 ppm in the nmr spectra of XIIIa, b, and c (to δ 2.70, 2.62, and 2.63, respectively) compared with the unsaturated analogs. Since H-9 α (see configurations I-X) is rigidly held in its position relative to the C-17-C-18 double bond, this effect is an example of deshielding along the *z* axis of a double bond in accordance with Jackman's³⁷ hypothesis and in agreement with the findings of Yamaguchi, *et al.*³⁸

The two dihydro carbinols XIIIb and c also provided evidence that more than just the shielding of the ring nitrogen atom is responsible for the upfield position of the H-8 α lines. In the spectrum of XIIIb, the H-8 α lines are obscured, but they could not be higher than about δ 0.9; this was *ca.* -0.2 ppm or more downfield from the H-8 α lines (δ 0.69) in the unsaturated precursor (XIIb). This same situation was observed for the dihydro compound XIIIc; H-8 α could not be higher than about δ 1.1, and was therefore *ca.* >0.3 ppm downfield from the corresponding lines (δ 0.79) in the un-

saturated analog IIIa. The δ 0.9 region in the spectra of the dihydro compounds was obscured, probably by the C-17 and C-18 aliphatic proton patterns (which are absent from this region when H-17 and H-18 are olefinic). Coincidental decoupling of these aliphatic proton patterns prevented location of any H-8 α lines by the usual spin-decoupling experiments. The upfield position of the H-8 α resonances in the bicyclo[2.2.2]octene analogs XIIb and IIIa, compared with their saturated counterparts XIIIb and XIIIc, respectively ($\Delta\delta = +0.2$ -0.3 ppm), is similar to that observed for simpler bicyclo[2.2.2]octene derivatives^{6c} and demonstrates that the C-17-C-18 double bond may also be responsible, *in part*, for the upfield position of the H-8 α lines observed in the spectra of the C-19 carbinols studied. However, these effects are not operable in the case of the carbinols IIIb and XIa (H-8 α *ca.* δ 1.2 and 1.2, respectively).

In summary, considering the structural variations examined by nmr, the following additional conclusions are evident. There is only one major deshielding effect on H-9 α in these 6,14-*endo*-ethenotetrahydrothebaine derivatives, along the *z* axis of the C-17-C-18 double bond. Saturation of the double bond allows H-9 α to shift upfield to around δ 2.6 (a reasonable position for this type of proton). The magnitude of the various changes in the chemical shifts of H-8 α and H-8 β are undoubtedly significant, but the complexity of a number of competing effects makes a complete analysis of these shifts difficult. Particularly perplexing are explanations for the downfield shift to a more normal (bicyclo[2.2.2]octene) position of the H-8 α lines in the 7 α secondary carbinol diastereomer XIb (δ 1.20), the 7 α tertiary ether VIII (δ 1.18), and the 7 β tertiary carbinol IIIb. Although the marked separations of the shifts for the geminal 8 α and 8 β protons are clearly involved with both the nearby nitrogen atom and with the presence of the C-17-C-18 double bond, better interpretation of the observed shifts for H-8 α has not been possible, partly due to uncertainties about the conformation of C-19 substituents. Additional investigations of these interesting variations are continuing.

Acknowledgment. We wish to thank Dr. K. W. Bentley for valuable discussions and for providing generous samples of compounds as noted. Microanalyses carried out by Mr. L. Brancone and group, partition column separations carried out by C. Pidacks and group, literature assistance by Dr. M. G. Howell, and editorial service by Mrs. D. Budd are gratefully acknowledged. We also wish to thank Dr. J. J. Denton for interest and encouragement throughout these investigations.

(36) Compounds XIIIa and XIIIc were obtained from the Reckitt and Sons Ltd., Laboratories through the courtesy of Dr. K. W. Bentley. Compound XIIIb was synthesized by catalytic hydrogenation of XIIb and described by Bentley and co-workers.^{1b}

(37) A. A. Bothner-By and J. A. Pople, *Ann. Rev. Phys. Chem.*, **16**, 43 (1965). The authors interpret Jackman's hypothesis as implying deshielding on the *z* axis of a carbon-carbon double bond.

(38) S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull. (Tokyo)*, **11**, 1465 (1963).

The Crystal and Molecular Structure of Triclinic Tetraphenylporphyrin

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Abstract: The crystal and molecular structure of triclinic tetraphenylporphyrin (TPP) has been solved using X-ray crystallographic techniques. The molecule is centrosymmetrical with two independent pyrrole and phenyl groups. Although the individual pyrrole and phenyl groups are planar within the error of their determination (<0.005 Å), the porphyrin ring is nonplanar. One pair of centrosymmetrical pyrroles is essentially coplanar with the nuclear least-squares (NLS) plane of the porphyrin ring; the other pair, carrying the central hydrogen atoms, is inclined $\pm 6.6^\circ$ to this plane. The tilt of the latter is such that the distance between the central hydrogens is increased by 0.2 Å, to 2.36 Å. Both phenyl groups of TPP are rotated out of the NLS plane by about 60° ; one phenyl is additionally inclined to this plane by $\pm 9.1^\circ$. Although the porphyrin ring is nonplanar, the atoms of the inner 16-membered ring are individually planar, and the bond distances of this ring resemble those of a heterocyclic aromatic system. The 1,2 and 3,4 bond lengths of the independent pyrroles correspond closely to isolated double bonds and to this extent appear isolated from the inner ring; the phenyl groups also appear to be electronically isolated from the ring through shortened single bonds. The structure described herein corresponds closely with the hybrid of the two classical resonance forms of the porphyrin molecule. Finally, the fine points of the structure are discussed in terms of the molecular packing in the crystal.

Tetraphenylporphyrin (α , β , γ , δ) ($C_{44}H_{30}N_4$, see Figure 2), hereinafter referred to as TPP, is a synthetic nonmetalloporphyrin derivative. TPP is related to naturally occurring porphyrins by having the same macrocyclic skeletal structure, which consists of four pyrrole groups alternately linked through methine carbon bridges.

The metalloporphyrin ring is found in a variety of important biological systems where it is either the active component of the system or in some way intimately connected with the activity of the system. Many of these biological porphyrin systems differ markedly in their behavior and it appears that this is due in large part to: (a) the effects of a central metal ion on the bonding system of the porphyrin ring, (b) the ease with which the porphyrin ring can assume various nonplanar conformations, (c) the chemistry and the stereochemistry of side chains of the porphyrin ring, and (d) the general molecular environment of the porphyrin in the biological system.

Porphyrins also possess an intrinsic interest in that they are examples of an extremely stable heteromacrocyclic π -bonding system with the ability to complex readily with many different metal ions. Although there are other ligands that behave similarly, the porphyrins are unusual in that they, as the ligand, act as the host to the metal ion. In the case of free-base porphyrins, additional interest centers about the exact nature of the central acidic hydrogen atoms. If the porphyrin skeleton were planar or nearly so, the two central hydrogens bound to opposite pyrrole groups would approach one another within about 2.0 Å. This would indeed be a close van der Waals contact and at the onset of this work, it seemed unlikely. Therefore, in the beginning, the nature of the central hydrogen atoms and their environment were of most concern to this structural determination. However, it has resulted since that other structural characteristics of the molecule of at least equal interest.^{2,3}

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Experimental Section

Single crystals of TPP were grown by slowly evaporating solutions of TPP in benzene, chloroform, and dioxane.⁴ All the crystals were elongated purple prisms, but those grown from benzene and chloroform were soft and did not diffract X-rays well. The crystals from dioxane, grown under a nitrogen atmosphere, were hard, slightly translucent, and good X-ray scatterers. One of these crystals, with approximate dimensions of $0.75 \times 0.20 \times 0.05$ mm and with well-developed end faces, was used for X-ray examination because of its size and apparent crystal quality.

All the X-ray work was carried out with Cu K α radiation and a General Electric XRD-5 equipped with a single-crystal orienter and a scintillation counter assembly. A survey of the diffraction pattern indicated that the crystal system was triclinic. By convention, the unit cell was chosen to be primitive and reduced with the three axes forming a right-handed coordinate system. The unit cell so chosen has the dimensions: $a = 6.44 \pm 0.01$, $b = 10.42 \pm 0.01$, $c = 12.41 \pm 0.01$ Å, $\alpha = 96.06 \pm 0.05$, $\beta = 99.14 \pm 0.05$, $\gamma = 101.12 \pm 0.05^\circ$, $V = 801.9 \pm 1.2$ Å³. The crystal density calculated on the basis of these dimensions and one molecule of TPP per unit cell is 1.273 g/cm³. The density of several single crystals was measured to be 1.27 ± 0.01 g/cm³ by suspending the crystals in a solution of silver nitrate and water. Thus, the number of molecules per unit cell was taken to be one.

In the triclinic case the required intensity data are confined within half of the limiting sphere. Since the single-crystal orienter used in this work was a quarter-circle model, once the crystal was mounted the segment of the sphere to be collected was fixed. Mosaic spreads of several reflections were therefore measured only to ensure that the crystal quality was sufficient for intensity data collection purposes. The spreads proved to be symmetrical and ranged from 0.3 to 0.6° in width, from background to background.

The intensities of the reflections were measured by the stationary crystal-stationary counter technique. In order to avoid K α_1 and K α_2 splitting effects, the data collection was confined to reflections with scattering angles (2θ) less than 110° , which corresponds to 0.94-Å resolution. Of the 2007 independent reflections possible to this limit, the intensities of 1726 (86%) were large enough to be observed. During the intensity measurements the crystal was exposed to X-rays for about 33 hr, but its reflecting power was

(2) For extensive reviews of structural studies of porphyrins, see T. A. Hamor, W. S. Caughey, and J. L. Hoard, *J. Am. Chem. Soc.*, **87**, 2305 (1965); L. E. Webb and E. B. Fleischer, *J. Chem. Phys.*, **43**, 3100 (1965), and references contained therein.

(3) For a preliminary report of this work, see S. Silvers and A. Tulinsky, *J. Am. Chem. Soc.*, **86**, 927 (1964).

(4) A highly purified sample of TPP was kindly provided by Dr. Henry E. Rosenberg.

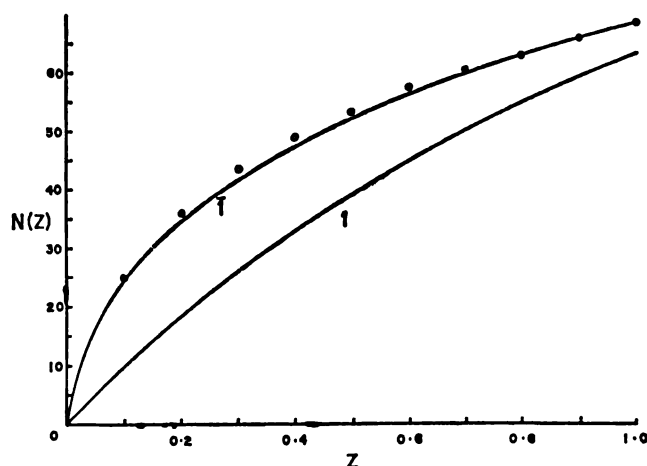


Figure 1. The observed intensity distribution of TPP, O, and theoretical distributions for P1 and $\bar{P}1$, —.

not thereby altered; the intensities of four reflections which were monitored throughout the measurement period remained constant.

The intensities were corrected for absorption with a correction obtained by averaging intensity vs. ϕ curves (azimuthal orientation) of two reflections with χ values of 90° ; the average curve had a maximum:minimum ratio of 1.10. The intensities so corrected were converted to structure amplitudes, and the latter were then scaled with the results of Wilson's method to approximate an absolute scale.

Structure Determination

The Center of Symmetry. The observed reflections were divided according to scattering angle into five groups. These were: (1) $2\theta < 30.00$, (2) $30.00 \leq 2\theta < 56.16$, (3) $56.16 \leq 2\theta < 75.00$, (4) $75.00 \leq 2\theta < 92.99$, and (5) $92.99 \leq 2\theta \leq 110.00^\circ$. The first group, containing 50 reflections, was ignored in further considerations for theoretical reasons.⁵ For each of the other four, the percentage, $N(z)$, of reflections with $|F|^2$ less than or equal to a fraction, z , of the group average was plotted as a function of z . The unobserved reflections were included with zero structure amplitudes. In Figure 1, the average of these plots is indicated by open circles and the two theoretical distributions for P1 and $\bar{P}1$ are shown by solid curves. Clearly, the observed $|F|^2$ distribution is centrosymmetric and the space group of the crystal is therefore $\bar{P}1$.

The Patterson Function and the Orientation of TPP. Since there is only one TPP molecule per unit cell and the space group is $\bar{P}1$, the molecule itself must be centrosymmetric. By taking the molecular center of symmetry as the unit cell origin, the translational parameters of TPP are fixed. Since the gross structure of the molecule was known, the determination of a trial structure reduced simply to the determination of an approximate angular orientation for the molecule.

In order to determine the angular orientation of the TPP molecule, a three-dimensional Patterson function was computed using the squares of the observed amplitudes as coefficients. The significant positive regions of this function were confined to the region of the plane which is parallel to the $(\bar{1}\bar{2}1)$ planes and passes through the origin. If the vectors between atoms lie close to a plane, the atoms themselves also must lie close to that plane. Therefore, the $(\bar{1}\bar{2}1)$ plane was concluded

(5) A. J. C. Wilson, *Acta Cryst.*, 2, 318 (1949).

to be the approximate mean plane of the molecule. In support of this conclusion, the structure amplitudes of the $(\bar{1}\bar{2}1)$, $(\bar{1}\bar{3}1)$, and $(\bar{1}\bar{2}0)$ reflections were, in that order, the largest reflections of all those observed and significantly so.

At this stage, the molecule was assumed to be strictly planar except for undertermined rotations of the four phenyl groups about the bonds joining them to the bridge carbon atoms between the pyrroles. The mean plane of the molecule, in accordance with the Patterson function, was taken to pass through the origin and lie parallel to the $(\bar{1}\bar{2}1)$ planes. Thus, there remained to be determined only the orientation of the model molecule within this plane. As a further simplification, this planar model of TPP was assigned a fourfold rotation axis so as to fix its orientation within 90° .

The model was then systematically rotated about its fourfold axis 12 times (7.5° each time). In this way, the "correct" orientation would approach within 3.75° of one of these 12 positions (since a 90° rotation superimposes the model upon itself). For each orientation the coordinates of the model molecule (excluding the four atoms of each phenyl group which were expected for steric reasons to lie rotated out of the plane) were determined and a set of structure factors was computed. An over-all isotropic thermal parameter of 2.0 \AA^2 , estimated from Wilson's method, was used in each calculation. The R value for each set of structure factors was then examined as a function of the orientation of the model. The R values fluctuated about the value of 0.73 ± 0.03 but one was considerably smaller than all the others (0.68). The point Patterson function of the model in the orientation corresponding to this minimum R was then compared with the observed Patterson in the $(\bar{1}\bar{2}1)$ plane. Since the principal features of the two were in good agreement the orientation of the TPP molecule was taken to correspond with the minimum R value.

The phases of this set of structure factors were assigned to the observed amplitudes and an electron density (ρ_1) was computed. The carbon and nitrogen atoms of the porphyrin nucleus all appeared in ρ_1 at peak heights of approximately 6 e\AA^{-3} or more. However, the positions of these peaks were in some cases noticeably different from those of the model structure. This was expected, since the deduced orientation of the model was not exact and its planarity and fourfold symmetry were approximations.

The eight next-to-the-largest peaks in ρ_1 (average peak height of 3.7 e\AA^{-3}) besides those of the 16 model atoms were recognized to be the phenyl carbon atoms not included in the model. The terminal atom of one phenyl group in the model appeared in ρ_1 as an atom adjacent to the true terminal position. This phenyl group, as observed in ρ_1 , was thus bent out of the plane of the model as well as rotated about the bond from its proximal atom to the porphyrin ring. The other phenyl group was not bent out of the plane but only rotated and its terminal atom corresponded to that of the model. Thus, although the phases employed to obtain ρ_1 were determined by a model which was a considerable oversimplification of the true structure, nevertheless, they were able to reveal a structure that was neither planar nor fourfold symmetrical, which corresponded in most of its essentials to that of the final structure.

Table I. Final Atomic Parameters, Carbon and Nitrogen^a

Atom	<i>x</i>	<i>y</i>	<i>z</i>	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	Peak height, eÅ ⁻³
C-1	0.1447	0.9597	0.6741	0.0254	0.0101	0.0072	0.0011	0.0037	-0.0002	6.3
C-2	0.3195	0.0528	0.7251	0.0278	0.0096	0.0065	0.0010	0.0034	0.0002	6.3
C-3	0.4046	0.7191	0.8866	0.0255	0.0100	0.0072	-0.0005	0.0016	0.0005	6.5
C-4	0.4799	0.7166	0.7913	0.0244	0.0094	0.0070	-0.0007	0.0019	0.0005	6.3
C-5	0.0216	0.9194	0.7558	0.0214	0.0075	0.0063	0.0012	0.0020	-0.0002	6.8
C-6	0.3128	0.0721	0.8397	0.0214	0.0071	0.0061	0.0008	0.0021	0.0004	7.0
C-7	0.4327	0.1904	0.0308	0.0204	0.0073	0.0059	0.0007	0.0013	0.0002	7.2
C-8	0.3110	0.1929	0.1852	0.0217	0.0068	0.0059	0.0008	0.0002	0.0000	6.9
C- α	0.4535	0.1661	0.9204	0.0218	0.0075	0.0069	0.0018	0.0023	0.0009	7.1
C- β	0.1790	0.1685	0.2634	0.0218	0.0072	0.0062	0.0010	0.0009	0.0002	7.0
N-1	0.1300	0.9885	0.8554	0.0204	0.0070	0.0062	0.0018	0.0012	0.0001	8.6
N-2	0.2641	0.1371	0.0769	0.0214	0.0068	0.0061	0.0006	0.0017	0.0002	8.7
$\phi_{\alpha-1}$	0.3634	0.7481	0.1171	0.0202	0.0084	0.0065	0.0018	0.0028	0.0009	7.2
$\phi_{\alpha-2}$	0.2087	0.7995	0.1608	0.0255	0.0106	0.0093	0.0040	0.0037	0.0016	6.3
$\phi_{\alpha-3}$	0.0428	0.7191	0.1968	0.0245	0.0127	0.0096	0.0015	0.0038	0.0023	5.7
$\phi_{\alpha-4}$	0.0315	0.5849	0.1885	0.0279	0.0116	0.0085	-0.0016	0.0029	0.0017	6.3
$\phi_{\alpha-5}$	0.1842	0.5318	0.1438	0.0338	0.0089	0.0086	0.0008	0.0044	0.0015	5.8
$\phi_{\alpha-6}$	0.3505	0.6128	0.1096	0.0292	0.0080	0.0082	0.0013	0.0024	0.0003	6.3
$\phi_{\beta-1}$	0.2579	0.2393	0.3788	0.0295	0.0079	0.0062	0.0009	0.0019	0.0005	6.5
$\phi_{\beta-2}$	0.4446	0.2222	0.4422	0.0286	0.0140	0.0063	0.0012	-0.0011	0.0018	5.8
$\phi_{\beta-3}$	0.4859	0.7101	0.4509	0.0376	0.0168	0.0069	-0.0003	-0.0014	0.0023	5.1
$\phi_{\beta-4}$	0.3981	0.3729	0.5913	0.0557	0.0151	0.0081	0.0011	0.0018	0.0001	4.7
$\phi_{\beta-5}$	0.2136	0.3893	0.5297	0.0514	0.0133	0.0069	0.0039	0.0014	-0.0025	5.1
$\phi_{\beta-6}$	0.1422	0.3232	0.4236	0.0406	0.0112	0.0073	0.0040	0.0030	-0.0014	5.7
$\sigma \times 10^4$	6-10	4-5	3-4	15-30	5-10	4-7	6-14	5-11	3-7	

^a Anisotropic temperature factor = $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

Refinement of the Structure

The Fourier Refinement. New atomic coordinates were obtained from ρ_1 for all the carbon (22) and nitrogen (2) atoms; they were used to compute a new set of structure factors and the new phases were used to compute ρ_2 . The phenyl groups in ρ_2 were all of the order of 5–6 eÅ⁻³ at peak height and their positions indicated considerable shifts from their ρ_1 coordinates. Coordinates from ρ_2 were used to begin a series of four structure-factor and related electron- and difference-density computations. Individual isotropic temperature factors were introduced after one cycle and the *R* factor went 0.46, 0.33, 0.19, and 0.16 for the four cycles of refinement. The last difference density showed clearly positive and negative regions in the vicinity of atomic positions, indicating anisotropic thermal motion. At this state it was decided to introduce anisotropic thermal parameters and to continue the refinement by the method of least squares.

The Least-Squares Refinement. A weighting scheme similar to that of Hughes was chosen for the least-squares refinement. For $|F_o| \leq 6.0$, the assigned weight was $1/(0.6)^2$, and for $|F_o| > 6.0$, it was $1/(0.1|F_o|)^2$. The initial parameters for least-squares refinement were those of the last Fourier cycle. These included isotropic temperature factors which, before conversion to anisotropic, were varied with scale factor for two cycles of least-squares refinement. The shifts from the second cycle were small and isotropic refinement was terminated at *R* = 0.122.

Refinement including anisotropic thermal parameters proceeded by varying the thermal parameters of only six atoms per cycle. The four groups of six atoms chosen were the two phenyl and the two pyrrole plus methene bridge atom groups. The groups were chosen to be physically distinct, since only the temperature parameters of atoms adjacent to one another are likely to have interdependent shifts. Each group of thermal

parameters (6 per atom, 36 total) was varied for one cycle. At the end of these four cycles, the *R* factor was 0.091.

A difference density was then computed based on the last structure-factor computation. The 15 largest peaks in this density, varying from 0.3 to 0.6 eÅ⁻³, were located in the vicinity expected for the 15 hydrogen atoms of the asymmetric unit. They included the peak of the central hydrogen atom whose location was of particular interest. The hydrogen atoms, each with coordinates taken from the difference density and anisotropic thermal parameters identical with the atoms to which they were bonded, were included in the structure factors computed for the next least-squares cycle. This cycle varied the positions of all carbon and nitrogen atoms and the position and thermal parameters of the central hydrogen atom. The adjusted thermal parameters of the central hydrogen were not positive definite; consequently, the changes were ignored. A new set of structure factors was computed and these were used to compute a final difference density. The regions of all the atomic positions in this density were close to zero and, except for hydrogen atoms, no significant parameter shifts were indicated. The largest positive regions were of the order of 0.2 eÅ⁻³. A final structure factor computation included all 39 atoms. The hydrogen atom coordinates for this computation incorporated shifts from the final difference density; all other atomic parameters were those of the last least-squares cycle. The final value of *R* was 0.056.

Results

The final coordinates and anisotropic thermal parameters of the carbon and nitrogen atoms are listed in Table I, the atoms therein labeled according to Figure 2. Hydrogen atom coordinates are given in Table II; their thermal parameters are the same as the atoms to which they bond. In Table III are listed the three

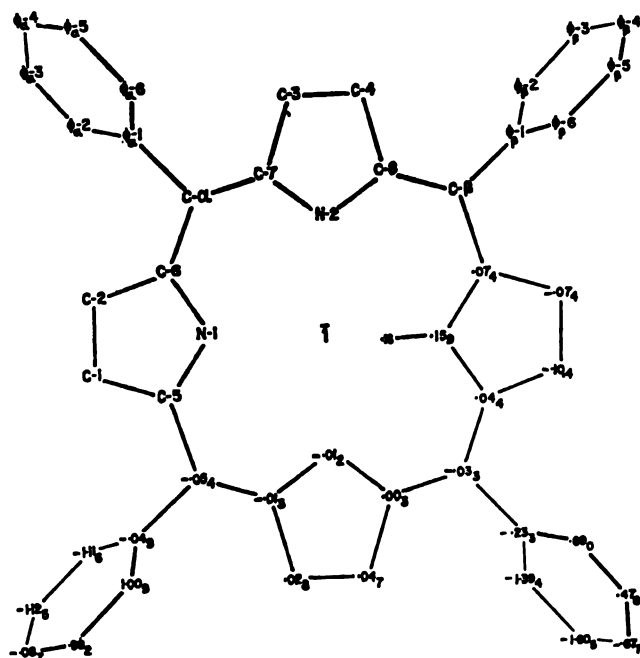


Figure 2. Deviations (in Å) of the atoms of TPP from the nuclear least-squares plane (NLS). The labeling system of the atoms is also shown.

principal axes of the thermal ellipsoid of each atom, the direction cosines of each principal axis with respect to the direct cell axes, and the mean-square atomic displacement along each principal axis.

Table II. Final Hydrogen Atom Coordinates

Atom	x	y	z	Peak height, eÅ ⁻¹
H(C-1)	0.109	0.922	0.592	0.6
H(C-2)	0.433	0.098	0.685	0.5
H(C-3)	0.263	0.671	0.903	0.5
H(C-4)	0.417	0.653	0.719	0.5
H(N-1)	0.082	0.988	0.922	0.4
H($\phi_{\alpha-2}$)	0.229	0.900	0.179	0.4
H($\phi_{\alpha-3}$)	0.079	0.239	0.780	0.5
H($\phi_{\alpha-4}$)	0.076	0.468	0.774	0.5
H($\phi_{\alpha-5}$)	0.180	0.426	0.136	0.5
H($\phi_{\alpha-6}$)	0.466	0.577	0.075	0.6
H($\phi_{\beta-2}$)	0.467	0.844	0.587	0.6
H($\phi_{\beta-3}$)	0.361	0.731	0.422	0.5
H($\phi_{\beta-4}$)	0.453	0.423	0.669	0.4
H($\phi_{\beta-5}$)	0.123	0.449	0.557	0.3
H($\phi_{\beta-6}$)	0.017	0.665	0.621	0.5

A plane was fitted to the 24 carbon and nitrogen atoms of the porphyrin nucleus by the method of least squares.⁶ The determined plane, which necessarily passes through the center of symmetry of the molecule, has the equation of $(3.799)x - (9.112)y + (3.042)z = 0$. In Figure 2, the perpendicular distances of the atoms from this plane are given. Least-squares planes were determined similarly for the individual phenyl and pyrrole groups of TPP. For comparison, the distances of the respective atoms from these planes are given in Table IV.

(6) V. Schomaker, J. Waser, R. E. Marsh, and G. Bergman, *Acta Cryst.*, 12, 600 (1959).

Table III. The Principal Axes of the Anisotropic Thermal Ellipsoids for the Carbon and Nitrogen Atoms of TPP. Direction Cosines of the Principal Axes Are with Respect to the Unit Cell Axes \vec{a} , \vec{b} , \vec{c}

Atom	$\cos(\vec{a}, \vec{p})$	$\cos(\vec{b}, \vec{p})$	$\cos(\vec{c}, \vec{p})$	$8\pi^2 \mu^2, \text{Å}^2$
C-1	0.4745	-0.7374	0.5873	5.42
	0.7050	0.5330	-0.0156	3.55
	-0.5268	0.4151	0.8092	3.63
C-2	0.7077	-0.6987	0.3710	5.16
	0.0680	0.6124	0.6510	3.50
	-0.7030	-0.3698	0.6626	3.69
C-3	0.7285	-0.8097	0.0415	5.29
	0.6173	0.5622	0.1673	3.18
	-0.2892	-0.1756	0.9856	4.40
C-4	0.7243	-0.8022	0.1150	5.10
	0.6231	0.5939	0.0801	3.00
	-0.2940	-0.0623	0.9903	4.20
C-5	0.2661	-0.6294	0.7853	4.21
	0.3121	0.7263	0.3378	2.75
	-0.9120	0.2764	0.5189	3.45
C-6	-0.5856	-0.6109	0.5952	3.87
	0.4390	0.7534	0.0845	2.69
	-0.6812	0.2432	0.7993	3.51
C-7	0.4290	-0.7237	0.6324	3.76
	0.4931	0.6389	0.2521	2.61
	-0.7567	0.2606	0.7327	3.61
C-8	-0.7412	0.0432	0.7804	4.11
	0.3816	0.6617	0.3644	2.44
	0.5520	-0.7485	0.5083	3.56
C- α	-0.0014	-0.1288	0.9875	4.08
	0.4266	0.7974	-0.0752	3.00
	-0.9044	0.5896	0.1388	3.56
C- β	-0.6024	-0.0410	0.8822	3.99
	0.4045	0.6906	0.2885	2.67
	0.6878	-0.7221	0.3724	3.71
N-1	-0.2540	-0.3605	0.9512	3.94
	0.3007	0.7499	0.3084	2.71
	0.9192	-0.5547	-0.0108	3.30
N-2	0.5104	-0.6098	0.6599	3.85
	0.3836	0.7600	0.1743	2.55
	-0.7693	0.2247	0.7311	3.63
$\phi_{\alpha-1}$	0.3411	-0.4745	0.8274	3.94
	-0.8669	-0.3098	0.3132	2.95
	-0.3636	0.8238	0.4664	3.57
$\phi_{\alpha-2}$	0.0660	0.0063	0.9620	5.48
	-0.9961	0.2509	0.2132	3.80
	-0.0585	-0.9685	0.1705	4.35
$\phi_{\alpha-3}$	-0.2448	0.6416	0.6949	5.91
	-0.8774	-0.2925	0.2954	3.49
	0.4124	-0.7088	0.6559	5.34
$\phi_{\alpha-4}$	-0.7162	0.8144	0.1251	6.34
	-0.6907	-0.5757	0.2375	3.30
	0.0977	-0.0726	0.9634	4.99
$\phi_{\alpha-5}$	0.8563	-0.4294	0.3322	5.83
	-0.3444	-0.8497	0.2807	3.38
	-0.3846	0.3060	0.9005	4.90
$\phi_{\alpha-6}$	0.2063	-0.3838	0.9089	5.02
	0.2111	0.8694	0.1392	3.17
	-0.9553	0.3109	0.3938	4.80
$\phi_{\beta-1}$	0.9633	-0.4482	-0.0969	4.97
	0.2334	0.8106	0.2626	3.08
	-0.1320	-0.3769	0.9600	3.78
$\phi_{\beta-2}$	-0.6285	0.8122	0.3250	6.63
	0.4940	-0.0626	0.7662	3.08
	-0.6008	-0.5800	0.5544	4.83
$\phi_{\beta-3}$	-0.7124	0.7683	0.2988	8.71
	0.3712	-0.0566	0.8480	3.54
	-0.5955	-0.6366	0.4378	5.51
$\phi_{\beta-4}$	-0.9589	0.4631	0.1200	9.60
	0.1116	0.3255	0.8410	4.50
	-0.2607	-0.8244	0.5275	6.43
$\phi_{\beta-5}$	-0.9958	0.1088	0.2009	8.23
	-0.0162	0.5051	0.7713	2.98
	0.0888	-0.8561	0.6039	7.12
$\phi_{\beta-6}$	0.9655	-0.2828	0.0958	6.34
	-0.1357	0.6141	0.7097	3.24
	-0.2227	-0.7366	0.6979	5.99

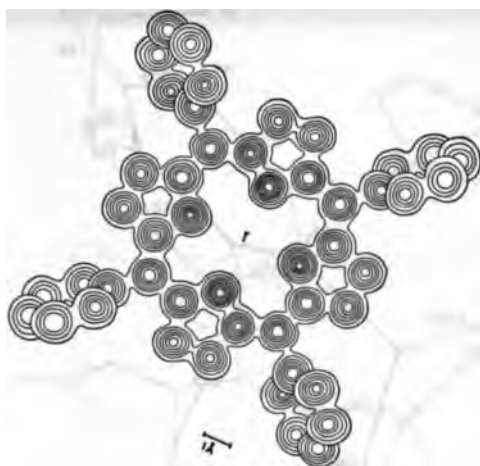


Figure 3. Final electron density for TPP viewed perpendicular to the NLS plane. Contours at 1-eA^{-3} intervals, starting at 1 eA^{-3} .

Figure 3 views the final electron density along the perpendicular to the least-squares plane of the porphyrin nucleus. The hydrogen atoms, obtained from the difference density preceding the final one, are seen in the same manner in Figure 4. In Figure 5, intramolecular distances and angles are given.

Table IV. The Atomic Deviations from the Least-Squares Planes of the Individual Pyrrole and Phenyl Rings

Atom	<i>d</i> , Å	Atom	<i>d</i> , Å
Pyrrole N-1		Pyrrole N-2	
N-1	0.006	N-2	0.008
C-1	0.006	C-3	0.006
C-2	-0.003	C-4	-0.001
C-5	-0.007	C-7	-0.008
C-6	-0.002	C-8	-0.004
σ	0.005	σ	0.006
Phenyl α		Phenyl β	
$\phi_{\alpha-1}$	0.001	$\phi_{\beta-1}$	0.003
$\phi_{\alpha-2}$	0.003	$\phi_{\beta-2}$	-0.002
$\phi_{\alpha-3}$	-0.002	$\phi_{\beta-3}$	-0.001
$\phi_{\alpha-4}$	-0.004	$\phi_{\beta-4}$	0.003
$\phi_{\alpha-5}$	0.008	$\phi_{\beta-5}$	-0.002
$\phi_{\alpha-6}$	-0.006	$\phi_{\beta-6}$	-0.002
σ	0.004	σ	0.003

Standard deviations of the carbon and nitrogen atom coordinates and the thermal parameters were obtained from the least-squares refinement. Their range is indicated at the end of Table I. The atomic parameters are determined most accurately in the porphyrin nucleus, less accurately in phenyl α , and least accurately in phenyl β . The standard deviation of the final electron and difference densities is estimated at $0.15\text{--}0.20\text{ eA}^{-3}$. The standard deviations of the lengths and angles of the carbon-carbon and carbon-nitrogen bonds are approximately $0.005\text{--}0.01\text{ Å}$ and $0.5\text{--}0.8^\circ$, respectively; those of the carbon-hydrogen and nitrogen-hydrogen bond distances are of the order of 0.05

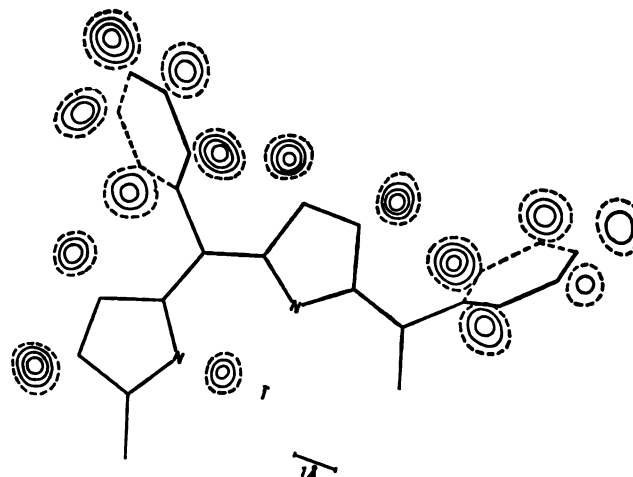


Figure 4. Hydrogen atom regions for TPP viewed perpendicular to the NLS plane. Contours at 0.1-eA^{-3} intervals, starting at 0.2 eA^{-3} , ----.

A. Again, the accuracy is better for the bonds and angles of the porphyrin nucleus than for those of the phenyl groups.

Discussion of the Results

From Figure 2, it can be seen that the TPP molecule in the triclinic crystal form is significantly nonplanar in several respects: the phenyl and pyrrole rings are separately planar within the error of their determinations (see Table IV) but they are rotated and inclined with respect to the nuclear least-squares (NLS) plane of the molecule.

The N-1 pyrrole groups are tilted out of the NLS plane about an axis lying in the plane and passing through the C-2-C-6 and C-1-C-5 bonds. The perpendicular to the N-1 pyrrole plane makes a 6.6° angle with that of the NLS plane. The N-2 pyrrole groups are only tilted 1.4° with respect to the NLS plane about an axis through C-7 and the C-4-C-8 bond. The former and larger tilt causes the central hydrogen atom of one N-1 pyrrole group to lie 0.18 Å above the NLS plane and that of the centrosymmetrically related group to lie the same distance below. Consequently, the distance between the two central hydrogen atoms (2.36 Å) is about 0.2 Å greater than it would be for a planar conformation.

As the relationships of the two types of pyrrole group to the NLS plane differ, so do those of the two types of phenyl group. The 1-4 axis of phenyl α is tilted much more with respect to the NLS plane than is the same axis of phenyl β , and in a different manner. The phenyl α 1-4 axis makes a 9.1° angle with its projection onto the NLS plane and intercepts the plane near C- α ; the corresponding angle for the phenyl β axis is only 0.8° . If the phenyl groups were coplanar with the NLS plane, then to transform them to their true positions, they must be first tilted along their 1-4 axis so that atoms 1 and 4 are in their correct positions, and then the phenyl groups must be rotated about these axes. The required angles of tilt are given above; the rotation angles are 61.0° for phenyl α and 63.1° for phenyl β .

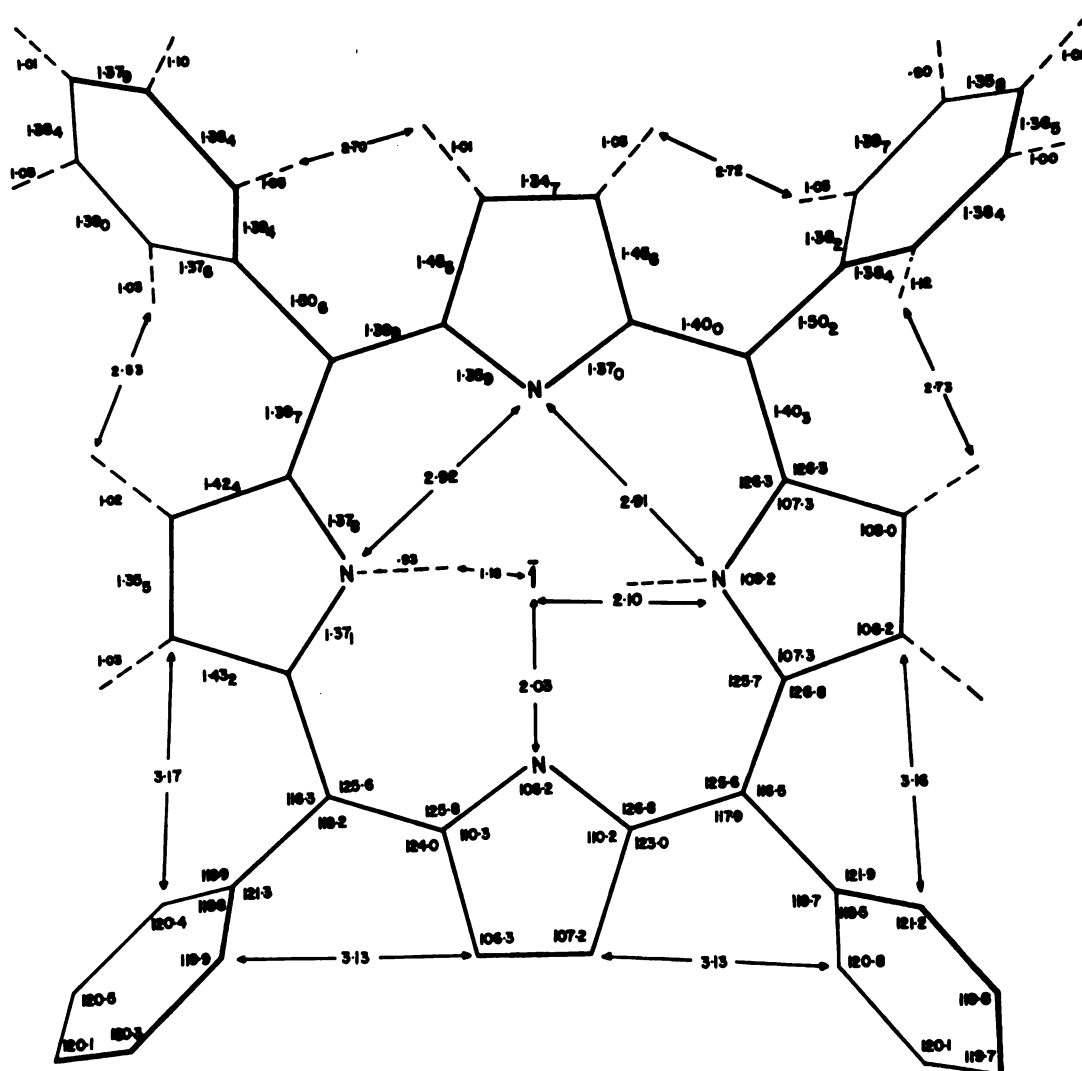


Figure 5. Distances (in Å) and bond angles (in degrees) for TPP. Bonds to hydrogen atoms are broken.

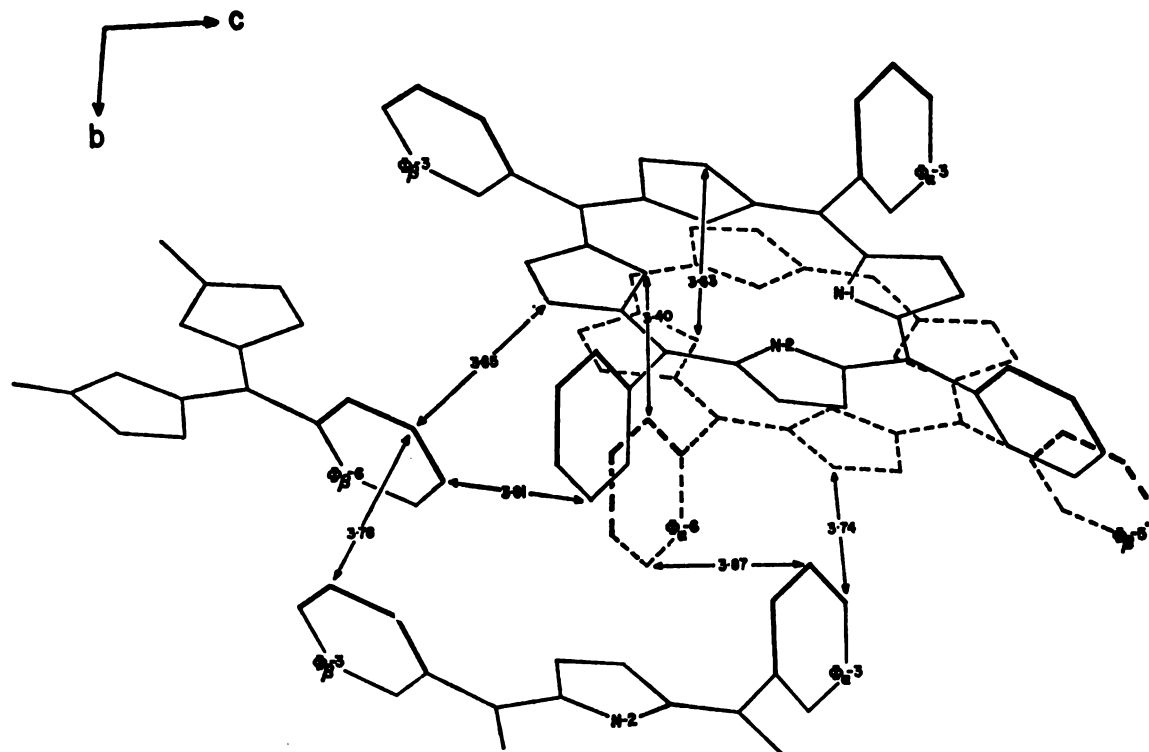
The phenyl groups are thus rotated more than 60° out of the NLS plane and, furthermore, the α groups are tilted so the $\phi_{\alpha-4}$ lies 0.68 Å from the plane. The phenyl rotation is as expected, since otherwise the phenyl hydrogen atoms proximal to the porphyrin ring would interfere with the pyrrole hydrogen atoms. The tilt, however, is unexpected. Conceivably, it could result from bond angle requirements of the central π -bonding system (preserving individual planar atoms, as is observed). However, it is more likely due to the manner in which the molecules pack. The closest intermolecular contact (3.40 Å, see Figure 6) occurs between N-1 of one molecule and $\phi_{\alpha-2}$ of the neighboring molecule along the \bar{a} direction.

Also of note is the packing mode of the pyrrole groups of molecules adjacent along the \bar{a} direction. If the molecules are viewed along the perpendicular to the NLS plane, it is seen that an N-1 and an N-2 pyrrole group of one molecule lie, respectively, perpendicularly above an N-2 and N-1 group of the molecule below. The pyrrole pair in the upper molecule is related by a center of symmetry and an \bar{a} translation to the lower pair. The closest intermolecular contact between these pyrrole groups is 3.63 Å, from C-3 in one molecule to N-1 of the other. This contact and the way in which

phenyl groups of neighboring molecules are related are shown in Figure 6.

Temperature-factor anisotropy (see Table III) is least for atoms of the porphyrin ring; it increases for the phenyl α atoms and is largest for the phenyl β atoms. The mean-square atomic displacements vary from atom to atom in the same manner as do the standard deviations of the atomic parameters. The mean-square displacement of a particular atom in the radial direction (toward or away from the molecular center) is usually less than in its tangential directions. The above properties of the thermal motion may probably be partly attributed to quasi-rigid angular oscillations about the molecular center. The larger mean-square displacements of phenyl β relative to phenyl α are probably a consequence of the closer packing of phenyl α .

From Figure 5, it appears that the atoms of the *interior ring* of the porphyrin skeleton form a heterocyclic aromatic system (C-5, N-1, C-6, C- α , C-7, N-2, C-8, C- β). The carbon-carbon bond distances of this system average 1.400 ± 0.002 Å and the carbon-nitrogen distances average 1.370 ± 0.007 . Furthermore, although the atoms of this system do not lie in a plane, the bonding about C-5, C-6, C- α , C-7, C-8, C- β is in



6. Packing of TPP molecules of neighboring unit cells viewed in the $-a^*$ direction. In relation to the molecule shown completely, the molecule on the left is translated along $-a$, the molecule on the right is translated along $-c$, and the molecule in the foreground is translated along b and a . Close intermolecular contacts are given (in Å).

are planar (sum of the bond angles equals 360°). The C-1-C-2 and C-3-C-4 bonds of the pyrroles correspond closely in length to double bonds and to this these atoms appear to be isolated from the inner ring system with the bonds joining these four to the interior ring being shorter than normal bonds. Finally, the phenyl groups appear to be electronically isolated from the inner ring system; the phenyls are bound to the bridge positions through essentially shortened single bonds.

Adding Remarks

Closing, it should be interesting to note that the pyrrole structure herein described corresponds closely to the structure expected of a hybrid of the two prevalent classical resonance forms of the porphyrin molecule. These two forms are shown in Figure 7a and b; Figure 7c is an attempt at representing the expected nature of the hybrid. Also given in Figure 7c are the carbon-carbon and carbon-nitrogen distances of the independent pyrrole groups (observed distances), the carbon-carbon distance involving the methene bridges (an observed average with a standard deviation of ± 0.002 Å) and the differences between the average distances of the independent pyrroles and differences (Δ) between corresponding bonds in the manner expected of the hybrid.

Since a corresponding trend can also be detected considering the bond angles, the behavior is probably constant.

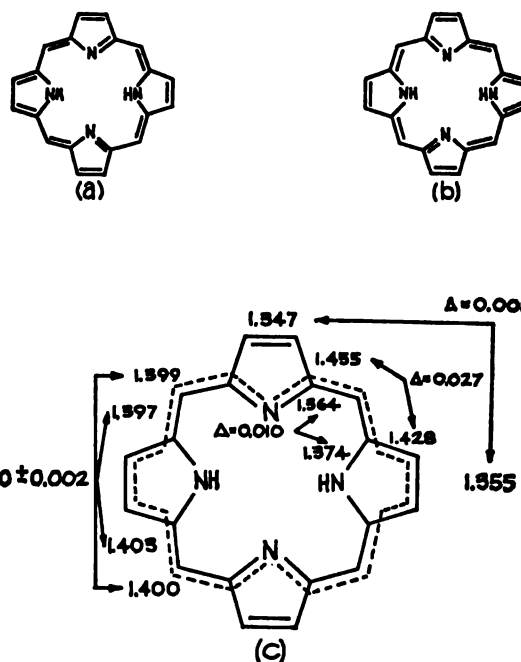


Figure 7. (a and b) Two dominant resonance structures of TPP. (c) Expected nature of the hybrid; the mean observed distances of independent pyrroles and differences (Δ) between corresponding bonds are also shown.

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Biosynthesis of Cholesterol by Seedlings of *Digitalis purpurea*

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Abstract: Three- and four-week old seedlings of *Digitalis purpurea* were incubated with mevalonic acid-2-¹⁴C and found to incorporate 4.8 and 3.6% of the label into a mixture of sterols. Of the radioactivity of the sterol fraction 24–31% was found associated with cholesterol. Cholesterol comprises about 3% of the weight of all sterols. The high incorporation of radioactivity into cholesterol and its small weight compared to other sterols support the hypothesis that cholesterol is an intermediate in plant sterol biosynthesis. The sterols were found as water-soluble conjugates.

For many years cholesterol was thought to be a sterol peculiar to animals. This view could no longer be maintained when Tsuda, *et al.*,¹ found cholesterol in red algae; Johnson, *et al.*,² found the sterol in *Solanum tuberosum* and *Dioscorea spiculiflora*; Devys and Barbier³ found it in the pollen of *Hypochoris radicata*; and Linde, *et al.*,⁴ found it as constituent of "γ"-sitosterol from *Digitalis canariensis*. Recently, Caspi, *et al.*,⁵ have shown that cholesterol can be degraded to pregnenolone by whole *D. purpurea* plants, and Tschesche and Lilienweiss⁶ have demonstrated that the steroid in pregnenolone-β-D-glucopyranoside can be converted to digitoxigenin by excised leaves of *D. lanata*. These reports have led to speculation that cholesterol represents an intermediate in the biosynthesis of plant steroids. In the present paper we describe the synthesis of radiocholesterol from mevalonic acid-2-¹⁴C by seedlings of *D. purpurea*.

Experimental Section

Materials. Seeds of *D. purpurea* were acquired from Burnett-Seedsman, New York, N. Y. dl-Mevalonic acid-2-¹⁴C, as the dibenzylethylenediamine salt, was purchased from New England Nuclear Corp. All chemicals were reagent grade. Methylene chloride, alcohols, benzene, and water were distilled.

Growth and Incubation of Seedlings. Two experiments with separate batches of seeds were performed. Experiment 1 was run 8 months prior to the other and will be described in detail. Experiment 2 differed from the first in age and amount of seedlings and quantity of administered mevalonic acid-2-¹⁴C, as indicated below.

Seeds of *D. purpurea* were grown on nutrient agar plates for 21 days at room temperature and in the dark. Seeds were briefly soaked in 95% ethanol, transferred to a 1% sodium hypochlorite solution, washed with water, and blotted on several layers of filter paper under aseptic techniques. Approximately 2400 seeds were spread over the surface of an agar plate in a glass dish, 10 cm in diameter and 8 cm high. The agar was prepared by adding 1% of Difco "Noble" agar to White's standard medium,⁷ without the color indicator. Of this medium, 150 ml was placed into each glass dish which was then autoclaved for 30 min. The dishes, after setting of the gel and seeding, were covered and placed in a dark cabinet without further attendance for 21 days at room temperature. Of each batch of 12 dishes, one or two were usually found contaminated

with microorganisms. These were discarded as soon as noticed. If no contamination occurred during the first week after seeding, none would occur at a later time.

The seedlings were pulled from the agar after softening the latter by heating to 35°. To each of three 250-ml erlenmeyer flasks provided with silicone rubber stoppers were added 150 ml of inorganic salt solution prepared according to White,⁷ 13.8 g of seedlings, and 1 ml of water containing 0.196 mg of mevalonic acid-2-¹⁴C as the dibenzylethylenediamine salt (specific activity 8.5 μcuries/mg). The flasks were shaken slowly for 5 days and were opened daily for 1 hr. At the end of the time period the salt solution was decanted and the seedlings were washed three times with 100 ml of water each time and blotted on filter paper.

Isolation of Cholesterol. All seedlings were combined, 150 ml of water was added, and the mixture was homogenized first in a Waring blender at high speed for 30 sec and then in a Potter-Elvehjem tissue grinder.

To remove fatty substances, the product was shaken thoroughly for 1 hr with 200 ml of petroleum ether (bp 60–90°) and separated. This extraction was repeated three more times. The aqueous phase was acidified to pH 4 with hydrochloric acid, and 40 g of sodium chloride was added and dissolved with stirring. The mixture was extracted four times with an equal volume of 1-butanol each time. The pooled alcoholic extracts were taken to dryness by water-pump suction at 60–70°. The dry residue was refluxed for 2 hr with 30 ml of 4 N hydrochloric acid made up by diluting one volume of concentrated hydrochloric acid with one volume of water and one volume of methanol.⁸ After cooling to room temperature, the hydrolysate was extracted three times with 30 ml of benzene each time. The pooled benzene extracts were washed once with 10 ml of 1 N sodium hydroxide and five times with 10 ml of water and evaporated to dryness under vacuum. The residue was chromatographed on four thin layer plates of 0.50-mm-thick silica gel in the system 5% petroleum ether in methylene chloride so that the solvent front ran up a distance of 15 cm from the origin. Material corresponding to sterols by comparison with standards moved with an *R_f* value between 0.13 and 0.23. Unidentified radioactivity remained at the origin and, except for the sterol spot, no significant counts were present elsewhere on the plate. The silica gel in the region between 2 and 3.5 cm was scraped off, and substances were eluted exhaustively with methanol and ethyl ether and dried.

The residue contains sterols and unidentified substances. It was subjected to a second thin layer separation on three similar plates in the system 8.5% ethanol in methylene chloride. All of the radioactivity was localized in an area between *R_f* values of 0.60 and 0.73, corresponding to authentic sterols. The rest of the plate contained only background counts. The silica with the radioactive spot was scraped off and exhaustively extracted, as before. A product weighing 3.5 mg and having a total radioactivity of 23,350 cpm was obtained. One-thousandth of this material was subjected to gas chromatography.

Gas chromatography was performed on a Barber-Colman Model 10 instrument, equipped with a 150-cm U-shaped column 4 mm in diameter. The supporting medium consisted of Gas Chrom Q, 100–120 mesh, coated with 0.8% of SE-52. The column was bled at 255° for 114 hr and used for analysis at 219°. The sample injection port temperature was 270°, and the detector temperature

(8) This method was found optimal for the hydrolysis of saponins by E. S. Rothman, M. E. Wall, and H. A. Walens, *J. Am. Chem. Soc.*, **74**, 5791 (1952).

(1) K. Tsuda, S. Akagi, and Y. Kishida, *Chem. Pharm. Bull.* (Tokyo), **6**, 101 (1958).

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(4) H. Linde, N. Ergenc, and K. Meyer, *Helv. Chim. Acta*, **49**, 1246 (1966).

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(6) R. Tschesche and G. Lilienweiss, *Z. Naturforsch.*, **19**, 265 (1964).

(7) P. R. White, "The Cultivation of Animal and Plant Cells," The Ronald Press, New York, N. Y., 1963, p 60.

I. Specific Activities* of Crystallized Sterols in Experiment 1

No. of crystallizations	Stigmasterol		Cholesterol acetate		Cholesterol		Cholesterol benzoate	
	Crystals	Supernatant	Crystals	Supernatant	Crystals	Supernatant	Crystals	Supernatant
1	6912	6120	359	1000	462	637	179	
2	4860	7550	588	559	323	477	190	82
3	4220	6200	738	569	311	498	225	128
4	3450	6160	727	705	337	467	266	278
5	2775	6400	734	Iq ^b	318	402	295	315
6	2178	6750			302	350	303	328
7	1710	3000			297	Iq ^b	305	301
8							302	Iq ^b

Counts per minute per milligram. ^b Iq = insufficient quantity.

267°. A β -ionization chamber with ⁹⁰Sr was the detecting device. A flow rate of 52–60 cc/min of argon was maintained. Retention times were 15, 18.5, 20.5, and 24 min, respectively, for cholesterol, campesterol, stigmasterol, and β -sitosterol. The active acetates showed peaks at 20.5, 27.5, 30, and 35 min.

One milligram of authentic stigmasterol was added to the sterol obtained from the final thin layer chromatography plates. Stigmasterol was recrystallized seven times from methanol. The mother liquor of each stigmasterol crystallization, except the last, showed a small cholesterol peak on the gas chromatogram. The residue of the seventh supernatant the cholesterol peak disappeared and the specific activity was reduced to less than half. The specific activity of crystals decreased with each successive crop, but the rate of decrease slowed down. It is likely that these were associated with stigmasterol. All supernatants were dried, taken to dryness, and acetylated. One-fiftieth was subjected to thin layer chromatography according to the procedure of Waters and Johnson,⁹ and it was found that the major amount of radioactivity was associated with the cholesterol acetate area. Gas chromatography of the acetates indicated peaks which coincided with peaks for standard cholesterol, campesterol, stigmasterol, and sterol acetates. Thereupon 10 mg of cholesterol acetate was added to the combined residue, which weighed 1.3 mg, and one-eighth of the material was recrystallized five times.

The rest of the cholesterol acetate mixture was divided into two portions. Portion 1 was hydrolyzed with 6% potassium hydroxide in ethanol for 0.5 hr in a boiling water bath. Water was added and the hydrolysate was extracted with ether. After evaporation of ether a quantity of standard cholesterol approximately equal to the weight of the residue was added and recrystallized five times. Portion 2, remaining from the above, was also hydrolyzed and then benzoated in the usual manner. Standard cholesterol benzoate was added and recrystallized eight times.

Seedlings used in expt 2 were 29 days old and weighed 66.3 g. They were incubated with a total of 0.30 mg of mevalonic acid-2-¹⁴C, as the dibenzylethylenediamine salt (specific activity 7.0 μ curies/

The seedlings were homogenized, as described, sonicated for 1 min, homogenized again, and resonicated. This procedure was necessary in order to break up all of the cells, as determined by power microscopy. To the residue, after thin layer chromatography in both systems described, was added 10 mg of cholesterol. The latter was crystallized five times.

Scintillation counting was done on a Nuclear Chicago Series 720 counter at room temperature with enough radioactive material to give a net count at least double the background rate and for most samples appreciably more. The scintillation fluid consisted of 10 ml of a solution of toluene, containing 5 g of 2,5-diphenyloxazole and 300 mg of 1,4-bis(2-(5-phenyloxazolyl))benzene per liter. Counting time varied between 20 and 100 min. The efficiency was 78%. The mevalonic acid-2-¹⁴C was dissolved in 0.5 ml of ethanol before the scintillation fluid was added.

Results

Table I shows the specific activity of the sterol crystals and the mother liquors from each crystallization of expt 1, obtained after incubation with mevalonic acid-2-¹⁴C. In three instances residues from the final supernatants were too small to be transferred to a microcentrifuge. The radioactivity of stigmasterol decreased

J. A. Waters and D. F. Johnson, *Arch. Biochem. Biophys.*, **112**, 1965).

Table II. Specific Activities* of Cholesterol in Experiment 2

No. of crystallizations	Cholesterol	
	Crystals	Supernatant
1	1701	4173
2	1283	1475
3	1297	1325
4	1295	1307
5	1271	1315

* Counts per minute per milligram.

throughout the crystallization steps, but the rate of decrease appears to approach asymptotically a level above 1200 cpm/mg. The pooled petroleum ether extracts of the defatting stage contained a total of 38,500 cpm. Analysis by gas chromatography showed a number of peaks appearing during the first 17 min. No peaks corresponding to the four sterols assayed here could be detected in this fraction. The aqueous phase contained 453,000 cpm. Gas chromatography of the sterol mixture in the aqueous phase after hydrolysis and separation in both thin layer systems indicated the presence of 0.075 mg of cholesterol, 0.43 mg of campesterol, 1.44 mg of stigmasterol, and 1.64 mg of β -sitosterol, by comparison with standards.

The petroleum ether extracts from expt 2 contained 1360 cpm and the aqueous phase 1,460,000 cpm. Quantitation of sterols by planimetry of gas chromatograph peaks gave the following values: 0.175 mg of cholesterol, 0.80 mg of campesterol, 1.69 mg of stigmasterol, and 2.00 mg of β -sitosterol. The specific activities of crystallized cholesterol and the residues from the mother liquors are indicated in Table II.

Discussion

Incubation with mevalonic acid-2-¹⁴C permits the isolation of cholesterol acetate, cholesterol, and cholesterol benzoate of constant specific activities after the second, first, and fourth crystallizations, respectively, as indicated in Tables I and II. It took somewhat longer for the benzoate to reach constant specific activity, presumably because of the presence of benzoic acid in the extract. The specific activities of the residues from the terminal supernatants coincided with that of the crystals. The substrate was added as the dibenzylethylenediamine salt. Rilling and Bloch¹⁰ found no difference in results in squalene formation in yeast from mevalonate as the potassium salt or as the dibenzylethylenediamine salt.

(10) H. C. Rilling and K. Bloch, *J. Biol. Chem.*, **234**, 1424 (1957).

The thin layer chromatographic systems for free sterols do not separate campesterol, stigmasterol, β -sitosterol, and cholesterol. The system for the acetates⁹ separates these sterols, although β -sitosterol and campesterol acetates run together. Chromatography of the acetates presented the first evidence that cholesterol was labeled. The gas chromatographic method separates all four sterols, but the cholesterol peak of the plant extract was so small that at first no significance was attached to it.

From the specific activity of the cholesterol acetate of expt 1 it can be calculated that 7300 cpm, or 31% of the total activity of the sterol mixture, was due to cholesterol. No more than 0.075 mg of cholesterol by weight was present in this mixture, and thus the specific activity of cholesterol was at least 97,000 cpm/mg in the native extract. The specific activity of stigmasterol can be roughly estimated at 5000 cpm/mg and, since 1.44 mg of this sterol was present, 7200 cpm or one-third of the total sterol activity can be accounted for by this sterol. Similarly, from expt 2, it can be calculated from the specific activity of cholesterol that 24% of the radioactive counts of the mixture was due to cholesterol. Because of the large amount of endogenous substance, radioactive stigmasterol produced during the course of the experiment has been extensively diluted.

Cholesterol was found in the aqueous phase after defatting with petroleum ether. It became soluble in a nonpolar solvent only after hydrolytic treatment with mineral acid. It is supposed that cholesterol can be conjugated at C-3 and that it may occur as glycoside. It is also possible that cholesterol can be conjugated with sulfuric acid. This speculation is reinforced by the recent findings of cholesterol sulfate in the human organism.^{11,12} No other water-soluble conjugate of cholesterol has been discovered in nature.

With the finding of cholesterol in plants,¹⁻⁴ increased attention has been drawn to the intermediate role of this substance in plant sterol biosynthesis. Cholesterol comprises but 3% by weight of the total sterol mixture, yet its rate of formation is rapid. One-quarter to one-third of the radioactivity found in all sterols became associated with cholesterol during the incubation period. The high rate of incorporation of label into cholesterol is consonant with the expectation that cholesterol fulfills an intermediary role in formation of other sterols. Data indicate that the turnover rate of cholesterol must be high.

Animals seem to be restricted in their ability to degrade cholesterol, and on a weight basis this compound is the most important of all steroid-nucleus-containing substances. Plants appear to convert cholesterol rapidly to a number of compounds which occur side by side. Bergmann¹³ has pointed out that cholesterol has achieved a position of dominance at higher levels of evolution until it has become the principal sterol of vertebrate animals. It remains to be seen whether higher animals have achieved an advantage by limiting the means of biochemical modification of

the steroid side chain. Lipid esters in the circulatory system have been shown to be of advantage when present in excess at C-22, a reaction not rendering the side chain vulnerable with subsequent loss of a ring. This and other transformations of cholesterol may act together to increase its solubility. It was pointed out in the water-soluble portion of the extract that conjugation at C-3 and modification at C-22 may act together to increase efficiency in the ability to transport sterol compounds in the blood. The conversion of cholesterol to other sterols is peculiar to plants and is responsible for organic material of varying levels of the sterol.

Reports in the literature suggest that plants arise by a pathway similar to that for animals and yeast. Carotenoids can be incorporated into plant sterols;^{15,16} *Ocimum basilicum* into stigmasterol in tomatoes;¹⁸ into stigmasterol in *flora*,¹⁹ and tomatoes;²⁰ into *Rauwolfia serpentina*,²¹ *Dioscorea* *officinalis* and *S. sclarea* in peas;¹⁶ and into digitoxigenin and *D. lanata*.²⁴⁻²⁶ In several cases, incorporation of carbons or label into sterols has been coincident with the expected location or with the expected ¹⁴C/¹²C ratio. When administered as free compound, leaves of *Digitalis lanata*, digitoxigenin, digitoxin, and diosgenin applied to the surface of *spiculiflora* appears as diosgenin. Bergmann describes an extensive incorporation of ¹⁴C into cholesterol when sterols are present. The small concentration of all plant sterols in the conversion of cholesterol to other sterols appears to fulfill the animals: that of key intermediates.

Acknowledgments. We thank the Distillation Products Industry and Dr. R. T. Rapala of Lilly, Indianapolis, Ind., for sample.

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Communications to the Editor

Chemical Shift Anisotropies from Nuclear Magnetic Resonance Studies of Oriented Molecules

Sir:

It is now well known that anisotropy in nuclear magnetic shielding can be obtained through measurement of a shift due to partial molecular alignment.¹⁻³ If the molecule is linear, or if the bond containing the nucleus has an axis of symmetry, it is possible to determine $\sigma_{\parallel} - \sigma_{\perp}$, the difference in the shielding for fields parallel and perpendicular to the bond. If the mean shielding constant, $(\sigma_{\parallel} + 2\sigma_{\perp})/3$, is also known through measurements on an isotropic sample, both σ_{\parallel} and σ_{\perp} are then available.

Recently the shifts and splittings in the proton and fluorine spectra of CH_2F in *p,p'*-di-*n*-hexyloxyazobenzene were observed.⁴ It was reported that $(\sigma_{\parallel} - \sigma_{\perp})^{\text{F}} = -179 \pm 15$ ppm and that the difference in the mean proton shielding parallel and perpendicular to the threefold axis is -28 ± 4 ppm; if the bond angles are tetrahedral and the CH bonds axially symmetric, the latter result entails $(\sigma_{\parallel} - \sigma_{\perp})^{\text{H}} = +84 \pm 12$ ppm, a value rightly described⁴ as "unexpectedly large." The actual shifts were evidently about -195 cps (-2.08 ppm) and -32 cps (-0.32 ppm) for the F and H resonances.

The purpose of this communication is to point out that a small nmr shift between the nematic and isotropic phases of a liquid crystal solution (relative to an external reference) cannot easily be related to shielding anisotropy. The difficulty is due to shifts arising from the environment of the solute. The isotropic \rightarrow nematic transition is a first-order phase change, and there is a small decrease in the mean volume susceptibility of the medium leading to a downfield shift. However, there is a more important effect due to the anisotropy in the bulk susceptibility brought about by the more-or-less complete molecular alignment in the nematic phase in the strong magnetic field. If the sample is in a cylinder at right angles to a magnetic field H_0 , the volume susceptibility is χ_{\parallel} in the direction of the field, and χ_{\perp} at right angles to it, and the field strength inside the cylinder is

$$H_{\text{c}}[1 + 2\pi\chi_{\parallel}]^{-1} \approx H_0 \left[1 - 2\pi\chi - \frac{4\pi}{3}\Delta\chi \right]$$

where $\chi = 1/3(\chi_{\parallel} + 2\chi_{\perp})$ is the mean volume susceptibility and $\Delta\chi = \chi_{\parallel} - \chi_{\perp}$. In a spherical sample, the field inside is

$$H_{\text{c}} \left[1 + \frac{4\pi}{3}\chi_{\parallel} \right]^{-1} \approx H_0 \left[1 - \frac{4\pi}{3}\chi - \frac{8\pi}{9}\Delta\chi \right]$$

The "effective field" acting on a molecule is $(1 + 4/3\pi\chi_{\parallel})$ times the actual field in the medium, so there

is no bulk susceptibility shielding in a spherical sample, but the equivalent shielding constant in a cylinder is

$$\sigma_{\text{b}} = \frac{2\pi}{3}\chi_{\parallel} = \frac{2\pi}{3}\chi + \frac{4\pi}{9}\Delta\chi$$

The shift $(2\pi/3)\chi$ is well known,⁵ but the second term appears to be new and gives rise to an upfield shift when the solution goes nematic. Measurements of the difference in the field strength needed to produce resonance in a cylinder and a sphere would yield σ_{b} and hence valuable information about the volume susceptibility.⁶

There are other environmental contributions to the shielding that might change significantly when the medium undergoes the isotropic \rightarrow nematic transition. In particular, there is the "solvent anisotropy effect," σ_{a} ,⁷ which arises from the link between the shape of the solvent molecules and their magnetic susceptibilities. Thus in benzene, the large diamagnetic susceptibility in the direction perpendicular to the ring, coupled with the fact that solute molecules can approach a benzene molecule most closely in this direction, leads to a high-field shift of about $1/3$ ppm.⁷ But if the benzene molecules were aligned with the ring planes parallel to the magnetic field, this high-field shift would be converted into a shift $-1/2\chi_{\parallel}(\chi_{33} - \chi_{11})^{-1}$ times as large, where $\chi_{11} = \chi_{22}$ is the magnetic susceptibility in the plane of the ring and χ_{33} that at right angles to it; this ratio is approximately -0.9 for benzene, and the resulting change in σ_{a} is about -0.6 ppm.

It is not possible to prescribe definite values for $\Delta\sigma_{\text{b}}$ and $\Delta\sigma_{\text{a}}$ in the isotropic \rightarrow nematic transition in solutions in *p,p'*-di-*n*-hexyloxyazobenzene. Although it is apparently a first-order phase change, the decrease in volume, and hence in χ , is small and probably less than 1%.⁸ However, $\Delta\chi$ may be about 0.13 ppm (its value for *p*-azoxyanisole⁹) so that $\Delta\sigma_{\text{b}} \sim +0.18$ ppm. The change in σ_{a} is doubtless much smaller than that calculated above for benzene, and a figure of -0.3 ppm is reasonable. Thus we would expect a downfield shift when the solvent goes nematic, and this could greatly reduce $(\sigma_{\parallel} - \sigma_{\perp})^{\text{H}}$. If it is assumed that $(\sigma_{\parallel} - \sigma_{\perp})^{\text{H}}$ is zero, the solvent shift is -0.32 ppm and the corrected anisotropy $(\sigma_{\parallel} - \sigma_{\perp})^{\text{F}}$ is -150 ppm.

From the point of view of evaluating shielding anisotropies, it would seem to be preferable to use an internal reference comprising a molecule of high symmetry; thus CH_4 would be appropriate for proton spectra, and CF_4 or SF_6 for F resonances. Even with internal referencing, special care may be needed in interpreting small shifts, for the change in the environment could affect the solute and reference differently.

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Synthesis of Transition Metal-Monocarbon Carborane Complexes

Sir:

We wish to report the facile synthesis of complexes of the $B_{10}H_{10}CH_3^{3-}$ and $B_{10}H_{10}CNH_2R^{2-}$ ions with several transition metals.¹ The syntheses are based on two general reactions very closely related to the preparative methods recently described for the (3)-1,2-dicarbollyl sandwich complexes:^{2,3} (1) $Na_3B_{10}H_{10}CH$ and anhydrous metal chloride, and (2) $CsB_{10}H_{12}CH$, aqueous sodium hydroxide, and metal chloride.

Table I. Analyses

Compound	Calculated, %			Found, %						
	C	H	N	B	Metal	C	H	N	B	Metal
$[(CH_3)_4N]_3Co(B_{10}H_{10}CH)_2$	30.91	10.74	7.72	39.78	10.84	30.99	10.80	7.58	39.73	10.6
$Cs_2Ni(B_{10}H_{10}CH)_2$	4.09	3.78	...	36.84	10.00	3.77	3.90	...	36.55	9.8
$[(CH_3)_4N]_3Fe(B_{10}H_{10}CH)_2$	31.05	10.80	7.78	40.07	10.30	30.92	10.98	7.59	...	9.8
$(CH_3)_4NCo(B_{10}H_{10}CNH_2C_2H_5)_2$	24.83	9.59	8.69	44.70	12.18	25.09	9.63	8.67	...	12.6
$Ni(B_{10}H_{10}CNH_2C_2H_5)_2$	22.01	8.76	6.42	49.45	13.44	22.05	9.08	6.40	...	12.9

The $B_{10}H_{10}CH_3^{3-}$ ion is readily prepared as a sparingly soluble sodium salt (I) by deamination and deprotonation of $B_{10}H_{12}CN(CH_3)_3$ with sodium metal in tetrahydrofuran (THF).⁴ Addition of I to a solution of anhydrous $CoCl_2$ in THF yielded a precipitate of cobalt metal and sodium chloride. The $Co^{III}(B_{10}H_{10}CH)_2^{3-}$ ion (II) was isolated as either the cesium or tetramethylammonium salt. The salts of II are diamagnetic and yellow [λ_{max} (ϵ): 279 (36,600) and 422 $m\mu$ (382)].

The second type of reaction is illustrated by the synthesis of the $Ni^{IV}(B_{10}H_{10}CH)_2^{2-}$ ion (III). An aqueous mixture of $NiCl_2$ (13.5 mmoles), $CsB_{10}H_{12}CH$ (22.1 mmoles), and sodium hydroxide (270 mmoles) was heated at 40° with air injection for 20 hr. The yellow, diamagnetic cesium salt of III could be isolated in yields as high as 82% from this reaction. By this method one can also obtain good yields of II and salts of the red $Fe^{III}(B_{10}H_{10}CH)_2^{3-}$ ion (IV).

Preliminary X-ray data on $Cs_2Ni^{IV}(B_{10}H_{10}CH)_2$ yield the cell parameters: $a = 20.25$, $b = 12.77$, $c = 14.64$ Å, $z = 8$, $d(calcd)$ 2.08, $d(found)$ 2.04. The ^{11}B nmr spectra of II and III extend over 29 ppm and are grossly similar to one another but have not been completely interpreted. The paramagnetic ion (IV) has a ^{11}B nmr spectrum which extends over approximately 300 ppm and does not appear to show ^{11}B - 1H coupling.⁵

Treatment of $B_{10}H_{12}CNH_2C_2H_5$ with $NiCl_2$ in aqueous base gives in good yield, orange, diamagnetic $Ni^{IV}(B_{10}H_{10}CNH_2C_2H_5)_2$ (V). The mass spectrum of V cuts off sharply at m/e 444 corresponding to the parent ion, $^{12}C_8^{1}H_{38}^{14}N_2^{11}B_{20}^{62}Ni^+$. Orange, diamagnetic $(CH_3)_4NCo^{III}(B_{10}H_{10}CNH_2C_2H_5)_2$ (VI) was obtained in the same manner. Methylation of V with sodium bicarbonate and methyl iodide gives dark orange

$Ni^{IV}(B_{10}H_{10}NH(CH_3)C_2H_5)_2$. The ^{11}B nmr spectra of these amine derivatives extend over 29 ppm and are similar to those of the unsubstituted complexes but are not as well resolved. Analyses of the compounds are given in Table I.

The striking similarity in properties of the metal complexes reported in this paper and their isoelectronic dicarbollide analogs leads us to suggest that the transition metal in these compounds is π -bonded to the open face of two monocarbon carborane (carbollide) icosahedral fragments. Thus the Co^{III} species II and VI are apparent analogs of the cobalticinium ion

and the Fe^{III} species IV analogous to the ferricinium ion. A single crystal X-ray study now in progress should lend support to this postulate.

Salts of the $(B_{10}H_{10}CH)Mn(CO)_5^{2-}$ and $Cu^{III}(B_{10}H_{10}CH)_2^{3-}$ ions have also been obtained from $BrMn(CO)_5$ and copper(II) acetylacetonate, respectively, by the anhydrous route with $Na_3B_{10}H_{10}CH$. The ^{11}B nmr spectra of these ions which extend over 20 ppm are similar to one another but dissimilar to the spectra of the nickel and cobalt derivatives.

Further synthetic and structural studies of these new carbollyl-transition metal complexes are in progress and will be reported at a later date.

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Transition Metal Complexes of $B_{10}H_{10}CNH_2^{2-}$ and $B_{10}H_{10}CH^{3-}$

Sir:

A series of sandwich complexes of transition metals with the $B_9C_2H_{11}^{2-}$ anion has been reported by Hawthorne and co-workers.¹ These complexes are formally analogous to metallocenes because the metal in both cases is bonded to a pentagonal face which can contribute three bonding molecular orbitals and six electrons.^{2,3}

This communication reports the preparation of similar metal complexes of $B_{10}H_{10}CNH_2^{2-}$ and $B_{10}H_{10}CH^{3-}$

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Table I. Representative Analyses

Compound	Calculated, %					Found, %				
	B	C	H	N	M	B	C	H	N	M
$\text{Cs}_2(\text{B}_{10}\text{H}_{10}\text{CH})_2\text{Cr} \cdot \text{H}_2\text{O}^a$	29.6	3.3	3.3	30.2	3.5	3.1
$[(\text{CH}_3)_2\text{NH}]_2(\text{B}_{10}\text{H}_{10}\text{CH})_2\text{Mn}$	49.5	21.9	9.7	6.4	12.5	49.5	22.6	9.5	6.2	11.7
$\text{Cs}_2(\text{B}_{10}\text{H}_{10}\text{CH})_2\text{Co} \cdot \text{H}_2\text{O}^a$	29.3	3.2	3.2	...	8.0	29.6	3.0	3.3	...	8.0
$[(\text{CH}_3)_2\text{N}]_2(\text{B}_{10}\text{H}_{10}\text{CH})_2\text{Co}$	46.0	25.5	9.8	6.0	12.6	45.4	25.6	9.9	6.2	12.2
$\text{Cs}_2(\text{B}_{10}\text{H}_{10}\text{CH})_2\text{Ni}$	36.8	10.0	36.7	10.1
$(\text{CH}_3)_4\text{N}(\text{B}_{10}\text{H}_{10}\text{CNH}_2)_2\text{Fe}$	51.0	17.0	9.0	9.9	13.1	50.0	17.1	9.5	9.7	13.3
$[(\text{CH}_3)_2\text{N}]_2\text{B}_{10}\text{H}_{10}\text{CNH}_2\text{CoB}_{10}\text{H}_{10}\text{CNH}_2$...	23.9	9.9	11.2	11.8	...	23.9	10.2	11.0	11.9
$[\text{B}_{10}\text{H}_{10}\text{CNH}(\text{CH}_3)_2]_2\text{Ni}$	53.0	17.6	8.4	6.8	14.3	53.0	17.7	8.9	7.2	14.3
$[(\text{CH}_3)_2\text{N}]_2(\text{B}_{10}\text{H}_{10}\text{COH})_2\text{Ni}$	43.1	24.0	9.2	5.6	11.8	42.9	24.0	9.4	5.8	11.7

^aThe presence of water of hydration was established by infrared analysis.

CH^{2-} by the reactions of $\text{B}_{10}\text{H}_{12}\text{CNH}_2$ ⁴ and $\text{B}_{10}\text{H}_{12}\text{CH}^{4-}$ with transition metal halides under basic conditions.⁵ The facile, essentially one-step, preparation of $\text{B}_{10}\text{H}_{12}\text{CNH}_2$ from decaborane and sodium cyanide makes the $\text{B}_{10}\text{H}_{10}\text{CNH}_2^{2-}$ -metal complexes particularly accessible; $\text{B}_{10}\text{H}_{12}\text{CH}^{2-}$ is prepared in two steps from $\text{B}_{10}\text{H}_{12}\text{CNH}_2$.⁴

Cobalt, nickel, manganese, and iron complexes have been prepared from both $\text{B}_{10}\text{H}_{12}\text{CNH}_2$ and $\text{B}_{10}\text{H}_{12}\text{CH}^{2-}$; in addition a chromium complex has been prepared from the latter. These species have the general formulas $(\text{B}_{10}\text{H}_{10}\text{CNH}_2)_2\text{M}$ and $(\text{B}_{10}\text{H}_{10}\text{CH})_2\text{M}$. The over-all charge is dependent on the formal valence of the metal and, for the aminated complexes, also on the degree of protonation of the nitrogen. For example, the complex of Co(III) with the aminated ligand has been isolated as salts of the $\text{B}_{10}\text{H}_{10}\text{CNH}_2\text{CoB}_{10}\text{H}_{10}\text{CNH}_2^{2-}$ and $(\text{B}_{10}\text{H}_{10}\text{CNH}_2)_2\text{Co}^{2-}$ anions.

It has been shown^{1c} that the $\text{B}_9\text{C}_2\text{H}_{11}^{2-}$ ligand stabilizes relatively high metal oxidation states; e.g., $(\text{B}_9\text{C}_2\text{H}_{11})_2\text{Ni}^{2-}$, which is a Ni(III) complex, can be oxidized to a Ni(IV) species, $(\text{B}_9\text{C}_2\text{H}_{11})_2\text{Ni}$. The $\text{B}_{10}\text{H}_{10}\text{CNH}_2^{2-}$ and $\text{B}_{10}\text{H}_{10}\text{CH}^{2-}$ ligands also stabilize high oxidation states; in fact, they may be superior to $\text{B}_9\text{C}_2\text{H}_{11}^{2-}$ in this respect because in their complexes Ni(IV) is the preferred oxidation state (i.e., the isolated products contain Ni(IV) without the need for an additional oxidation step). Furthermore, the yellow-orange, diamagnetic $(\text{B}_{10}\text{H}_{10}\text{CH})_2\text{Co}^{2-}$ anion, which contains Co(III), is oxidized by ceric ion to an almost black, paramagnetic $(\text{B}_{10}\text{H}_{10}\text{CH})_2\text{Co}^{3-}$ ion, which formally contains Co(IV). The formal oxidation states in the manganese, iron, cobalt, and chromium complexes as isolated are IV, III, III, and III, respectively. Analyses of representative compounds are given in Table I.

The preparations of the complexes are simple and consist of adding *n*-butyllithium to a mixture of a metal(II) halide (except that CrCl_3 is used to prepare the chromium compound) and $\text{B}_{10}\text{H}_{12}\text{CNH}_2$ or a salt of $\text{B}_{10}\text{H}_{12}\text{CH}^{2-}$ in tetrahydrofuran. An even more convenient preparation of the cobalt and nickel complexes consists of treating CoCl_2 or NiCl_2 with $\text{B}_{10}\text{H}_{12}\text{CNH}_2$ or $\text{B}_{10}\text{H}_{12}\text{CH}^{2-}$ in aqueous sodium hydroxide. The isolated Fe(III) products are formed by spontaneous air oxidation of the analogous Fe(II) species; oxidation of the other metals to the states observed in the isolated products occurs with concurrent reduction of excess metal halide. The two-electron oxida-

tions ($\text{M(II)} \rightarrow \text{M(IV)}$) may involve both air oxidation and disproportionation.

The iron-, nickel-, chromium-, and cobalt(III) complexes are quite stable in air and are not readily decomposed by acids, consistent with the behavior reported¹ for the $\text{B}_9\text{C}_2\text{H}_{11}^{2-}$ metal complexes. The manganese complexes decompose slowly in acetonitrile solution; the products have not been identified.

Although the structures of the complexes have not been unequivocally established, it is quite reasonable to assume they are analogous to those of the $\text{B}_9\text{C}_2\text{H}_{11}^{2-}$ metal sandwich species.¹⁻³ This assumption is based on the isoelectronic relationship of $\text{B}_9\text{C}_2\text{H}_{11}^{2-}$ with $\text{B}_{10}\text{H}_{10}\text{CH}^{2-}$ and $\text{B}_{10}\text{H}_{10}\text{CNH}_2^{2-}$ and on the chemical similarities noted above for their respective metal complexes. The proposed structure is shown in Figure 1.

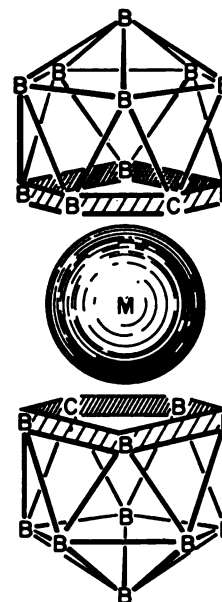


Figure 1. Proposed skeletal structure for metal sandwich complexes of $\text{B}_{10}\text{H}_{10}\text{CH}^{2-}$ and its derivatives

The metal complexes derived from $\text{B}_{10}\text{H}_{12}\text{CNH}_2$ are of particular interest, not only because of the facile preparation of this aminocarborane, but also because the amine group provides convenient access to other C-substituted complexes. For example, the reactions of $(\text{B}_{10}\text{H}_{10}\text{CNH}_2)_2\text{Ni}$ with nitrous acid and with dimethyl sulfate have given $(\text{B}_{10}\text{H}_{10}\text{COH})_2\text{Ni}^{2-}$ and $[\text{B}_{10}\text{H}_{10}\text{CNH}(\text{CH}_3)_2]_2\text{Ni}$, respectively. An N-alkylated analog, $(\text{B}_{10}\text{H}_{10}\text{CNH}_2\text{CH}_2\text{C}_6\text{H}_5)_2\text{Ni}$, has also been pre-

(4) W. H. Knoth, *J. Am. Chem. Soc.*, **89**, 1274 (1967).

(5) Closely related work has been reported: D. E. Hyatt, J. L. Little, J. T. Moran, F. R. Scholer, and L. J. Todd, *ibid.*, **89**, 3342 (1967).

pared by the reaction of $B_{10}H_{12}CNH_2CH_2C_6H_5$ ⁴ with $NiCl_2$ in aqueous sodium hydroxide.

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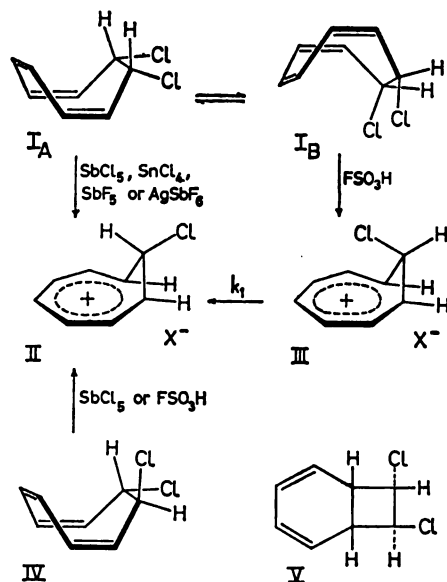
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endo- and exo-8-Chlorohomotropylum Salts

Sir:

The occurrence of an 8-halohomotropylum ion as an intermediate in the halogenation of cyclooctatetraene is conceivable. It would explain the unique features of this reaction.¹ To provide evidence for this mechanistic possibility, we prepared *exo*- and *endo*-8-chlorohomotropylum salts. von Rosenberg, Mahler, and Pettit² obtained stable homotropylum salts by the reaction of cyclooctatetraene with strong acids. Further studies in the laboratories of Winstein³ and Pettit⁴ confirmed the homoaromatic character of the cationic species.

We treated *cis*-7,8-dichlorocycloocta-1,3,5-triene⁵ (IA and IB) with antimony pentachloride in dichloromethane at -15° and isolated the crystalline, colorless *exo*-8-chlorohomotropylum hexachloroantimonate (II, $X^- = SbCl_6^-$) in 95% yield.⁶ The salt (mp $82-85^\circ$ dec in a sealed tube) is stable at room temperature but decomposes on exposure to moist air. Structural assignment is based on the nmr spectrum (CD_3NO_2).⁷ The homoaromatic protons at positions 2-6 are centered at τ 1.1 (multiplet); protons 1 and 7 give rise to a triplet at τ 2.82 with $J_{12} = J_{18} = 8.2$ cps. The aromatic ring current shifts the triplet of the *endo*-8-H to τ 8.20.



(1) R. Huisgen, G. Boche, and H. Huber, *J. Am. Chem. Soc.*, **89**, 3345 (1967).

(2) J. L. von Rosenberg, J. E. Mahler, and R. Pettit, *ibid.*, **84**, 2842 (1962).

(3) S. Winstein, H. D. Kaesz, C. G. Kreiter, and E. C. Friedrich, *ibid.*, **87**, 3267 (1965); S. Winstein, C. G. Kreiter, and J. I. Braumann, *ibid.*, **88**, 2047 (1966).

(4) C. E. Keller and R. Pettit, *ibid.*, **88**, 604, 606 (1966).

(5) R. Huisgen, G. Boche, W. Hecht, and H. Huber, *Angew. Chem.*, **78**, 595 (1966); *Angew. Chem. Intern. Ed. Engl.*, **5**, 585 (1966).

(6) Satisfactory carbon and hydrogen analyses were obtained.

(7) Determined on a Varian A-60 spectrometer with TMS as internal standard.

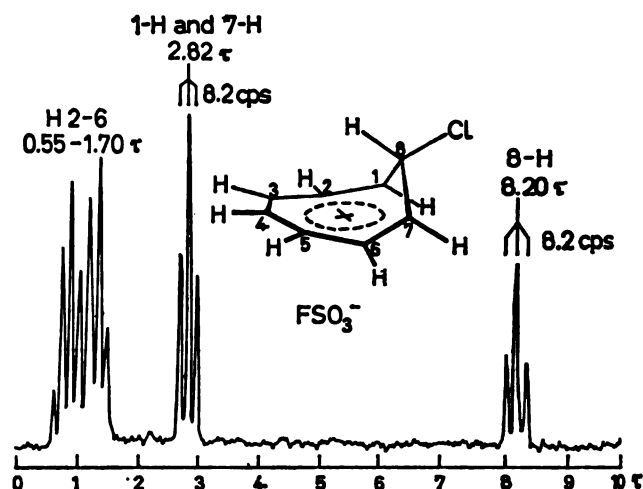


Figure 1. Nmr spectrum (FSO_3H) of *exo*-8-chlorohomotropylum fluorosulfonate at 20° .⁸

The spectrum corresponds well with that of the homotropylum hexachloroantimonate² after making allowance for the effect of the *exo*-8-chlorine. The spectrum of II ($X^- = FSO_3^-$) in fluorosulfonic acid (Figure 1) is very similar.

IA and IB exist at -15° in a mobile 46:54 equilibrium.⁵ Besides $SbCl_5$ (in CH_2Cl_2 or SO_2), $SnCl_4$ (in CH_2Cl_2 ; II, $X^- = SnCl_6^-$)⁸ or $AgSbF_6$ (in SO_2 or CD_3NO_2), respectively, also cause chloride elimination from the *exo*,*cis*-dichloride IA to give the *exo*-8-chloro cation II.

In contrast, fluorosulfonic acid attacks the *endo*-dichloro conformer IB. Treatment with ≥ 4 equiv of FSO_3H in SO_2 or with pure FSO_3H below 0° converted IB to the *endo*-8-chlorohomotropylum salt III ($X^- = FSO_3^-$). Also shown by the nmr spectrum of III (Figure 2⁸) is the equality of vicinal coupling constants, leading to two triplets, one for 1-H and 7-H, the other for 8-H. The τ value of *exo*-8-H is shifted by 5.69 to lower field compared with *endo*-8-H in II.

On warming a solution of III in FSO_3H to 30.4° , a first-order isomerization to the *exo*-chloro cation took

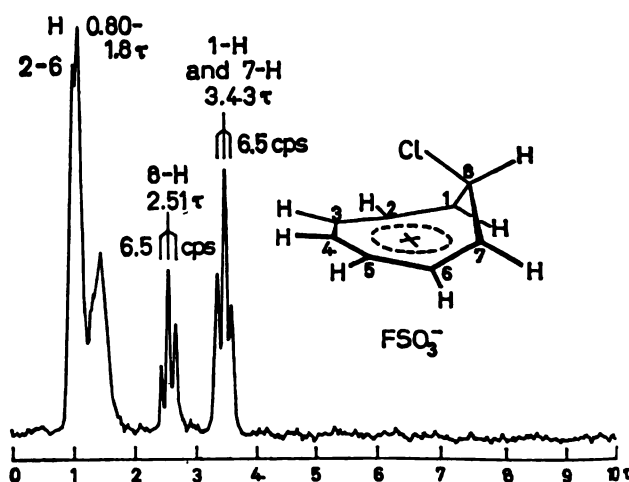


Figure 2. Nmr spectrum (FSO_3H) of *endo*-8-chlorohomotropylum fluorosulfonate at -40° .⁸

(8) TMS is destroyed by FSO_3H . Chemical shifts were corrected by using the same τ values for the two triplets as found for II ($X^- = SbCl_6^-$) in CD_3NO_2 . For mixtures of II and III in FSO_3H , analogous corrections were applied.

place with a half-life of 37.7 min. Additional kinetic measurements (nmr) at 15.5 and 20.0° furnished values for ΔH^\ddagger of 24.4 kcal/mole and for ΔS^\ddagger of 3.8 eu. The *exo*-chloride II, probably formed by ring inversion of the *endo*-chloride III, is the thermodynamically stable isomer since no III is detectable after complete isomerization. SbCl_5 does not catalyze the process $\text{III} \rightarrow \text{II}$. Winstein, *et al.*,³ found a half-life of 19 min for the equilibration of the *endo*-8-*d*-homotropylum ion in D_2SO_4 at ca. 32°.

On treating *trans*-7,8-dichlorocyclooctatriene⁵ (IV) with SbCl_5 in dichloromethane at -20°, the *exo*-chloro salt II precipitated. The same reaction in SO_2 at -40° resulted in a solution of which the nmr revealed solely the presence of II. Interestingly, fluorosulfonic acid at -20° converted IV to the same *exo*-chloro cation II. Thus, in the ionizations of I and IV, induced by FSO_3H , the chloride anion is removed from the *endo* side, while SbCl_5 gives in both cases the more stable *exo*-chloro cation. The origin of this dichotomy—all ionizations described above are unidirectional and kinetically controlled—is unknown.

Reppe's dichloride V⁶ is not transformed to a homotropylum salt by FSO_3H .

(9) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Ann. Chem.*, **560**, 1 (1948).

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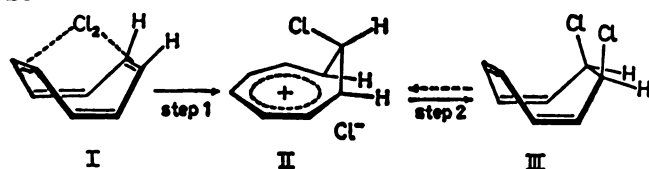
The Halogenation of Cyclooctatetraene via 8-Halohomotropylum Ions

Sir:

The 7,8-*trans*-dihalobicyclo[4.2.0]octa-2,4-dienes which Reppe, *et al.*,¹ obtained from cyclooctatetraene and halogen are the result of multistep reactions.^{2,3} In the chlorination, we isolated four isomeric dichlorides and elucidated their structures as well as their mutual relationships.³ The halogenation shows several unique features: (1) exclusive primary *cis* addition over the solvent range from hexane to acetonitrile; (2) unusually high rate; in the bromination at -55°, the solution remains colorless until the first drop of bromine exceeds 1 mole equiv; (3) the *cis*-7,8-dihalocycloocta-1,3,5-trienes isomerize readily to the *trans* isomers despite steric hindrance of allylic resonance in the tub form.

We propose [8-halohomotropylum cation (II) as an intermediate. The formation of this homoaromatic species would obviously explain the high rate of halogenation. This being the case, both steps of Scheme I, formulated for chlorination, should take place highly

Scheme I



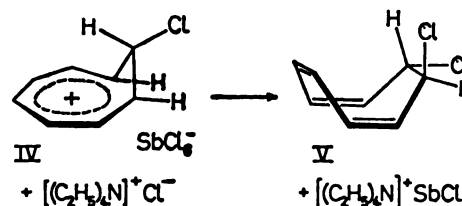
(1) W. Reppe, O. Schlichting, K. Klager, and T. Töpel, *Ann. Chem.*, **560**, 1 (1948).

(2) R. Huisgen and G. Boche, *Tetrahedron Letters*, 1769 (1965).

(3) R. Huisgen, G. Boche, W. Hecht, and H. Huber, *Angew. Chem.*, **78**, 595 (1966); *Angew. Chem. Intern. Ed. Engl.*, **5**, 585 (1966).

stereoselectively. Experimental evidence on step 2 is easily accessible.

Step 2. We added 1.1 equiv of tetraethylammonium chloride to *exo*-8-chlorohomotropylum hexachloroantimonate (IV)⁴ in SO_2 at -40° and recorded the nmr spectrum of the clear solution. Signals⁵ were observed indicating the presence of only *trans*-7,8-dichlorocyclooctatriene (V).³ Thus, the chloride anion approaches C-1 from the *endo* side.



cis-Dichloride III (2.6 mmoles) was treated with 10 mmoles of fluorosulfonic acid in 6 ml of SO_2 at -20° to give pure *endo*-8-chlorohomotropylum salt (II, FSO_3^- instead of Cl^-).⁴ After 5 min, 15 mmoles of tetraethylammonium chloride was introduced. The nmr spectrum of the clear solution (-40°, after 10 min) indicated 94% *cis*-dichloride III and 6% *trans* isomer V. The formation of the small amount of V is most likely not due to kinetic, but rather to thermodynamic, control.⁶ Thus, both homotropylum ions suffer *endo* attack by the nucleophilic Cl^- .

Step 1. Only the *endo*-chlorohomotropylum ion II is consistent with the quantitative formation of the *cis*-dichloride III in the chlorination of cyclooctatetraene. Conclusive evidence for the high stereoselectivity of step 1 ($\text{I} \rightarrow \text{II}$) is not available because with no known chlorinating reagent can the reaction be terminated reliably at the cationic stage II. We assume that $\text{Cl}_2 \cdots \text{SbHal}_5$ chlorinates faster than Cl_2 and gives directly 8-chlorohomotropylum hexachloroantimonate. In the reactions with Cl_2 and SbCl_5 in dichloromethane, the hexachloroantimonates II (SbCl_6^- instead of Cl^-) and IV precipitated and were weighed and analyzed by nmr in SO_2 at -40°. The use of Cl_2 and SbF_5 permitted direct nmr analysis of the clear reaction solutions.

The data of Table I reveal that the yield of *endo*-8-chlorohomotropylum salt rises with decreasing reac-

Table I. Reactions of Cyclooctatetraene with 1.0 Equiv of Cl_2 and SbHal_5 in Dichloromethane

Equiv of SbHal_5	Temp, °C	% hexahaloantimonate II and IV	<i>endo</i> -Cl(II): <i>exo</i> -Cl(IV)
1.2 SbCl_5	-20	75	17:83
4.0 SbCl_5	-20	78	47:53
1.2 SbCl_5	-93	77	50:50
3.0 SbCl_5	-93	76	62:38
2.0 SbF_5^a	-50	(100)	66:34
1.2 SbF_5^a	-93	(100)	56:44

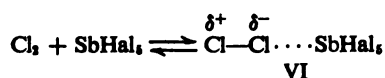
^a Solvent: $\text{CH}_2\text{Cl}_2\text{-SO}_2$.

tion temperature and increasing concentration of SbHal_5 ; SbF_5 appears to be more efficient than SbCl_5 .

(4) G. Boche, W. Hecht, H. Huber, and R. Huisgen, *J. Am. Chem. Soc.*, **89** 3344 (1967).

(5) The limit of nmr analysis of the *cis* isomer III in the presence of a large amount of V is ca. 6%.

(6) Uncatalyzed isomerization of the *cis*-dichloride III in SO_2 at -40° led to 15% V after 30 min and to 40% V after 5 hr.



We interpret these results as concurrent chlorinations by Cl_2 and reagent VI. The former yields the *cis*-dichloride III which is converted in a second step by SbHal_6 to give pure *exo*-chloro cation IV.⁴ The *endo*-chloro cation II (SbHal_6^- instead of Cl^-) can therefore only be the result of a direct attack of the complex VI on cyclooctatetraene. Consistent with this interpretation is the dependence of the ratio II:IV on temperature and SbHal_6 concentration; this substantiates the conclusion that the primary step of chlorination is the formation of the *endo*-chloro cation II.

On treating cyclooctatetraene with D_2SO_4 at -10° , Winstein, *et al.*,⁷ obtained *endo*- and *exo*-8-*d*-homotropylium salt in an 80:20 ratio. Our experiments with FSO_3D at -70° gave a 75:25 product ratio. The virtually quantitative formation of III in the chlorination requires a more specific *endo* attack of " Cl^+ " on cyclooctatetraene than in the deuteration. Possibly, initial formation of the π -complex I contributes to the high stereoselectivity observed.

***cis-trans* Isomerization.** A 66:34 equilibrium of dichlorides V:III is established in CCl_4 at -30° in the presence of alumina.³ The isomerization $\text{III} \rightarrow \text{V}$ in SO_2 at -40° ⁶ is accelerated by catalytic amounts of *p*-toluenesulfonic or fluorosulfonic acid. These observations are also highly suggestive of 8-chlorohomotropylium ions as intermediates. Since ring inversion of *endo*- and *exo*-chloro cation $\text{II} \rightarrow \text{IV}$ does not take place at -30° ,⁴ ionization of dichlorides III and V and or Cl^- attack on 8-chlorohomotropylium ions II and IV is, therefore, not absolutely stereospecific.

Inspection of models leaves no doubt that the π overlap between the orbitals at positions 1 and 7 of the homotropylium ion is substantially larger on the underside than on the side of the C-8 bridge. This may be the principal reason for the *endo* attack in both steps of Scheme I.

(7) S. Winstein, C. G. Kreiter, and J. I. Braumann, *J. Am. Chem. Soc.*, **88**, 2047 (1966).

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On the Mechanism of Electron Impact Induced Elimination of Ketene in Conjugated Cyclohexenones and Correlations with Photochemistry^{1,2}

Sir:

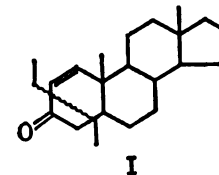
It is of significant mechanistic concern to note that, upon electron bombardment of certain molecules containing the 2-cyclohexenone moiety,³⁻⁶ a neutral

(1) Part XIII: High-Resolution Mass Spectrometry in Molecular Structure Studies; for part XII, see D. H. Smith, H. K. Schnoes, and A. L. Burlingame, in preparation.

(2) This research was supported in part by the National Aeronautics and Space Administration, Grant NsG 101, and Public Health Service Grant No. AM-709, National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(3) Previous experimenters have employed deuterium labeling to confirm the origin and identity of the specific atoms involved in the formation of ketene. See R. H. Shapiro, J. M. Wilson, and C. Djerassi,

species is eliminated containing which would formally require favorable^{7,8} scission of a vinyl androsten-3-one (I).



The extent of ketene elimination of a series of methyl-s is presented in Table I. The

Table I. Loss of Ketene from 2-C

Compound	Mass M - C ₂ H ₂ O
II, R ¹ -R ⁸ = H	54
III, R ¹ = CH ₃	68
IV, R ¹ , R ² = CH ₃	82
V, R ¹ = CH ₃	68
VI, R ¹ , R ⁴ = CH ₃	82
VII, R ⁴ = CH ₃	68
VIII, R ⁴ , R ^{4'} = CH ₃	82
IX, R ⁴ , R ^{4'} = CH ₃	82
X, R ¹ , R ⁴ , R ^{4'} = CH ₃ ^a	96
XI, R ⁴ = CH ₃ ^c	54
XII, R ⁴ , R ^{4'} , R ⁸ = CH ₃ ^c	82

^a Values are calculated from *c* for all compounds except IV, IX, otherwise specified. ^b J. H. Bowie (1966). ^c See ref 10.

by deuterium labeling⁹ a spectra¹⁰ is prominent in those compounds which have substituent at C-4. The steroid $\Delta^{1(10)}$ -4-methyl-2-octalone (X talone (XIV), *trans*- Δ^1 -9,10-*cis*- Δ^1 -9,10-dimethyl-2-octalone tetrahydroindan-5-one (XV one (XVIII), from which ketone impact, also fulfill the substituent at the carbon γ to

A related minimal structure established for the photolysis of *t*-butyl alcohol of cyclohexyl bicyclo[3.1.0]hexan-2-one system; substituents are required at C-4 the type VIII to XIX is observed in minimal structural requirements

Steroids, **11** (1963); H. Budzikiewicz "Interpretation of Mass Spectra of Day, Inc., San Francisco, Calif., 1964

(4) V. I. Zaretskii, N. S. Wulfson, *Letters*, **3879** (1966).

(5) M. Audier, M. Fetizon, and V. **415** (1964).

(6) R. H. Shapiro and C. Djerassi, (7) L. Ahlquist, R. Ryhage, E. Sten *Kemi*, **14**, 211 (1959).

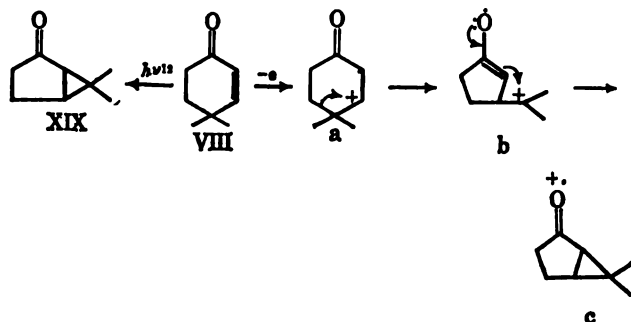
(8) K. Biemann, "Mass Spectrometry New York, N. Y., 1962, pp 98-99, 31

(9) M. Senn, W. J. Richter, and A. **87**, 680 (1965).

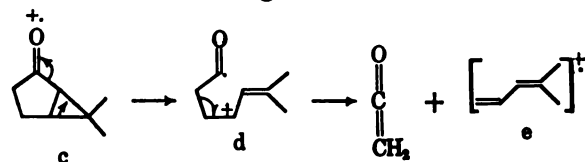
(10) In the case of C-6 substituted M - (41 + R₄).

(11) W. G. Dauben, G. W. Shaffer, observations.

before fragmentation occurs in the vibronically excited state, a rearrangement of some of the molecular ions of VIII occurs to molecular ion c, formally analogous to that of compound XIX, the photoisomer derived from the enone VIII. One pathway by which



the ketene could be lost would be the subsequent fragmentation of this rearranged molecular ion c.



In the high-resolution mass spectrum of the bicyclic photoproduct XIX, the ion formed by elimination of ketene from the molecular ion makes the major contribution ($\% \Sigma, 27.47$) to the total ion current. The loss of C-2 and C-3 is confirmed in the spectrum of 6,6-dimethylbicyclo[3.1.0]hexan-2-one-3,3- d_2 . It appears (see Figures 1 and 2) that the enone VIII generates a hydrocarbon fragmentation pattern primarily via loss of ketene and an oxygen fragmentation pattern by loss of ethylene. Decomposition of the bicyclic-[3.1.0] ketone XIX generates a strikingly similar hydrocarbon fragmentation pattern. Thus, 4,4-dimethyl-2-cyclohexenone may be another example in which rearrangement or fragmentation observed on photon absorption also occurs on electron impact.¹³⁻¹⁶

However, two points remain unexplained in this analogy to the photorearrangement. (a) Compounds I, VI, VII, and XIII, which do lose ketene on electron impact, have been observed not to rearrange on irradiation to the bicyclo system. (b) In addition, comparison of the mass spectrum of cholestenone's photoproduct¹⁷ with that of cholestenone indicates that the "photorearrangement" cannot be the major path under electron impact leading to loss of ketene from cholestenone.

Nonetheless, the bicyclo[3.1.0] system remains an attractive and reasonable general intermediate from which to lose ketene. The bicyclo[3.1.0] system could be generated by any of several bond migrations in the cyclohexenone molecular ion, including the "photorearrangement" VIII \rightarrow b. Migration to C-3 of a

(12) O. L. Chapman, T. A. Rettig, A. I. Dutton, and P. Fitton, *Tetrahedron Letters*, 2049 (1963).

(13) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

(14) N. J. Turro, D. C. Neckers, P. A. Leermakers, D. Seldner, and P. D. Angelo, *J. Am. Chem. Soc.*, **87**, 4097 (1965).

(15) P. Brown, J. Kossanyi, and C. Djerassi, *Tetrahedron Suppl.*, [I] **8**, 241 (1966).

(16) After submission of this manuscript, Professor Carl Djerassi of Stanford University informed us that similar observations had been recorded in his laboratory but with a different interpretation. See R. L. N. Harris, F. Komitsky, Jr., and C. Djerassi, *J. Am. Chem. Soc.*, in press.

(17) B. A. S. Goulders, W. W. Kwie, W. Klyne, and P. D. Gardner, *Tetrahedron*, **21**, 2973 (1965).

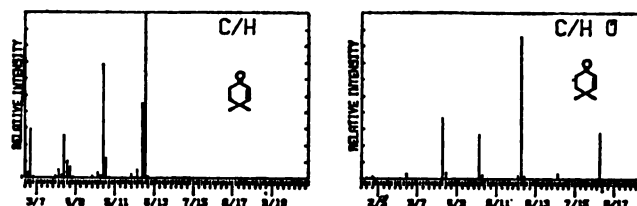


Figure 1. The complete high-resolution mass spectrum of 4,4-dimethylcyclohex-2-enone.

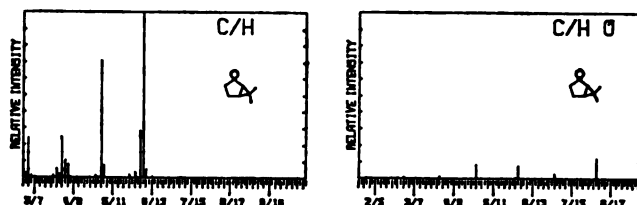
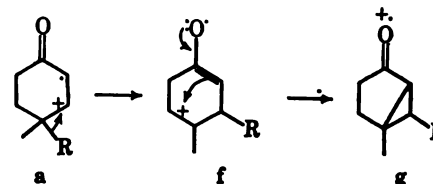


Figure 2. The complete high-resolution mass spectrum of 7,7-dimethylbicyclo[3.1.0]hexan-2-one.

methyl group from C-4¹⁸ as shown in a \rightarrow f could lead to formation of the ionized bicyclo[3.1.0]hexan-2-one derivative (f \rightarrow g) in a manner analogous to that postulated in b \rightarrow c. In polycyclic systems three different alkyl migrations are possible from the quaternary center γ to the carbonyl group. In VII and XIII



migration of the tertiary γ -hydrogen atom could also lead to a bicyclo[3.1.0]hexan-2-one (a \rightarrow g). The suggestion is made, then, that ketene is lost from cyclohexenone derivatives through a rearranged bicyclo-[4.1.0]hexan-2-one system, whose formation requires one or another bond migration from the substituted γ carbon.

The structural features reported above are necessary for the loss of ketene from conjugated cyclohexenones, although reports indicate that the relative importance of this elimination may be altered by the presence of additional functional groups¹⁸ and, in the rigid steroid systems, by different stereochemistry.¹⁹

Acknowledgment. We wish to thank Mr. B. Simoncit and Mr. D. H. Smith for determination of the high-resolution mass spectral data.

(18) S. H. Eggers, *Tetrahedron Letters*, 733 (1965).

(19) H. Egger, *Monatsh.*, **97**, 1290 (1966).

(20) (a) Hoffmann-LaRoche Company, Basel, Switzerland; (b) Public Health Service Predoctoral Fellow, 1965-1967.

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Intramolecular Migration of Tritium and Deuterium during Nonenzymatic Aromatic Hydroxylation

Sir:

It has recently been discovered that during enzymatic hydroxylation of aromatic substrates the substituent

Table I. The Absence of Intramolecular Migration of Deuterium during Electrophilic Aromatic Substitutions of Selectively Deuterated Substrates^a

Compound	Reagent	Product
[<i>p</i> - ³ H]Acetanilide (1.0)	Br ₂ -HOAc ^b	<i>p</i> -Bromoacetanilide (0.00)
[<i>p</i> - ³ H]Acetanilide (1.0)	(C ₆ H ₅) ₂ CHOH-trifluoroacetic acid	<i>p</i> -Acetamidophenyldiphenylmethane (0.03)
[<i>p</i> - ³ H]Acetanilide (1.0)	HNO ₃ -H ₂ SO ₄	Aromatic ring hydrogens exchange with solvent at room temperature
[<i>p</i> - ³ H]Toluene (0.73)	Br ₂	<i>p</i> -Bromotoluene (0.00)
[<i>p</i> - ³ H]Toluene (0.73)	(C ₆ H ₅) ₂ CHOH-trifluoroacetic acid	<i>p</i> -Tolyldiphenylmethane (0.01)
[<i>p</i> - ³ H]Toluene (0.73)	Succinic anhydride-AlCl ₃	AlCl ₃ catalyzes the exchange of the ring protons with the proton of the carboxylic acid ^c produced in the reaction
[5- ³ H]-Salicylic acid (0.38)	Br ₂ -HOAc	5-Bromosalicylic acid (0.02)
[<i>p</i> - ³ H]N,N-Dimethylaniline (1.0)	Diazotized anthranilic acid	Methyl red (0.02)
[<i>p</i> - ³ H]Phenol (0.44)	Cold, dilute H ₂ SO ₄ and HNO ₃	<i>p</i> -Nitrophenol (0.00)

^a The numbers in parentheses indicate the number of deuterium atoms per molecule. ^b With the *para*-tritio compound, no retention was obtained with brominations in HOAc, pyridine, 8% HBr in HOAc, water, or the solid state. ^c This result is in agreement with the observations of J. Eastham, J. Bloomer, and F. Hudson, *Tetrahedron*, **18**, 653 (1962).

Table II. Nonenzymatic Hydroxylations

Oxidizing system	Substrate	Product	% retention of heavy isotope
F ₂ CCOOH ^a	[<i>p</i> - ³ H]Acetanilide [<i>p</i> - ³ H]Acetanilide	[<i>m</i> - ³ H] <i>p</i> -Hydroxyacetanilide [<i>m</i> - ³ H] <i>p</i> -Hydroxyacetanilide	9.6 ^a 7.5
Fe(II), H ₂ O ₂ , EDTA ^b	[<i>p</i> - ³ H]Acetanilide	<i>p</i> -Hydroxyacetanilide	1.9
Fe(II), O ₂ , ascorbic acid, EDTA ^b	[<i>p</i> - ³ H]Acetanilide	<i>p</i> -Hydroxyacetanilide	1.0-1.2
Fe(III), H ₂ O ₂ , catechol ^c	[<i>p</i> - ³ H]Acetanilide	<i>p</i> -Hydroxyacetanilide	0.9-1.0
Fe(II), O ₂ , ascorbic acid, EDTA ^{b,d}	[5- ³ H]Salicylic acid	2,5-Dihydroxybenzoic acid	2.1
Elbs persulfate oxidation	[5- ³ H]Salicylic acid	2,5-Dihydroxybenzoic acid	2.1

^a Isotopically labeled acetanilides had less than 1% random label. The reaction procedure consists of storing a mixture of 1 ml of H₂O₂ (90%), 1 ml of trifluoroacetic acid, 0.5 ml of chloroform, and 1 mmole of acetanilide at 5° for 5 hr. Dilution of the reaction mixture with water, extraction with ethyl acetate, and paper chromatography of the residue left after evaporation of the solvent produced 1-2% yields of *p*-hydroxyacetanilide. The only other detectable product was *o*-hydroxyacetanilide. ^b Hydroxylated according to B. Brodie, J. Axelrod, P. Shore, and S. Udenfriend, *J. Biol. Chem.*, **208**, 741 (1954). Acetanilide underwent substantial *meta* hydroxylation. Salicylic acid formed both 2,3- and 2,5-dihydroxybenzoic acid. ^c H. Hamilton, J. Hanifin, and J. Friedman, *J. Am. Chem. Soc.*, **88**, 5266 (1966). ^d The random label in this substrate is approximately 2%. Microsomal hydroxylation of this substrate did not lead to significant retention (J. Daly, unpublished results). ^e This is the value obtained after the addition of cold carrier and recrystallization to constant specific activity.

(³H, ²H, Cl, Br, etc.) displaced by the entering hydroxyl migrates to an adjacent position in the aromatic ring.¹⁻⁶

We now wish to report that this novel intramolecular shift occurs also in certain nonenzymatic substitution reactions. Because cationoid intermediates might be expected to facilitate such migrations, a variety of typical electrophilic aromatic substitution reactions were examined. Selectively deuterated and tritiated compounds were prepared either by palladium-catalyzed hydrogenolysis of the corresponding chloro, bromo, or benzoxazolyl ether⁷ derivative or, in a few cases, such as the preparation of [*p*-³H] toluene, by neutralization of organolithium compounds with deuterium oxide (Table I). Hydrogenolysis of *p*-O-tosyloxyacetanilide

with Raney nickel in the presence of deuterium or tritium led to acetanilide with substantial randomization of label throughout the ring.

The position of the label in the deuterated compounds was ascertained by nmr spectroscopy and the extent of deuterium substitution measured by mass spectrometry. The products of electrophilic substitution from the specifically labeled compounds (Table I) showed no significant retention of deuterium, in agreement with earlier findings on bromination and nitration.⁸

Of the six nonenzymatic hydroxylating systems examined (Table II), only hydroxylation of [*p*-³H]- or [*p*-³H]acetanilide by trifluoroacetic acid led to significant migration rather than complete displacement of the *para* substituent.⁹

Unreacted starting material which was reisolated after the reaction retained the same specific activity and the label was still in the *para* position, since it was lost completely on bromination. The product, [*m*-³H]*p*-hydroxyacetanilide, had deuterium in the ring

(8) L. Melander, *Arkiv Kemi*, **2**, 211 (1950).

(9) The migration of a methyl substituent during hydroxylation of prehnitene with trifluoroacetic acid and boron trifluoride in principle provides a precedent and analogy: C. Buehler and H. Hart, *J. Am. Chem. Soc.*, **85**, 2177 (1963).

(1) G. Guroff, C. Reifsnyder, and J. Daly, *Biochem. Biophys. Res. Commun.*, **24**, 720 (1966).

(2) G. Guroff, M. Levitt, J. Daly, and S. Udenfriend, *ibid.*, **25**, 253 (1966).

(3) G. Guroff, K. Kondo, and J. Daly, *ibid.*, **25**, 622 (1966).

(4) J. Renson, J. Daly, H. Weissbach, B. Witkop, and S. Udenfriend, *ibid.*, **25**, 504 (1966).

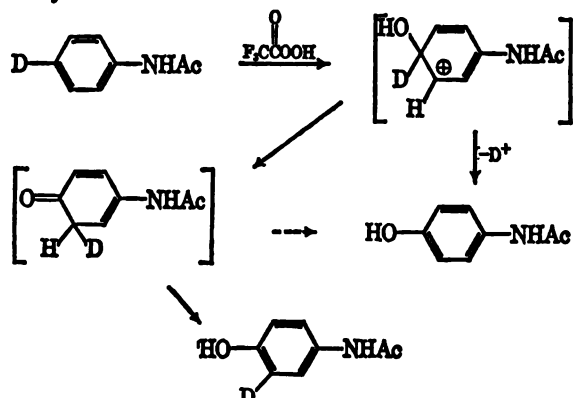
(5) S. Udenfriend, P. Zaltzman-Nirenberg, J. Daly, G. Guroff, C. Chidsey, and B. Witkop, *Arch. Biochem. Biophys.*, in press.

(6) G. Guroff, J. Daly, D. Jerina, J. Renson, S. Udenfriend, and B. Witkop, *Science*, in press.

(7) W. J. Musliner and J. W. Gates, Jr., *J. Am. Chem. Soc.*, **88**, 4271 (1966).

positions adjacent to the hydroxyl group by comparison of the intensity of the nmr signals of the 3,5-ring protons with those of the 2,6 protons. The retention of tritium (9.6%) and deuterium (7.5%) obtained on *para*-hydroxylation of acetanilide with trifluoroacetic acid may be compared to the retention of tritium (40–50%) and deuterium (15%) in the enzymatic hydroxylation of acetanilide.⁸

Mechanistically, the hydroxylation with trifluoroacetic acid is likely to involve attack by "OH⁺" or a related species and presumably proceeds by the pathway



The nature of the oxygenating species involved in the enzymatic hydroxylation of aromatic substrates is still a subject for speculation. The hydroxylating systems of Table II have served as models for the hydroxylases.¹⁰ The degree of retention in other model systems currently under investigation may serve as a useful further guide for the correlation of enzymatic and nonenzymatic hydroxylations.¹¹

(10) V. Ullrich and H. Staudinger, in "Biological and Chemical Aspects of Oxygenases," K. Bloch and O. Hayaishi, Ed., Maruzen Co., Ltd., Tokyo, 1966, pp 235–249.

(11) A related phenomenon, the oxidative coupling of 4-³H-2,6-xyleneols, gives *para*-substituted polymers with 23% retention of tritium. In this case a radical coupling mechanism has been proposed in which electron-transfer resonance stabilization leads to (rearranged) phenonium ions: W. A. Butte, Jr., and C. C. Price, *J. Am. Chem. Soc.*, **84**, 3567 (1962).

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Chemical Conversion of Tyrosine to 6-Hydroxyindoles

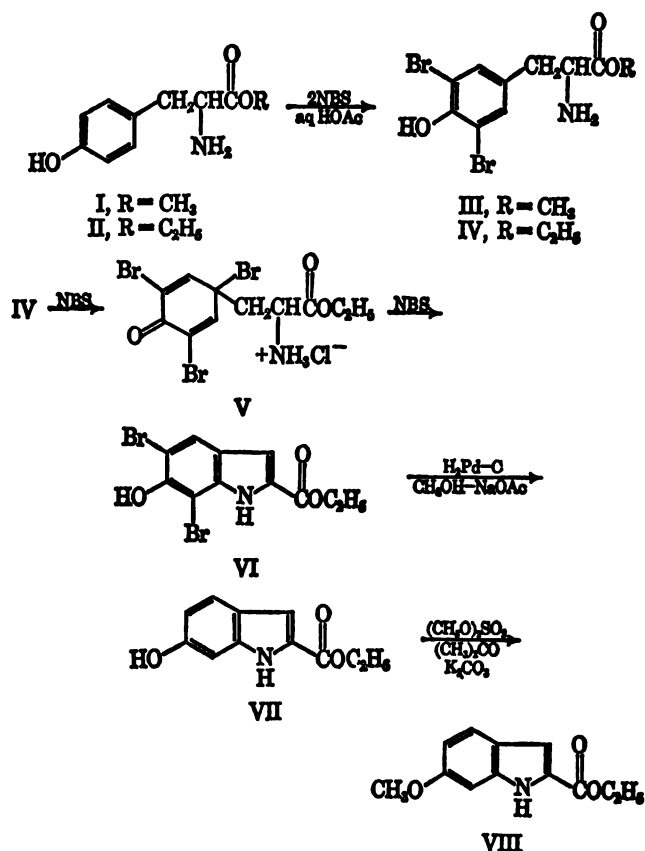
Sir:

Silver oxide, ferricyanide, and other oxidants convert 3,4-dihydroxyphenylalanine (DOPA), 3-hydroxytyramine, noradrenaline, and related catecholamines to 5,6-dihydroxyindole derivatives.¹ The transformation of tyrosine to 5,6-dihydroxyindole-2-carboxylic acid, however, is only known as an enzymatic reaction and requires *tyrosinase* to effect the initial oxidation to DOPA.²

We wish to report the first direct nonenzymatic conversion of methyl or ethyl tyrosinate (I and II, respectively) to the monohydroxyindole VI by the action of

(1) W. L. Dulière and H. S. Raper, *Biochem. J.*, **24**, 239 (1930); cf. R. A. Heacock, *Chem. Rev.*, **59**, 181 (1959).

(2) H. S. Raper, *Biochem. J.*, **21**, 89 (1927).



N-bromosuccinimide (NBS). This transformation was discovered when we observed that amino-terminal tyrosine peptides failed to undergo the expected cleavage on treatment with NBS.³

When 1.0 mM solutions of the tyrosine esters I–IV in 0.25 M HOAc were treated with aliquots of a 20 mM aqueous NBS solution, the rapid appearance of the characteristic bromo dienone chromophore ($\epsilon_{260-270} \sim 8000$) was observed. This absorption reached a maximum with 3 equiv of NBS on I or II and 1 equiv on the dibromo derivatives III and IV. The bromo dienone V was isolated on a preparative scale from II and from the dipeptides Tyr-Ala and Tyr-Phe. The reactive bromine in V liberated iodine in the starch-potassium iodide test. The analysis accounts for the introduction of three atoms of bromine to give the tri-bromo dienone hydrochloride V. This remarkable intermediate, which has been discussed previously in connection with the mechanism of cleavage,⁴ is apparently stabilized by the ionized amino group in close proximity to the dienone system. In such a labile system, intramolecular Michael addition of the amino group to the dienone would be competitive with the formation of the spirodienone lactone, the reaction underlying the cleavage of peptide bonds.

This was indeed found to be the case. In contrast to the comparatively stable bromo dienone lactone of the tyrosine peptide cleavage,⁴ the absorption of the labile dienone V at 260 m μ on standing decreased slowly, and a new absorption at 320 m μ began to develop. This absorption reached a maximum with 2 equiv of NBS on esters III and IV and 4 equiv on esters I and II after approximately 16 hr at room temperature or

(3) M. Wilchek and B. Witkop, *Biochem. Biophys. Res. Commun.*, **26**, 296 (1967).

(4) G. L. Schmir, L. A. Cohen, and B. Witkop, *J. Am. Chem. Soc.*, **81**, 2228 (1959).

10-min heating on a steam bath. In all cases identical spectra resulted, indicative of III and IV being intermediates in the reaction of I and II with NBS. Tyrosinamide and tyrosine-N-methylamide gave similar results. Free tyrosine, 3,5-dibromotyrosine, tyramine, and N-acetyl-3,5-dibromotyrosine ethyl ester failed to produce the 320-m μ chromophore on treatment with NBS.

When the reaction was carried out on a preparative scale, starting with II, IV, or tyrosinamide in 40% aqueous acetic acid, crystalline products were isolated in 20% yield after chromatography on silica (CHCl₃-CH₃OH, 9:1). Infrared, ultraviolet, nmr, and mass spectra and elemental analyses suggest the structure of ethyl 5,7-dibromo-6-hydroxyindole-2-carboxylate (VI) or its amide for the 320-m μ product. The amide [mp 247° dec, λ_{\max} 315 m μ (EtOH)] exhibited a triplet of parent peaks at m/e 331.879, 333.874, and 335.873 in the mass spectrometer consistent with the formula C₉H₆N₂O₂Br₂ [calcd, 331.88 (⁷⁹Br-⁷⁹Br), 333.879 (⁷⁹Br-⁸¹Br), and 335.878 (⁸¹Br-⁸¹Br)].

The formation of a side product, an unstable red aminochrome, λ_{\max} 480 and 320 m μ , is especially noticeable at pH values above 5. In addition, a colorless, crystalline, indolic compound [λ_{\max} 315 m μ (log ϵ 4.33), mp 152-155°, C₁₁H₁₀NO₄Br, m/e 298.979 and 300.979 (calcd 298.979 and 300.977 for ⁷⁹Br and ⁸¹Br)] is obtained from II or IV. The same product, ethyl 5,6-dihydroxy-7-bromoindole-2-carboxylate, was obtained from ethyl 3,4-dihydroxyphenylalanate on oxidation with NBS. NBS in this case converts tyrosine ester to products which as a rule arise only from DOPA.

The dibromoindole VI was reductively debrominated to VII with palladium on charcoal in buffered methanol [mp 169-175°; λ_{\max} (log ϵ) 320 m μ (4.32), 250 (3.95), 215 (4.28); parent m/e 205.078 (calcd for C₁₁H₁₁NO₃, 205.074)]. VII was methylated with dimethyl sulfate in anhydrous acetone containing fused potassium carbonate to give the known ethyl 6-methoxyindole-2-carboxylate (VIII). The ultraviolet spectrum [$\lambda_{\max}^{\text{EtOH}}$ 320 m μ (log ϵ 4.28), 250 (3.93), 215 (4.28); $\lambda_{\min}^{\text{EtOH}}$ 265 m μ (log ϵ 3.29)] and melting point (132-135°) agree with the reported data.⁵

The low-resolution mass spectrum reveals a parent peak (M) at m/e 219 and principal peaks at 204 (M - CH₃), 191 (M - CH₂=CH₂), 190 (M - C₂H₅), 173 (M - C₂H₅OH), 158 (M - C₂H₅OH - CH₃), 145 (M - C₂H₅OH - CO), 130 (M - C₂H₅OH - CH₃ - CO), 119 (M - C₂H₅OH - CO - CN), 102 (M - C₂H₅OH - CH₃ - 2CO), 76 (M - C₂H₅OH - CH₃ - 2CO - CN).

This transformation is now being used for the determination of amino-terminal tyrosine in proteins and for the synthesis of 6-hydroxyindole derivatives.

(5) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 574 (1958).

(6) Fellow in the Visiting Program of the U. S. Public Health Service, 1966-1967, on leave of absence from the Weizmann Institute of Science, Rehovoth, Israel.

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Amino Acid Sequence around the Histidine Residue of the α -Lytic Protease of *Sorangium* sp., a Bacterial Homolog of the Pancreatic Serine Proteases

Sir:

The elucidation of the amino acid sequence of chymotrypsinogen A,¹ chymotrypsinogen B,² trypsinogen,^{3,4} and, in part, elastase⁵ has established that the pancreatic serine proteases are homologous with respect to a subsequence in which two histidines and a cystine residue are components.⁶ In chymotrypsin, for example, these components are histidine-40 and -57 and the cystine residue comprised of half-cystine-42 and -58. The discovery of this common structure, in which a disulfide bond could be considered to have the function of bringing the two histidines close together, has prompted several proposals of reaction mechanisms⁷⁻⁹ which assign a catalytic function to both histidine residues. However, the kinetic evidence implicates only one.¹⁰

The α -lytic protease of *Sorangium* sp. is a bacterial protease which is unusual in two respects: it has the same active serine sequence as the pancreatic proteases, i.e., Asp-Ser-Gly-Gly, and it has only one histidine residue.¹¹⁻¹³ The sequences at its three disulfide bridges are under investigation and, in this communication, we report the sequence of a histidylcystine structure which establishes a further homology with the pancreatic enzymes.

The α -lytic protease, prepared by methods previously described,¹⁴ was digested with pepsin and submitted to the pH 6.5 diagonal procedure of Brown and Hartley.¹⁵ The resulting peptide map is shown in Figure 1. A single peptide (B1) staining for histidine was observed off the diagonal and was paired with a more acidic peptide B2. Peptide B1 stained red and B2 yellow with the cadmium-ninhydrin reagent of Heilmann, *et al.*¹⁶ Peptide B1, after isolation by preparative electrophoresis at pH 6.5, was found to be separable into two histidine peptides, B1A and B1B, by electrophoresis at pH 1.8 (60 v/cm for 60 min). Peptides B1A, B1B, and B2 were subjected to amino acid and sequential analysis from the N-terminal by the "dansyl-Edman" procedure.^{17,18} Peptide B1A

(1) B. S. Hartley, *Nature*, **201**, 1284 (1964).

(2) A. Furka, L. B. Smillie, K. Stevenson, and C. O. Parkes, *Federation Proc.*, **25**, 789 (1966).

(3) K. A. Walsh and H. Neurath, *Proc. Natl. Acad. Sci. U. S.*, **52**, 884 (1964).

(4) O. Mikeš, V. Holeyšovský, V. Tomášek, and F. Šorm, *Biochim. Biophys. Res. Commun.*, **24**, 346 (1966).

(5) B. S. Hartley, J. R. Brown, D. L. Kauffman, and L. B. Smillie, *Nature*, **207**, 1157 (1965).

(6) L. B. Smillie and B. S. Hartley, *Biochem. J.*, **101**, 232 (1966).

(7) K. A. Walsh, D. L. Kauffman, K. S. V. Sampath Kumar, and H. Neurath, *Proc. Natl. Acad. Sci. U. S.*, **51**, 301 (1964).

(8) B. S. Hartley in "Structure and Activity of Enzymes," T. W. Goodwin, J. L. Harris, and B. S. Hartley, Ed., Academic Press Inc., London, 1964, p. 47.

(9) M. L. Bender and F. J. Kézdy, *J. Am. Chem. Soc.*, **86**, 3704 (1964).

(10) F. J. Kézdy, G. E. Clement, and M. L. Bender, *J. Am. Chem. Soc.*, **86**, 3690 (1964).

(11) D. R. Whitaker, L. Jurásek, and C. Roy, *Biochem. Biophys. Res. Commun.*, **24**, 173 (1966).

(12) L. Jurásek and D. R. Whitaker, *Can. J. Biochem.*, **45**, 917 (1967).

(13) D. R. Whitaker and C. Roy, *ibid.*, **45**, 911 (1967).

(14) D. R. Whitaker, *ibid.*, **43**, 1935 (1965).

(15) J. R. Brown and B. S. Hartley, *Biochem. J.*, **101**, 214 (1966).

(16) J. Heilmann, J. Barollier, and E. Watzke, *Z. Physiol. Chem.*, **309**, 219 (1957).

(17) W. R. Gray and B. S. Hartley, *Biochem. J.*, **89**, 59P (1963).

(18) W. R. Gray and B. S. Hartley, *ibid.*, **89**, 379 (1963).

Table I. Amino Acid Composition (Ratios) and Sequence Analysis of Peptides Isolated from Peptic Digests of α -Lytic Protease of *Sorangium*^a

Peptide	Sequence												
B1A	Val	Thr	Ala	Gly	His	CySO ₃ H	Gly	Thr	Val	Asn	Ala		
	→	→	→	→	→	→	→	→	←	←	←		
	0.97	0.97	0.97	1.00	0.97	1.06	1.00	0.97	1.00	1.03	1.00		
	L1b	L1a					L4			L2a			
	→	→	→	→	→	→	→	→	→	→	→		
	1.08	0.92	1.00	1.00	0.93	0.80	1.33	1.00	0.93	0.93	1.07		
	L1c						L3						
	→	→	→	→	→	→	→	→	→	→	→		
	1.00	0.93	1.07	0.98	1.00	0.97	0.99	1.00	1.07				
							L2c						
							→	→	→	→	→		
							1.10	1.06	0.95	0.79	1.06	1.02	1.02
B1B	Phe	Val	Thr	Ala	Gly	His	CySO ₃ H	Gly	Thr	Val	Asn	Ala	
	→	→	→	→	→	→	→	→	→	→	→	→	
	0.60	1.02	0.97	1.12	1.07	0.87	1.07	1.07	0.97	1.02	1.07	1.12	
B2	CySO ₃ H	Ser	Val	Gly	Phe								
	→	→	→	→	→								
	0.96	1.02	1.02	1.04	0.96								

^a The symbols → → indicate N-terminal analyses by the "dansyl-Edman" procedure; ← represents C-terminal analyses with carboxypeptidase.

Table II. Histidine Disulfide Structures in α -Lytic Protease, Chymotrypsins A and B, Trypsin, and Elastase^a

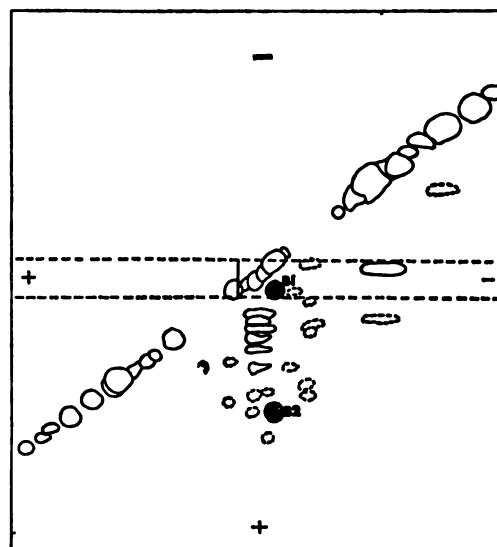
	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63
Chymo- trypsin A	Phe	His	Phe	Cys	Gly	Gly	Ser	Leu	Ile	Asn	Glu	Asn	Try	Val	Val	Thr	Ala	Ala	His	Cys	Gly	Val	Thr	Thr	Ser
Chymo- trypsin B	Phe	His	Phe	Cys	Gly	Gly	Ser	Leu	Ile	Ser	Glu	Asp	Try	Val	Val	Thr	Ala	Ala	His	Cys	Gly	Val	Thr	Thr	Ser
Trypsin	Tyr	His	Phe	Cys	Gly	Gly	Ser	Leu	Ile	Asn	Ser	Gln	Try	Val	Val	Ser	Ala	Ala	His	Cys	Tyr	Lys	Ser	Gly	Ile
Elastase	Ala	His	Thr	Cys	Gly	Gly	Thr	Leu								Thr	Ala	Ala	His	Cys	Val	Asp	Arg	Glx	
α -Lytic protease				Cys	Ser	Val	Gly	Phe						Phe	Val	Thr	Ala	Gly	His	Cys	Gly	Thr	-Val	Asn	Ala

^a The disulfide bridge is between residues corresponding to half-cystines-42 and -58 of chymotrypsin in each case.

was further degraded by digestion with α -lytic protease (molar ratio 100:1 in 0.05 M N-ethylmorpholine buffer, pH 8.0, for 16 hr at 37°). The resulting peptides (designated as L) were separated by high-voltage electrophoresis at pH 6.5 and 1.8 and subjected to amino acid and sequential analysis. Peptides B1A and B1A13 were also digested with carboxypeptidase to determine C-terminal residues. The results of these analyses are presented in Table I.

The above results assign sequences to peptides B1B and B2 which are compared in Table II with the sequences around histidine-40 and histidine-57 of the pancreatic serine proteases. Within the limits of the comparison, the histidine sequence of the bacterial enzyme shows as much homology with the histidine-57 sequences of the pancreatic enzymes as the latter do with one another; e.g., like trypsin, the bacterial enzyme has six direct matches with the chymotrypsin sequence from residues 52 to 63; in addition, it has a simple reversal of the chymotrypsin sequence at residues 60 and 61. As histidine-57 is the histidine which is alkylated when chymotrypsin^{19,20} and trypsin²¹ react with their chloromethyl ketone inhibitors, the homology is with sequences around a histidine of proven

significance. The existence of a "histidine loop" in the bacterial enzyme is unproven at present, and peptide B2 is placed on the N-terminal side of peptide

**Figure 1.**

B1B merely for comparison with the C-terminal sequences of histidine-40. Peptide B2 shows no homology with these sequences.

(19) E. B. Ong, E. Shaw, and G. Schoellmann, *J. Biol. Chem.*, **240**, 694 (1965).

(20) K. J. Stevenson and L. B. Smillie, *J. Mol. Biol.*, **12**, 937 (1965).

(21) V. Tomášek, E. S. Severin, and F. Šorm, *Biochem. Biophys. Res. Commun.*, **20**, 545 (1965).

The sequence of subtilisin has been reported recently.²² Its histidine and active serine sequences are completely different from those of the pancreatic enzymes. The present evidence indicates therefore that bacterial serine proteases have evolved along at least two independent pathways.

Acknowledgments. We thank Miss C. Nayler and Mr. E. Paradowski for expert technical assistance. This work has been supported by the Medical Research Council of Canada, The Life Insurance Medical Research Fund, and the National Institutes of Health, U. S. Public Health Service (Grant AM-06287).

(22) E. L. Smith, F. S. Markland, C. B. Kasper, R. J. De Lange, M. Landon, and W. H. Evans, *J. Biol. Chem.*, **241**, 5974 (1966).

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Kinetic Properties of the α -Lytic Protease of *Sorangium* sp.

Sir:

An accompanying communication¹ gives evidence that the amino acid sequence around the only histidine residue of a bacterial protease is homologous with the sequence around histidine-57 of chymotrypsin. This evidence, coupled with previous evidence² of homology

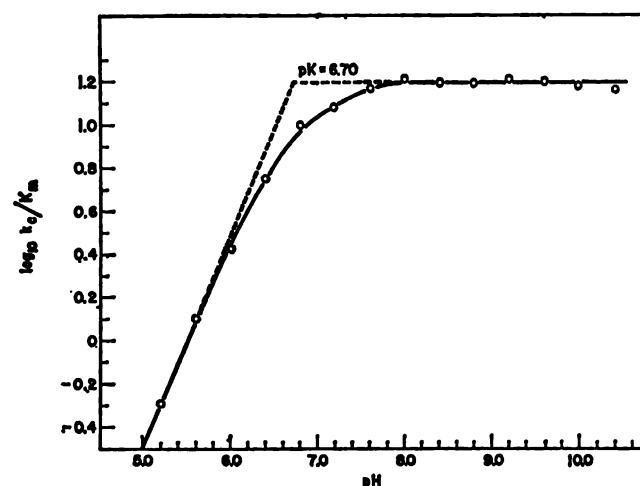


Figure 1. Hydrolysis of N-acetyl-L-valine methyl ester in 0.10 M KCl at 25.0°.

around the active serine residue, raises the question as to whether the reaction mechanism of the *Sorangium* enzyme differs in any way from that of chymotrypsin for, if it does not, reaction mechanisms which require chymotrypsin to have two catalytically functional histidines are clearly in need of reappraisal.

The kinetic data reported in this communication are based on measurements of esterase activity in a pH-Stat. The enzyme was prepared by a simplified version³ of the original procedure. Enzyme concen-

trations were determined from amino acid analyses and the known amino acid composition per mole of enzyme.⁴

Table I gives a comparison of esterase activities toward various N-benzoyl- and N-acetyl amino acid esters under reaction conditions which gave initial rates in direct proportion to both the enzyme and the substrate concentration. As the over-all kinetics are Michaelis-Menten kinetics, the second-order velocity constants are designated as k_c/K_m ratios where k_c is the catalytic rate constant (k_{cat}).⁵ It is evident from the range of substrate concentration which gave second-order kinetics that all values of K_m are greater than 10 mM. An earlier comparison⁶ of the enzyme's action pattern on the A and B chains of oxidized insulin had indicated a pancreatic elastase-like specificity for linkages involving the carbonyl groups of neutral, aliphatic amino acids; the specificity shown by Table I is in accordance with these findings.

Table I. Esterase Activities of the α -Protease at pH 8.0 in 0.10 M KCl at 25.0°

Substrate	[S] ₀ , mM	k_c/K_m , M ⁻¹ sec ⁻¹
Bz-Arg-OEt	11	0.00
Ac-Tyr-OEt	6.3	0.00
Ac-Trp-OMe	2.3	0.00
Bz-Gly-OMe	2.6-10.5	8.07
Ac-Val-OMe	0.60-6.0	16.3
Ac-Ala-OMe	1.0-3.0	26.3
Bz-Ala-OMe	1.02-10.2	723
Bz-D-Ala-OMe	11.0	0.00

* The enzyme concentration was 8.0×10^{-8} M for Bz-Ala-OMe and 5.0×10^{-8} M for the other esters.

Figure 1 shows the pH dependence of the hydrolysis of N-acetyl-L-valine methyl ester. The values of k_c and K_m for this substrate (Table II) were estimated from Eadie plots at higher substrate concentrations. When

Table II. K_m and k_c for Hydrolysis of N-Acetyl-L-valine Methyl Ester in 0.10 M KCl at 25.0°

pH	K_m , mM	k_c , sec ⁻¹
6.30	61 ± 8	0.28 ± 0.01
7.00	72 ± 6	0.94 ± 0.04
8.00	65 ± 4	1.1 ± 0.1

water is replaced by D₂O, the pK shifts from 6.7 (Figure 1) to 7.35, and k_c/K_m at the plateau is reduced 2.03-fold. The pH dependence of the hydrolysis of N-benzoyl-L-alanine methyl ester is essentially the same as that shown in Figure 1 (pK = 6.55) although, as indicated in Table I, the value of k_c/K_m at the plateau is much higher. Activity toward this substrate over the same pH range is unaffected by acetylation of the enzyme with acetic anhydride at pH 6.8 and 0°. The N-terminal alanine residue and the two ϵ -amino groups of the enzyme no longer react with 1-fluoro-2,4-dinitrobenzene or with cyanate⁷ after this treatment; the electrophoretic mobility of the enzyme at pH 5.0 is reduced by about one-third.

(3) D. R. Whitaker, *ibid.*, in press.

(4) L. Jurásek and D. R. Whitaker, *ibid.*, **45**, 991 (1967).

(5) B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, **86**, 3669 (1964).

(6) D. R. Whitaker, C. Roy, C. S. Tsai, and L. Jurásek, *Can. J. Biochem.*, **43**, 1961 (1965).

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(1) L. B. Smillie and D. R. Whitaker, *J. Am. Chem. Soc.*, **89**, 3350 (1967).

(2) D. R. Whitaker, L. Jurásek, and C. Roy, *Biochem. Biophys. Res. Commun.*, **24**, 173 (1966); D. R. Whitaker and C. Roy, *Can. J. Biochem.*, **45**, 911 (1967).

The pH dependence of k_c/K_m below pH 8 stems from the dependence of k_c , not of K_m , on pH (Table II). This pH dependence of k_c , the pK value of 6.7, its shift to 7.35 by D₂O, and the one-unit slope of the log k_c/K_m function all match the data for chymotrypsin and are consistent with a requirement for a single, unprotonated imidazole group.⁸ The isotope effect of 2.03 with D₂O is of the same magnitude as for chymotrypsin and is consistent with general basic catalysis by an imidazole group.⁹ The constancy of k_c/K_m from pH 8 to 10.5 and the activity of the acetylated enzyme indicate that the binding of neutral substrates is completely independent of pH and is not influenced by ionizations of α - or ϵ -amino groups of the enzyme. This represents the only contrast with chymotrypsin, as the latter undergoes a change in conformation at alkaline pH values and loses its ability to bind substrates.¹⁰

The above comparison thus supports the indications of the direct kinetic evidence for chymotrypsin, *i.e.*, that its reaction mechanism involves only one histidine group.

(8) M. L. Bender, G. E. Clement, F. J. Kézdy, and H. d'A. Heck, *J. Am. Chem. Soc.*, **86**, 3680 (1964); F. J. Kézdy, G. E. Clement, and M. L. Bender, *ibid.*, **86**, 3690 (1964).

(9) M. L. Bender, E. J. Pollock, and M. C. Neveu, *ibid.*, **84**, 595 (1962).

(10) H. L. Oppenheimer, B. Labouesse, and G. P. Hess, *J. Biol. Chem.*, **241**, 2720 (1966); M. L. Bender, M. J. Gibian, and D. J. Whelan, *Proc. Natl. Acad. Sci. U. S.*, **56**, 833 (1966).

(11) National Research Council of Canada Postdoctoral Fellow.

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Octahedral *vs.* Trigonal-Prismatic Coordination. The Structure of $(Me_4N)_2[V(mnt)_3]^{-1}$

Sir:

It has recently been shown that a large number of uncharged and monoanionic tris complexes of bidentate sulfur donor ligands possess trigonal-prismatic coordination and thus constitute the first examples of nonoctahedral six-coordinate complexes.²⁻⁶ However, prior to this work there has been no unequivocal evidence relating to the structures of the more highly reduced species having charges 2- and 3-. It has in fact been suggested² that some of these complexes could be closer to the classical octahedral configuration. In this communication, we report the molecular structure of $V(mnt)_3^{2-}$, which exhibits the first nontrigonal-prismatic coordination geometry for this class of compounds.

Black monoclinic crystals of $(Me_4N)_2[V(mnt)_3]^{-9}$

(1) Acknowledgment is made to the National Science Foundation for support of this research. We thank Professor R. Eisenberg of Brown University for several helpful discussions.

(2) E. I. Stiefel, R. Eisenberg, R. C. Rosenberg, and H. B. Gray, *J. Am. Chem. Soc.*, **88**, 2956 (1966).

(3) R. Eisenberg, E. I. Stiefel, R. C. Rosenberg, and H. B. Gray, *ibid.*, **88**, 2874 (1966).

(4) R. Eisenberg and J. A. Ibers, *ibid.*, **87**, 3776 (1965); *Inorg. Chem.*, **5**, 411 (1966).

(5) A. E. Smith, G. N. Schrauzer, V. P. Mayweg, and W. Heinrich, *J. Am. Chem. Soc.*, **87**, 5798 (1965).

(6) R. Eisenberg and H. B. Gray, to be published.

(7) The anion was first reported as the Ph_4As^+ salt by Davison and co-workers⁸ and later isolated using a somewhat different procedure as the $Ph_3P(Me)^+$ salt.⁹ The Me_4N^+ , Et_4N^+ , and Bu_4N^+ salts described

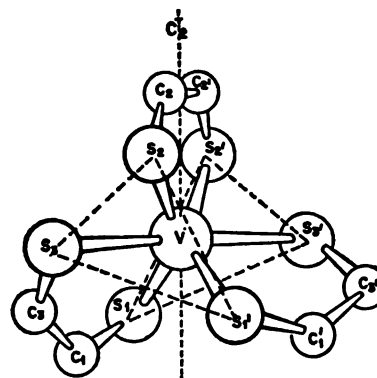


Figure 1. Perspective drawing of the molecular structure of the $V(mnt)_3^{2-}$ anion. The cyano groups are omitted.

were grown from acetone-2-propanol solutions. Precession photography revealed systematic extinctions indicating the space group $C2/c$ or C_c , with a cell of dimensions $a = 20.53$ Å, $b = 10.19$ Å, $c = 16.98$ Å, $\beta = 124^\circ 15'$ and vol. = 2935 Å³. The measured density of 1.37 ± 0.05 g cm⁻³ is consistent with four anions and eight cations in the unit cell of calculated density 1.40 g cm⁻³. Assuming the space group $C2/c$, the four vanadium atoms are required to occupy the 4c special positions of the space group and thus the anion is required to have a twofold symmetry axis. This assumption is verified by the satisfactory agreement ultimately obtained.

The intensity data were collected by the multiple film equiinclination Weissenberg technique using $Cu K\alpha$ radiation. Intensities were estimated visually and reduced to values of F_o by standard methods. The structure was solved by standard Patterson, least-squares, and Fourier methods. The R factor for 88 positional and thermal parameters (allowing the vanadium and three independent sulfurs to have anisotropic temperature factors) is currently 0.125 for 1187 independent nonzero reflections.

A perspective drawing of the coordination geometry is shown in Figure 1; some of the important bond distances are given in Table I. The vanadium lies on a

Table I. Important Bond Lengths in the $V(mnt)_3^{2-}$ Anion*

Bond	Bond length, Å	Bond	Bond length, Å
V-S ₁	2.36 ± 0.01	C ₁ -C ₂	1.37 ± 0.02
V-S ₂	2.35 ± 0.01	C ₂ -C ₃	1.29 ± 0.03
V-S ₃	2.36 ± 0.01	S ₂ -S ₂ '	3.17 ± 0.01
S ₁ -C ₁	1.72 ± 0.02	S ₁ -S ₂	3.11 ± 0.01
S ₂ -C ₂	1.74 ± 0.02	S ₁ '-S ₂	3.43 ± 0.01
S ₃ -C ₃	1.69 ± 0.02	S ₂ -S ₃	2.98 ± 0.01
		S ₁ '-S ₃	3.18 ± 0.01

* The prime denotes an atom related by the twofold axis.

twofold rotation axis which bisects one of the three ligands. The six sulfur donor atoms are located around the vanadium at an average distance of 2.36 ± 0.01 Å. The polyhedron described by these sulfur atoms is by no means a regular one, but for some purposes it is usefully described as a very distorted octahedron (*vide supra*). The intraligand S-S dis-

in this study were prepared by a procedure only slightly modified from that given in ref 8.

(8) A. Davison, N. Edelstein, R. H. Holm, and A. H. Maki, *J. Am. Chem. Soc.*, **86**, 2799 (1964).

(9) N. M. Atherton, J. Locke, and J. A. McCleverty, *Chem. Ind. (London)*, **29**, 1300 (1965).

tances are longer than those of other dithiolate complexes, being 3.17 ± 0.01 (on twofold) and 3.11 ± 0.01 Å for the other two ligands. Analogous distances have been found to be in the range 3.04–3.10 Å in all other structures.¹⁰

A useful criterion for discussion of coordination geometry in the systems under consideration is the average S–M–S angle involving pairs of donor atoms that are farthest apart. This angle averages $136 \pm 1^\circ$ in the known trigonal-prismatic structures^{2–6} and 180° for the perfect octahedron. However, we must first take into account the constraint imposed upon the idealized octahedron by the rigid nature of the maleonitriledithiolate ligands. Because of this constraint, the average for this angle in the chelated complex derived from an octahedron should be approximately 173° .¹¹ The average angle found for $V(mnt)_3^{2-}$ is 158.6° , which is somewhat closer to the “chelated octahedral structure.” The observed distortion is not simply a solid-state phenomenon since the rich electronic spectrum of $V(mnt)_3^{2-}$ remains essentially identical for various cations (Me_4N^+ , Et_4N^+ , Bu_4N^+ , and Ph_4As^+) in solid samples and in solutions. Furthermore, the infrared absorptions attributable to the anion are independent of the nature of the cation in solid samples. The distortion must then have an intramolecular electronic origin. We suggest that the two relatively short interligand S–S distances indicate some residual S–S bonding of the type which has been postulated as stabilizing the trigonal-prismatic structure in the uncharged complexes.² It is reasonable to expect the additional two electrons in the dianionic complex to cause the ligands to behave more like conventional dithiolates where a “classical” octahedral structure may be favored. Pitting these two effects against the geometric constants of the ligand, we can only say that nature has chosen an interesting compromise configuration; we have much work to do before we can begin to understand its subtleties.¹²

We have recently prepared the Ph_4As^+ salts of $M(mnt)_3^{2-}$ ¹³ for $M = Ti, V, Cr, Mn, Fe, Mo$,¹⁴

(10) (a) This is true for the three prismatic structures,^{2–4} the six square-planar structures,^{10b–c} and the two dimeric structures^{10b,i} which have been fully solved; (b) R. Eisenberg and J. A. Ibers, *Inorg. Chem.*, **4**, 605 (1965); (c) J. D. Forrester, A. Zalkin, and D. H. Templeton, *ibid.*, **3**, 1501 (1964); (d) *ibid.*, **3**, 1507 (1964); (e) C. J. Fritch, Jr., *Acta Cryst.*, **20**, 107 (1966); (f) D. Sartain and M. R. Truter, *Chem. Commun.*, **382**, (1966); (g) R. Eisenberg, Z. Dori, J. A. Ibers, and H. B. Gray, to be published; (h) J. M. Enemark and W. N. Lipscomb, *Inorg. Chem.*, **4**, 1729 (1965); (i) M. J. Baker-Hawkes, Z. Dori, R. Eisenberg, and H. B. Gray, to be published.

(11) For comparison, in $Cr(C_2O_4)_3^{2-}$, where the average “bite” O–Cr–O angle is 82° , we have calculated the average (largest) O–Cr–O angle to be 172° [J. N. van Niekerk and F. R. L. Schoenig, *Acta Cryst.*, **5**, 499 (1952)].

(12) For example, the V atom lies significantly out of the planes determined by the ligands alone. Pertinent geometrical parameters (such as interligand dihedral angles) determined solely from the MS_6 framework tend toward octahedral structure whereas related parameters set by the ligand planes suggest structure closer to trigonal prismatic. This finding may indicate that the ligand unit “prefers” the prism structure whereas the metal is desirous of octahedral coordination. Another interesting result arises on comparison of the C–C bond lengths in this structure with corresponding parameters from the $V(S_2C_2Ph)_3$ structure.¹⁴ The pertinent distances for $V(mnt)_3^{2-}$ are 1.37 ± 0.02 (two distances related by twofold axis) and 1.29 ± 0.03 Å, whereas the corresponding distances for $V(S_2C_2Ph)_3$ are 1.38 ± 0.01 and 1.46 ± 0.02 Å. The drastic shortening of one C–C bond (from 1.46 to 1.29 Å) suggests that the ligands do not participate equally in the two-electron reduction described by $VL_2 + 2e \rightarrow VL_2^{2-}$.

(13) E. I. Stiefel, L. Bennett, Z. Dori, C. Simo, T. H. Crawford, and H. B. Gray, to be published.

(14) Salts of these anions have also been prepared by M. Gerlock, S. F. A. Kettle, J. Locke, and J. A. McCleverty, *Chem. Commun.*,

Table II. Magnetic Properties of $M(mnt)_3^{2-}$ Complexes

Complex ^a	μ_{eff} , BM	Complex ^a	μ_{eff} , BM
$Ti(mnt)_3^{2-}$	Diamag ^b	$Fe(mnt)_3^{2-}$	3.00 ^b
$V(mnt)_3^{2-}$	1.82 ^c	$Cr(mnt)_3^{2-}$	3.90 ^c
$Cr(mnt)_3^{2-}$	2.89 ^c	$Co(mnt)_3^{2-}$	Diamag ^b
$Mn(mnt)_3^{2-}$	3.85 ^b		

^a Cation is Ph_4As^+ . Magnetic moments are for solid samples at room temperature. ^b Details reported in ref 13. ^c From ref 8.

W,¹⁴ and Re. We find that the Ti, V, and Cr complexes have nearly identical X-ray powder patterns and thus appear isomorphous. It is also interesting to note the magnetic properties of these first-row complexes. If the ligands are considered to be dianions, then the central metal is in the formal IV oxidation state and the moments are found to be those typical of low-spin octahedral compounds (see Table II). Furthermore, spectral studies indicate a certain similarity in the electronic structures of the complex anions. In view of the evidence, then, we suggest that all the first-row $M(mnt)_3^{2-}$ complexes have distorted octahedral structures. Thus, the picture seems to be emerging that the more highly reduced species will approach the classical octahedral stereochemistry, while the oxidized forms will invariably possess the unusual trigonal-prismatic coordination.

29 (1966). The magnetic results reported initially by these authors for the Mn and Fe compounds are apparently in error; our results are in agreement with their latest values (J. A. McCleverty, private communication).

(15) National Science Foundation Graduate Fellow, 1965–1967.

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Chronology in Photochemical Mechanisms.

The Reaction of 6-Phenyl-6-*p*-cyanophenylbicyclo[3.1.0]hex-3-en-2-one. Mechanistic Organic Photochemistry. XXV¹

Sir:

One of the most challenging questions in photochemistry concerns the chronology in photochemical reaction mechanisms. In particular, one would like to know at which point in a transformation electronic excitation is lost.

In the type B rearrangement² of 6,6-disubstituted bicyclo[3.1.0]hex-3-en-2-ones the first step seems without doubt to be fission of bond 2–4 (cyclohexane numbering; see Chart I) of the triplet³ excited state (1^*) of the bicyclic ketone; fission of this internal three-ring bond converts carbons 2 and 4 to valency-deficient centers to which aryl (or alkyl in nonaryl cases) migration might occur. However, the migration to C-2 and C-4 could occur immediately following bond 2–4 fission and therefore be a reaction of a triplet excited state (e.g., 2^*), or

(1) For paper XXIV see H. E. Zimmerman, R. W. Binkley, R. S. Givens, and M. A. Sherwin, *J. Am. Chem. Soc.*, in press.

(2) See H. E. Zimmerman, *Science*, **153**, 837 (1966).

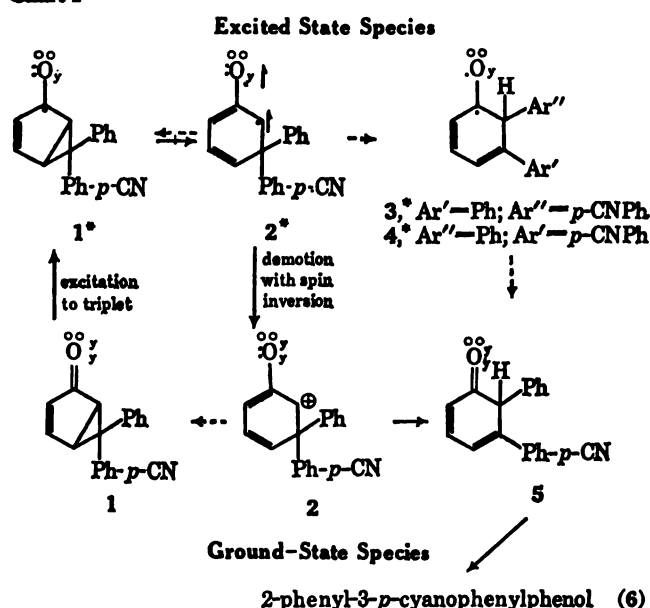
(3) Evidence for involvement of the triplet has been presented by H. E. Zimmerman, R. Keese, J. Nasielski, and J. S. Swenton, *J. Am. Chem. Soc.*, **88**, 4895 (1966).

Table I. Irradiation Runs of 6-*p*-Cyanophenyl-6-phenyl[3.1.0]bicyclohex-3-en-2-one

Run	Reactants	Type run	Recovered bicyclic ketone, %	Product distribution, % ^{a,b}		
				2-Phenyl-3- <i>p</i> -cyanophenylphenol	3- <i>p</i> -Cyanophenyl-4-phenylphenol	Photo acids ^c
1	Ketone 1a	<i>d</i>	86	34 ± 1	12 ± 2	55 ± 4
2	Ketone 1a	<i>d</i>	35	37 ± 1	12 ± 2	51 ± 4
3	Ketone 1b	<i>d</i>	71	14 ± 1	6 ± 2	80 ± 5
4	Ketone 1b	<i>d</i>	45	22 ± 1	7 ± 1	70 ± 4
5	Ketone 1a	<i>e</i>	89	45 ± 2	23 ± 6	32 ± 4
6	Ketone 1b	<i>e</i>	86	43 ± 2	21 ± 6	37 ± 4

^a Per cent of products other than recovered bicyclic ketone. ^b Mass balance 100 ± 2%. ^c Per cent based on total material. ^d Direct irradiation runs. ^e Sensitized runs with acetophenone absorbing over 97% of the light. ^f 6,6-Diaryl-3,5-hexadienoic acid stereoisomers (see ref 3).

instead might follow electron demotion and thus be a reaction of the ground-state zwitterion 2. The latter mechanism is the one proposed by us earlier⁴ to account for the products of the type B process.

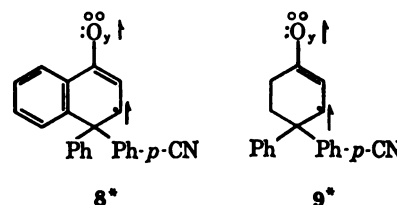
Chart I^a

^a Processes ruled out, — — —.

An approach likely to provide the answer involved the study of the photochemical behavior of 6-phenyl-6-*p*-cyanophenylbicyclo[3.1.0]hex-3-en-2-one (1). If the electronically excited state 2* rearranges after 2,4-bond fission, then *p*-cyanophenyl migration should be preferred. Such a result would be in accord with Rüchardt's finding of a strong preference (19:1 to 35:1) for cyanophenyl over phenyl migration in free-radical rearrangements.⁵ Additionally, such a result would have analogy in our earlier studies of excited-state migratory aptitudes; here the excited states of 4-phenyl-4-*p*-cyanophenyl-1(4H)-naphthalenone (8) and 4-phenyl-4-*p*-cyanophenylcyclohexenone (9) were shown to undergo a preferred *p*-cyanophenyl migration (2.2:1 for 8*; 15:1 for 9*) to the β carbon of the excited enone moiety.^{6,7}

On the other hand, if the ground-state zwitterion

rearranges, preferential phenyl migration should ensue since phenyl bearing an electron-withdrawing group as cyano should not migrate readily to a cationic center.



6-Phenyl-6-*p*-cyanophenylbicyclo[3.1.0]hex-3-en-2-one (1) was prepared by a synthesis involving irradiation of 4-phenyl-4-*p*-cyanophenylcyclohexadienone (10) and affording both epimers of 1.⁸

The results of irradiation of 6-phenyl-6-*p*-cyanophenylbicyclo[3.1.0]hex-3-en-2-one (1) are collected in Table I. The first striking observation noted is that irradiation of either stereoisomer of 1 gives the *same* distribution of phenolic products, with the 2,3-diarylphenol predominating over the 3,4 isomer, as was the case for the diphenyl analog. Additionally, it was found that on short irradiations recovery of bicyclic ketone gave only the stereoisomer used as reactant. Thus there is evidence for a species common to both reactant stereoisomers in which the internal three-ring bond is broken and memory of the reactant stereochemistry is lost. Furthermore, once this central bond is broken, there is no reclosure; such reclosure would afford a mixture of bicyclic ketones. Other three-ring bond openings followed by free rotation are similarly precluded.

Secondly, there is a dramatic contrast between the previously studied cases where cyanophenyl migrates in preference^{6,7} and the present reaction where only phenyl migration is observed. Thus, mainly 2-phenyl-3-*p*-cyanophenylphenol (6) and smaller quantities of 3-*p*-cyanophenyl-4-phenylphenol (7) were found. No *p*-cyanophenyl migration products could be detected. The preferred phenyl migration provides strong support for zwitterion 2 being the species undergoing aryl migration, and electron demotion thus occurring prior to the migration. We note that it is insufficient to select one group as migrating preferentially in photochemical reactions; one must inspect the details of the reaction and determine at which stage migration occurs. In the present instance of the type B rearrangement the scheme

(8) Synthetic details and structure proofs will be reported in our full paper in press. All new compounds were properly characterized and acceptable elemental analyses were obtained.

(4) (a) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **83**, 1196 (1961); (b) *ibid.*, **84**, 4527 (1962).

(5) C. Rüchardt and S. Eichler, *Ber.*, **95**, 1921 (1962); C. Rüchardt and R. Hecht, *ibid.*, **98**, 2471 (1965).

(6) H. E. Zimmerman, R. C. Hahn, H. Morrison, and M. C. Wani, *J. Am. Chem. Soc.*, **87**, 1138 (1965).

(7) H. E. Zimmerman, R. D. Rieke, and J. R. Scheffer, *ibid.*, **89**, 2033 (1967).

in Chart I rationalizes the information⁹ that the triplet excited state¹⁰ of product is not reached.

Acknowledgment. Support of this research by a National Science Foundation Predoctoral Fellowship for J. O. G. and by an Army Research Office (Durham) grant is gratefully acknowledged.

(9) The demotion is shown as occurring just subsequent to internal three-ring bond fission with 2^* pictured as a discrete species; this is a convenience. Thus 2^* may not be an energy minimum, and demotion may occur by crossing or close approach of potential energy surfaces⁸ and change in configuration at a slightly earlier or later point in the transformation.

(10) The intervention of the triplet in the phenol-forming reactions is suggested by the formation of the same products in the photosensitized runs as in the direct runs and by analogy to the diphenyl analog⁸ where the phenolic product was shown to arise from the triplet and the acidic product from triplet and singlet.

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Received April 7, 1967

Molecular and Electronic Structure of Pentacyanocobaltate¹

Sir:

The complex $\text{Co}(\text{CN})_5^{2-}$ has occasioned a good deal of interest in late years. Its action as a hydrogenation catalyst² for certain unsaturated organic molecules and the kinetics of its free-radical type reactions with some organic halides^{3,4} have been subjects of recent

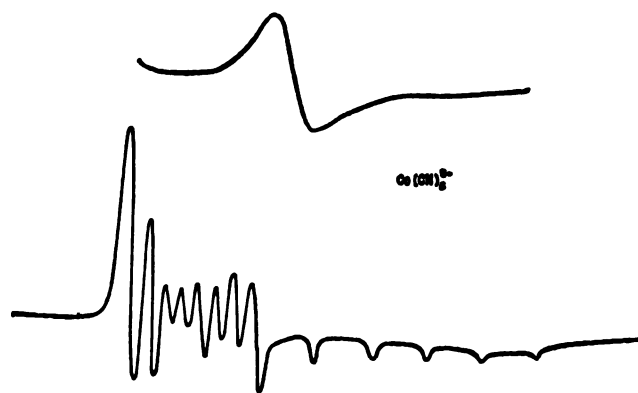


Figure 1. Electron spin resonance spectra for $\text{Co}(\text{CN})_5^{2-}$ in 2:1 ethylene glycol-water: upper curve, 300°K; lower curve, 77°K in frozen solution. Spectra in pure ethylene glycol are not significantly different.

investigation. ESR and optical spectral studies^{5,6} of oxidation products of $\text{Co}(\text{CN})_5^{2-}$ have also been carried out.

Up to now, the geometry of $\text{Co}(\text{CN})_5^{2-}$ in solution has been unknown; supposing it to be five-coordinate, the two most likely idealized spatial arrangements are the trigonal bipyramid (of D_{3h} symmetry) and the square pyramid (of C_{4v} symmetry). (This latter symmetry would also hold if weak axial solvation made the complex six-coordinate.)

- (1) This research was supported by the National Science Foundation.
- (2) J. Kwieciek, I. L. Mader, and J. K. Seyler, *Advances in Chemistry Series*, No. 37, American Chemistry Society Washington, D. C., 1963, p 201.
- (3) J. Halpern, *J. Am. Chem. Soc.*, **85**, 2517 (1963).
- (4) (a) J. Halpern and S. Nakamura, *ibid.*, **87**, 3002 (1965); (b) J. Halpern and P. J. Maher, *ibid.*, **87**, 5361 (1965).
- (5) J. H. Bayston, F. D. Looney, and M. E. Winfield, *Australian J. Chem.*, **16**, 557 (1963).
- (6) J. H. Bayston, R. N. Beale, N. K. King, and M. E. Winfield, *ibid.*, **16**, 954 (1963).

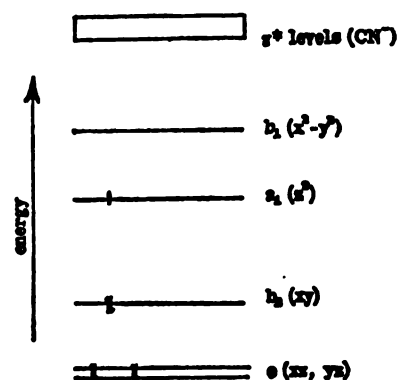


Figure 2. Partial diagram of electronic energy levels and suggested ground state for square-pyramidal $\text{Co}(\text{CN})_5^{2-}$.

We have measured optical and esr spectra of pentacyanocobaltate(II) under a variety of conditions; here we show how the data from these experiments point to an idealized square-pyramidal ground-state geometry for this system.

Solutions for esr spectra were prepared by dissolving $\text{K}_3\text{Co}_2(\text{CN})_{10} \cdot 4\text{H}_2\text{O}^7$ in 2:1 ethylene glycol-water and in pure ethylene glycol. Examination of the optical spectra of these solutions at 300°K and frozen at 77°K reveals the absorption pattern characteristic of the paramagnetic ($S = 1/2$), monomeric $\text{Co}(\text{CN})_5^{2-}$ species.⁸ In particular, the intensity of the band peaking at 10,350 cm^{-1} shows $\text{Co}(\text{CN})_5^{2-}$ to be the predominant species under the conditions of our experiment at 77°K. Confirmation of the existence of $\text{Co}(\text{CN})_5^{2-}$ in the frozen solutions was necessary in light of results which indicate that dimerization and oxidation may readily occur under these conditions.^{5,6}

Figure 1 shows esr spectra for $\text{Co}(\text{CN})_5^{2-}$ at 300 and 77°K. At 300°K, a broad resonance lacking hyperfine structure and centered at $g = 2.11 \pm 0.01$ is seen. On freezing the solution at the lower temperature, the pattern observed is a 16-line resonance expected from an axially symmetric ^{59}Co ($I = 7/2$) species, with two of the g_{\parallel} lines hidden under the second and fifth lines of the g_{\perp} pattern. Analysis of this spectrum gives $g_{\parallel} = 1.992 \pm 0.005$, $g_{\perp} = 2.157 \pm 0.005$, and hyperfine tensor components $A = 87 \pm 2$ and $B = 28 \pm 2$ gauss.

The axial symmetry of the g tensor combined with the value of 1.992 for g_{\parallel} strongly suggest a square-pyramidal structure for $\text{Co}(\text{CN})_5^{2-}$ with the unpaired electron placed in an orbital of d_{xy} symmetry (2A_1 ground state). This is nicely compatible with the electronic energy levels expected for a square-pyramidal pentacyano complex (Figure 2). The ground state in a d^7 case would be $(e)^4(b_2)^2(a_1)^1 = ^2A_1$. Furthermore, none of the ground-state possibilities in a trigonal-bipyramidal geometry is consistent with the esr results.⁹

The electronic spectrum of $\text{Co}(\text{CN})_5^{2-}$ in aqueous solution shows⁸ bands at 10,350 cm^{-1} (ϵ 233), 16,200 (7), 23,300 (65), 31,700 (527), 35,700 (4030), 38,100 (980 sh), and 43,300 (6500). The rich pattern of weak-

- (7) A. W. Adamson, *J. Am. Chem. Soc.*, **73**, 5710 (1951).
- (8) Our electronic spectral measurements are in essential agreement with those reported by N. K. King and M. E. Winfield, *ibid.*, **73**, 3366 (1951).
- (9) The ground state $(e')^4(e'')^3 = ^3E'$ expected for D_{3h} $\text{Co}(\text{CN})_5^{2-}$ should give $g_{\parallel} \gg 2.0$. The fact that a slight Jahn-Teller distortion would be expected does not affect this conclusion.

and medium-intensity absorptions, especially in the 10,000–25,000-cm⁻¹ range, again points to a system of electronic levels appropriate for a square-pyramidal Co(CN)₅³⁻. At least two reasonable assignment schemes exist based on the splitting diagram shown in Figure 2.¹⁰ Contrariwise, simple extrapolation of electronic levels from analogous trigonal bipyramidal complexes indicates that an approximately D_{3h} Co(CN)₅³⁻ would not exhibit electronic bands between 8000 and 20,000 cm⁻¹.¹¹ Thus, the combined esr and optical spectral data require a square-pyramidal structure for Co(CN)₅³⁻ in solution.

(10) We tentatively suggest the following assignments: 10,350 cm⁻¹, ²A₁ → ²B₁ (x² → x² - y²); 16,200 cm⁻¹, doublet → quartet; 23,300 cm⁻¹, ²A₁ → ²B₂ (xy → z²); 31,700 cm⁻¹, ²A₁ → ²A₂ (xy → x² - y²). The intense bands at 35,700 and 43,300 cm⁻¹ probably represent allowed M → π*(CN⁻) transitions.

(11) The observed ligand field bands in trigonal bipyramidal Ni[PPh(OR)₂]₂(CN)₂ complexes (B. B. Chastain, R. Pruett, E. A. Rick, and H. B. Gray, to be published) are at approximately 25,000 and 29,000 cm⁻¹. In addition, there is very little difference in the positions of the lowest ligand-field bands in Ni(CN)₅³⁻ and Ni[PPh(OR)₂]₂(CN)₂. Thus, we may expect a trigonal bipyramidal Co(CN)₅³⁻ to have an e' → e' band below 8000 cm⁻¹ and an e' → a₁' band at about 25,000 cm⁻¹.

(12) National Science Foundation Predoctoral Fellow, 1964–1966.

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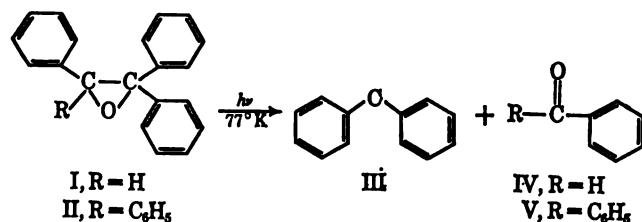
Received May 3, 1967

Direct Evidence for the Formation of Diphenylmethylenes in the Photolysis of Triphenyl- and Tetraphenyloxirane

Sir:

Recent studies have shown that the photolytic reactions of oxiranes can give rise to products which have been interpreted in terms of carbene (methylene) intermediates.¹ We wish to report convincing direct evidence for the formation of diphenylmethylenes (III) in the photolysis of triphenyloxirane (I) and of tetraphenyloxirane (II) (Scheme I).

Scheme I



Irradiations were carried out in methylcyclohexane glass at 77°K. Typically, a solution (10⁻⁴ M) of the oxirane was irradiated² with 2537-Å light for 5–30 sec. The photolysis products were identified by a combination of epr and luminescence techniques.

The total luminescence spectrum³ obtained after II

(1) (a) H. Kristinnson and G. W. Griffin, *Angew. Chem. Intern. Ed. Engl.*, **4**, 868 (1965); *Angew. Chem.*, **77**, 859 (1965); (b) H. Kristinnson and G. W. Griffin, *J. Am. Chem. Soc.*, **88**, 1579 (1966); (c) H. Kristinnson, *Tetrahedron Letters*, 2343 (1966); (d) H. Kristinnson, R. A. Mateer, and G. W. Griffin, *Chem. Commun.*, 415 (1966); (e) G. W. Griffin and co-workers, unpublished work.

(2) An air-cooled Rayonet Chamber Reactor (Southern New England Ultraviolet Co., Middletown, Conn.) was used as the light source equipped with 16 8-w low-pressure mercury lamps.

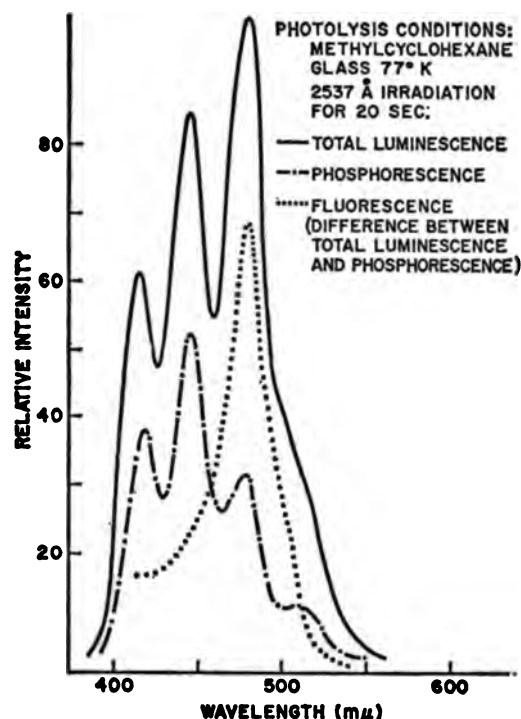


Figure 1. Photolysis of tetraphenyloxirane: luminescence of products.

was irradiated is shown in Figure 1. By use of a phosphoroscope it was possible to show that part of this luminescence was phosphorescence which corresponded closely with that of benzophenone, and the remaining luminescence was identified as the fluorescence previously reported for diphenylmethylenes (III).⁴

Further confirmation for the presence of III was obtained from epr studies. The epr absorption spectrum of the same photolyzed solution which had been used in the luminescence measurements was attributed to a ground-state triplet molecule with zero-field parameters $D/hc = 0.4053$ cm⁻¹, $E/hc = 0.0190$ cm⁻¹. The comparable values for these parameters which had been obtained for III (in benzophenone) are: (a) randomly oriented sample:⁵ $D/hc = 0.4055$ cm⁻¹, $E/hc = 0.0194$ cm⁻¹; and (b) single crystal:⁶ $D/hc = 0.40505$ cm⁻¹, $E/hc = 0.01918$ cm⁻¹.

When a solution of I was photolyzed, the phosphorescence of benzaldehyde was detected as well as the fluorescence of III. The epr of III was detected with zero field parameters $D/hc = 0.4056$ cm⁻¹, $E/hc = 0.0188$ cm⁻¹. However, no epr absorption signals corresponding to those of phenylmethylenes⁷ were detected and no phosphorescence which could be ascribed to benzophenone was observed. This is to be contrasted with the results obtained in solution where products which could be derived from both phenyl- and diphenylcarbene were observed.^{1a}

(3) The luminescence spectra were recorded on an Aminco-Kiers spectrophotofluorometer (American Instrument Co., Silver Spring, Md.).

(4) (a) W. A. Gibbons and A. M. Trozzolo, *J. Am. Chem. Soc.*, **88**, 172 (1966); (b) A. M. Trozzolo and W. A. Gibbons, *ibid.*, **89**, 239, (1967).

(5) A. M. Trozzolo, E. Wasserman, and W. A. Yager, *J. Chem. Phys.*, **61**, 1663 (1964); E. Wasserman, A. M. Trozzolo, W. A. Yager, and R. W. Murray, *J. Chem. Phys.*, **40**, 2408 (1964).

(6) R. W. Brandon, G. L. Closs, and C. A. Hutchison, Jr., *ibid.*, **37**, 1878 (1962); R. W. Brandon, G. L. Closs, C. E. Davoust, C. A. Hutchison, Jr., B. E. Kohler, and R. Silbey, *ibid.*, **43**, 2006 (1965).

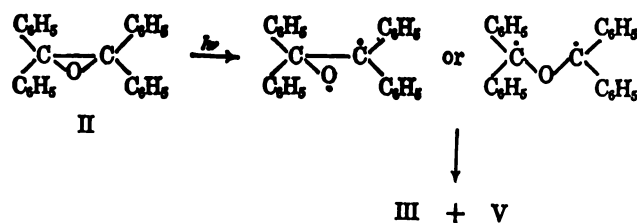
(7) A. M. Trozzolo, R. W. Murray, and E. Wasserman, *J. Am. Chem. Soc.*, **84**, 4990 (1962).

The effects of variations in wavelength and irradiation times also are noteworthy. Both I and II do not absorb light having a wavelength greater than 3000 Å. However, when the sample was irradiated for only a short time (~5 sec) with 2537-Å light, cleavage occurred with the production of III and the corresponding carbonyl compound (IV or V), and subsequent irradiation with 3500-Å light caused further photolysis, suggesting that sensitization was occurring. Photosensitizers such as benzophenone and acetophenone appeared qualitatively to give increased yields of III over those obtained in unsensitized photolyses. Such effects had not been observed earlier in previous work in solution.^{1e}

These experimental data, besides confirming the previous postulation that methylene intermediates may be produced upon photolysis of oxiranes, also show that oxiranes provide another set of precursors for the epr study of methylenes, in addition to the diazo compounds⁸ and bisazides⁹ which have been used previously.

The mechanism by which the methylene is formed in the photolysis of these oxiranes is of some interest. The present work does not exclude a two-step homolytic process such as that formulated in Scheme II.

Scheme II



However, in epr studies in the magnetic field region where monoradicals or triplets with smaller spin-spin interaction (such as would be anticipated for VI) might exhibit resonance absorption, only a relatively weak signal was observed. Thus, one is tempted to conclude that if VI or VII is formed in a rigid glass, it has a rather short lifetime, and either reverts to II or fragments to III and V. Furthermore, in view of recent observations¹⁰ on the solvolytic photochemical cleavage of cyclopropanes (a reaction which competes with the fragmentation to carbene) we should consider an ionic intermediate perhaps formed by initial heterolytic cleavage or in a later step from VI or VII. Further studies on the mechanism of the photolysis of oxiranes are continuing.¹¹

(8) See ref 4b for bibliography.

(9) L. Barash, Abstracts of Papers, 150th National Meeting of the American Chemical Society, Atlantic City, Sept 1965, p 54S; L. Barash, E. Wasserman, and W. A. Yager, to be published.

(10) C. S. Irving, R. C. Petterson, I. Sarkar, H. Kristinsson, C. S. Aaron, G. J. Boudreaux, and H. W. Griffin, *J. Am. Chem. Soc.*, **88**, 5675 (1966).

(11) NOTE ADDED IN PROOF. According to P. Petrellis (unpublished results), diphenylcarbene is formed also in the photolysis of 2-methoxy-2,3,3-triphenyloxirane. The carbene was trapped in methanol as the methyl ether of benzhydrol. Methyl benzoate, the accompanying fragment, was isolated by glpc and compared with authentic material. The presence of III was detected by epr and luminescence studies. These data confirm and are consistent with the results of T. I. Temnikova and I. P. Stepanov, *Zh. Organ. Khim.*, **2**, 1525 (1966); *Chem. Abstr.*, **66**, 54820j (1967).

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Inversion of Positional Reactivity Mechanisms of Hydrogen-Deuterium Exchange for Pyridine

Sir:

Considerable confusion has arisen over the positional reactivity order of exchange for pyridine. Relative rates at positions 4, 3, 5, and 2, 6 are 10³, and 1, respectively, in NaOD. These deprotonations were said to involve an anionic intermediate resulting from an amide ion to substrate. By contrast, it is reported not to exchange in I (220°) exclusive deprotonation said to result.^{1,2}

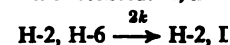
We wish to present a clarification of the exchange for pyridine. We have observed inversion in the relative positional reactivity in aqueous solution and for the mechanisms of deprotonation. Pyridine undergoes exchange at meta and para positions. In NaOD the exchange, but in the order 4 > 2, 6.

For kinetic runs in acidic solutions, mixtures of DCl were mixed, and heated (218°). Analysis of the products by nmr showed exchange only at positions 2 and 6. The pseudo-first-order rate constants are expressed as a function of the concentration of the pyridine. The resulting curve indicates that the mechanism for this exchange is the capture of the deuteriooxide ion on pyridine I. This ylide then captures the deuterium of the changed pyridine (path 1). This mechanism was found in separate experiments in pyridine in D₂O. At 2

(1) I. F. Tupitsyn and N. K. Semakova, *Chem. Abstr.*, **60**, 672 (1962).

(2) Y. Kawazoe, M. Ohnishi, and T. Kawanishi, *J. Org. Chem.*, **29**, 1384 (1964).

(3) We are unable to repeat these results. (4) Although deprotonation takes place at positions 2 and 6, for example, all rate constants for deprotonation at a single position are consistent with a single kinetic treatment of consecutive, first-



that the rate constant, *k*, for reaction expression ln ([H-2, H-6] + [H-2, I]) - concentration ratio in this expression was 1.

(5) That log [pyridine]/[pyridinium ion] + p*K*_a follows from the expression for the acidity of pyridine. The p*K*_a value is known from the conditions of our experiments, but the rate constant is accurately known from the experiment employed.

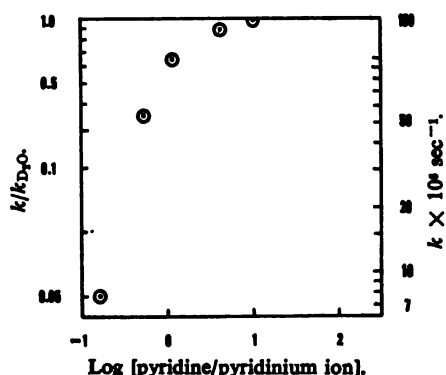
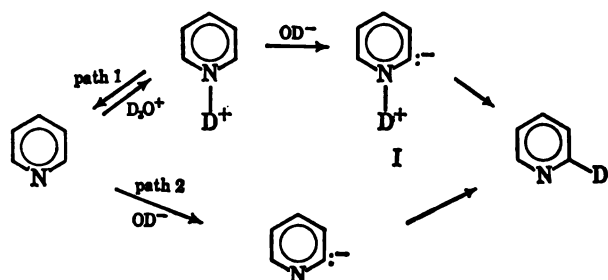


Figure 1. Log-log plot for the rate of hydrogen-deuterium exchange for pyridine at positions 2,6 in D_2O at 218° as a function of acidity. Left ordinate gives the ratio of the rate of exchange in pyridine-pyridinium ion mixtures to the rate of exchange in neutral water. Right ordinate indicates the observed rate constant. Total concentration of pyridine in all forms is $1.1 M$.

occurs at only the 2,6 positions and is inhibited by decreasing the deuterioxide ion concentration.⁶



There is considerable precedent for ylide I. Such an intermediate is said to result during the decarboxylation of pyridine-2-carboxylic acid and of the betaine N-methylpyridine-2-carboxylic acid.⁷ The dipolar intermediates which result during similar decarboxylations have been trapped.^{8,9}

In another series of experiments pyridine and D_2O -NaOD were heated in a Monel bomb ($198 \pm 3^\circ$).¹⁰ Pyridine, recovered in good yield, was analyzed for positional deuterium content by nmr using *t*-butyl alcohol as an internal standard. Rates of exchange at all positions showed dependence on deuterioxide ion concentration. At low base concentrations the rates of exchange at position 2 were much greater than at 3 or 4. At high base concentration, in contrast, the 4 position exchanged most rapidly, followed by 3, and then 2. Rate constants for each position are compared by a graphical method in Figure 2. A slope in these plots gives the ratio of rate constants for exchange at two positions.¹¹ Such a plot for the rate of exchange at position 4 vs. exchange at 3 has a slope of 1.3; therefore, k_4/k_3 is 1.3. Data from several

(6) Another possible mechanism, in which pyridine removes a proton from a C-H center of a pyridinium ion, can be eliminated by the shape of the pD-rate curve. This mechanism demands a rate maximum when [pyridine] and [pyridinium ion] are equal. This maximum is not observed.

(7) P. Haake and J. Mantecón, *J. Am. Chem. Soc.*, **86**, 5230 (1964), and references cited therein.

(8) For a list of examples of the Hammick reaction see E. P. Oliveto, "Pyridine and Its Derivatives," Part III, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, pp 207-208.

(9) H. Quast and E. Frankenfeld, *Angew. Chem. Intern. Ed. Engl.*, **4**, 691 (1965).

(10) Glass tubes could not be used with basic solutions at these temperatures because of severe etching.

(11) S. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp 98-99.

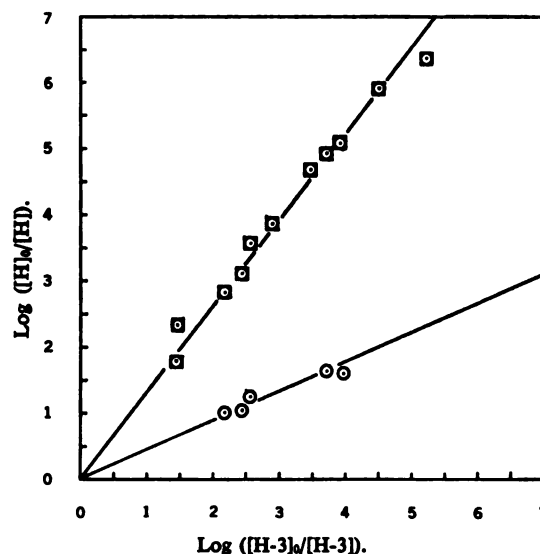


Figure 2. Log-log plot for the rate of hydrogen-deuterium exchange for pyridine in D_2O -NaOD at 198° . The ordinate expresses the inverse mole fraction of hydrogen remaining in either the 2,6 (circles) or 4 (squares) positions and the abscissa gives the inverse mole fraction of hydrogen remaining in the 3,5 positions. Approximate half-life for position 2 in $1.0 M$ NaOD is 0.9 hr.

determinations at different base concentrations were employed. Similarly k_3/k_2 is 2.3. For this latter comparison only data from runs in $1 N$ NaOD were used in order to minimize the effect of reaction at positions 2,6 by path 1. Relative rates of exchange of unprotonated pyridine at positions 4, 3, and 2 are 3.0, 2.3, and 1.0, respectively.

There can be little doubt about the positional reactivity order of base-catalyzed exchange for pyridine. We have found a similar order in *t*-butyl alcohol and in methanol at much lower temperatures. Exchange in liquid ammonia also follows the same pattern.¹ Furthermore, the rate of exchange for 3-chloropyridine at position 4 is much greater than at 2 in both methanol and liquid ammonia.¹²

The mechanism for exchange in basic solution most likely involves removal of a proton from pyridine by deuterioxide ion. The resultant pyridyl anion then abstracts a deuteron from solvent to form exchanged product (path 2). This mechanism is similar to that for exchange of chloropyridines in CH_3OD - CH_3ONa or NH_3 - $NaNH_2$.¹³

That two pathways exist for exchange at position 2 while only one mode is dominant for positions 3 or 4 is readily understandable. Zwitterionic intermediates which would result from deprotonation of a pyridinium ion at position 3 or 4 have much less coulombic stabilization than ylide I.¹³

(12) J. A. Zoltewicz and C. L. Smith, *J. Am. Chem. Soc.*, **88**, 4766 (1966).

(13) The rate of decarboxylation of N-methylpyridine-2-carboxylic acid is about three powers of ten larger than that for the other two isomeric acids.⁷

(14) Arts and Sciences Fellow, 1966-1967.

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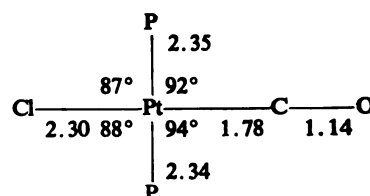
An Unexpected Product in the Reaction of $\text{PtHCl}(\text{P}(\text{C}_2\text{H}_5)_3)_2$ with C_2F_4 .

The Structure of the $\text{PtCl}(\text{CO})(\text{P}(\text{C}_2\text{H}_5)_3)_2^+$ Cation and Evidence for the Existence of the SiF_6^- Ion

Sir:

In a recent paper¹ one of us described the reaction of *trans*- $\text{PtHCl}(\text{P}(\text{C}_2\text{H}_5)_3)_2$ with C_2F_4 and postulated that one of the low-yield products isolated was a reaction intermediate, $\text{PtHCl}(\pi\text{-C}_2\text{F}_4)(\text{P}(\text{C}_2\text{H}_5)_3)_2$. We now report that studies of this compound by X-ray diffraction techniques, and further chemical characterization, have not confirmed the structure postulated. The compound is now known to contain the new cation *trans*- $\text{PtCl}(\text{CO})(\text{P}(\text{C}_2\text{H}_5)_3)_2^+$, which is isoelectronic with Vaska's compound² $\text{IrCl}(\text{CO})(\text{PR}_3)_2$, where R may be alkyl or aryl. We present evidence here that the anion is SiF_6^- when the reactions are carried out in silica tubes, and that both SiF_6^- and BF_4^- are formed when reactions are carried out in Pyrex glass tubes. The formation of SiF_4 as a by-product had been noted previously,¹ indicating attack by HF on the glass walls of the reaction vessel, but apparently the glass is degraded more thoroughly than had been thought.

A sample of the compound isolated from reactions in Pyrex glass tubes was recrystallized from methyl acetate. The unit cell, as determined from a number of crystals, is orthorhombic, with $a = 9.17$, $b = 16.01$, $c = 14.97$ Å; space group: either Pbcm or $\text{Pbc}2_1$. A formula weight of 574 is derived from the observed density of 1.73 ± 0.01 g/cm³ and the assumption of four formula units in the cell. Three-dimensional X-ray data were collected from a crystal of maximum dimension 0.15 mm, with the use of Mo $K\alpha$ radiation, by procedures previously described.³ Comparison of the intensities of the hkl and $h\bar{k}l$ reflections indicated that the space group is the polar noncentric one $\text{Pbc}2_1$, and this was confirmed by the positions of the Pt, Cl, and P atoms, as determined by Patterson and Fourier methods. By comparison of two least-squares refinements of the positions of the heavy atoms it proved possible to determine the direction of the polar axis at this stage, because of the anomalous scattering of the Pt atom. The positions of the ethyl carbon atoms could now be determined. The P atoms were seen to be *trans*, and the Pt-Cl direction was at right angles to the P-Pt-P axis. Structure factors calculated for this $\text{PtCl}(\text{P}(\text{C}_2\text{H}_5)_3)_2$ fragment led to a conventional R factor of 0.104. Inspection of the resulting difference Fourier map revealed no evidence of a π -bonded C_2F_4 fragment. Two strong peaks close to the Pt of heights 4.5 and 6.5 e/Å³ suggested a carbonyl group linearly bound to the Pt atom and completing a planar four-coordinate arrangement around the Pt. At a distance of at least 4 Å from the Pt atom was a group of four peaks in tetrahedral arrangement, heights 2-3 e/Å³, and there was a small peak at their center of gravity. These facts suggested refinement of a model corresponding to $\text{PtCl}(\text{CO})(\text{P}(\text{C}_2\text{H}_5)_3)_2^+\text{BF}_4^-$, and this resulted in an R factor of 0.055. Refinement continues, but at this stage the bond lengths and angles in the cation are



Apart from the ethyl groups, the cation is essentially planar. The small deviations make the coordination tend toward a flattened tetrahedron rather than a square pyramid, and it is thus extremely unlikely that there is a hydrogen atom coordinated to the Pt atom. We conclude that recrystallization of the original sample gave a pure BF_4^- salt, and this is confirmed by comparisons of the infrared spectra of the recrystallized sample with both the original sample (containing both BF_4^- and SiF_6^-) and a sample containing SiF_6^- only.

Further chemical and analytical studies have confirmed the chemical formulation suggested by the X-ray investigation. The original reactions were carried out in Pyrex glass tubes, which are now known to yield a mixture of BF_4^- and SiF_6^- anions, as noted above. On the basis of the analyses reported previously¹ (Found: Pt, 34.4; P, 10.7; F, 12.7), it is not possible to distinguish between the original postulate (Calcd for $\text{PtHCl}(\text{C}_2\text{F}_4)(\text{P}(\text{C}_2\text{H}_5)_3)_2$: Pt, 34.3; P, 10.9; F, 13.4) and the structure suggested by the X-ray study (Calcd for $\text{PtCl}(\text{CO})(\text{P}(\text{C}_2\text{H}_5)_3)_2^+\text{BF}_4^-$: Pt, 33.5; P, 10.6; F, 13.1). However, treatment of the product with sodium tetraphenylboron led to a water-soluble fraction that contained NaBF_4 and Na_2SiF_6 . Conductivity studies¹ were consistent with a formulation as a 1:1 electrolyte. The infrared spectrum¹ confirms the presence of the *trans*- $\text{PtCl}(\text{P}(\text{C}_2\text{H}_5)_3)_2$ fragment.^{4,5} The absorption at 2100 cm^{-1} may equally well be assigned as $\nu(\text{Pt-H})$ or $\nu(\text{C}\equiv\text{O})$, but the high-resolution mass spectrum of the pyrolysis products of the SiF_6^- salt confirms the presence of carbon monoxide. The sharp absorptions at 1094, 1060, and 881 cm^{-1} , which were previously assigned to C-F modes, are now known to be due to the anions. These spectra will be discussed in detail elsewhere, but we note that a splitting of the tetrafluoroborate ν_1 mode into two sharp absorptions (1094 and 1060 cm^{-1}) has not been reported previously.

The final confirmation of the structure is the rational synthesis of the tetrafluoroborate salt. *trans*- $\text{PtHCl}(\text{P}(\text{C}_2\text{H}_5)_3)_2$ reacts with carbon monoxide and aqueous tetrafluoroboric acid under pressure to yield *trans*-bis(triethylphosphine)chlorocarbonylplatinum(II) tetrafluoroborate, $[\text{PtCl}(\text{CO})(\text{P}(\text{C}_2\text{H}_5)_3)_2]\text{BF}_4$. Anal. Calcd for $\text{PtClC}_{13}\text{H}_{30}\text{P}_2\text{OBF}_4$: C, 26.9; H, 5.2; B, 1.86; F, 13.1. Found: C, 27.4; H, 5.4; B, 2.0; F, 13.4.

When the original reaction between $\text{PtHCl}(\text{P}(\text{C}_2\text{H}_5)_3)_2$ and C_2F_4 is carried out in a silica tube, then the pure SiF_6^- salt can be isolated. That this is a SiF_6^- salt, rather than a SiF_6^{2-} salt, is strongly suggested both by the analytical data and the X-ray molecular weight. Anal. Calcd for $\text{PtCl}(\text{CO})(\text{P}(\text{C}_2\text{H}_5)_3)_2\text{SiF}_6$: C, 25.3; H, 4.9; Si, 4.5; F, 15.4; Pt, 31.6; P, 10.0; Cl, 5.7. Found: C, 24.9; H, 4.6; Si, 4.7; F, 15.2; Pt, 32.2; P, 9.9; Cl, 5.8. This salt is not isomorphous with the BF_4^- analog, although the unit cells are related. The

(1) H. C. Clark and W. S. Tsang, *J. Am. Chem. Soc.*, **89**, 529 (1967).

(2) L. Vaska and J. W. DiLuzio, *ibid.*, **84**, 679 (1962); **83**, 2784 (1961).

(3) P. W. R. Corfield, R. J. Doedens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).

(4) P. L. Goggin and R. J. Goodfellow, *J. Chem. Soc., Sect. A*, 1462 (1966).

(5) H. C. Clark and K. R. Dixon, unpublished observations.

space group is $Pbca$, with $a = 16.9$, $b = 18.9$, $c = 14.7$ Å. The formula weight from these data and the observed density is $611 (\pm 1\%)$ (calcd for $[PtCl(CO)(P(C_2H_5)_3)_2]SiF_6$: 618; calcd for $0.5[PtCl(CO)(P(C_2H_5)_3)_2]SiF_6$: 566).

Although the previous conclusions¹ are now known to be incorrect, the reactions described above are remarkable in several ways. (a) The formation of a platinum carbonyl and BF_4^- under such mild conditions, presumably by interaction of C_2F_4 with the glass surface in contact with the hydride, is remarkable. It can be related to, but is more extreme than, the ability of the isoelectronic Ir(I) and Rh(I) systems to abstract carbon monoxide from oxygen-containing organic solvents.^{2,6} (b) The cation is isoelectronic with Vaska's compound² and may show similar properties. These are being investigated. (c) This is the first reported isolation of the SiF_6^- ion. Further detailed studies of this species are currently in progress.

Acknowledgment. This work was supported in part by the National Science Foundation.

(6) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc., Sect. A*, 1711 (1966).

(7) (a) University of Western Ontario; (b) Northwestern University.

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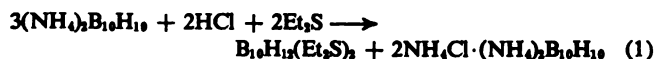
Opening the $B_{10}H_{10}^{2-}$ Cage to Produce $B_{10}H_{12}(Et_2S)_2$

Sir:

The preparations of $B_{10}H_{12}(base)_2$ derivatives have been reported from reactions of decaborane with soft bases.^{1,2} These have been converted further to the $B_{10}H_{10}^{2-}$ structure by action of more or harder base.³ We wish to report the synthesis of $B_{10}H_{12}(Et_2S)_2$ from $(NH_4)_2B_{10}H_{10}$, which is the first time, to our knowledge, that the $B_{10}H_{10}^{2-}$ cage has been opened to clearly reestablish the decaborane skeleton.

This reaction takes on further significance with the recent preparation in these laboratories of the $B_{10}H_{10}^{2-}$ ion from simple borohydrides.⁴ $B_{10}H_{12}(Et_2S)_2$, other $B_{10}H_{12}(base)_2$ compounds,^{2,3} and carboranes,⁵ for example, can now be prepared from simple starting materials, by-passing decaborane as an intermediate.

The product is obtained from the reaction of $(NH_4)_2B_{10}H_{10}$ and anhydrous HCl in ethyl sulfide (eq 1).



Reaction occurs readily at room temperature. A double salt, $NH_4Cl \cdot (NH_4)_2B_{10}H_{10}$, insoluble in ethyl sulfide, is produced as the by-product. $B_{10}H_{12}(Et_2S)_2$ is recovered in approximately 92% yield based on the above equation from the filtrate by vacuum evaporation of the excess ethyl sulfide. Infrared, X-ray, and

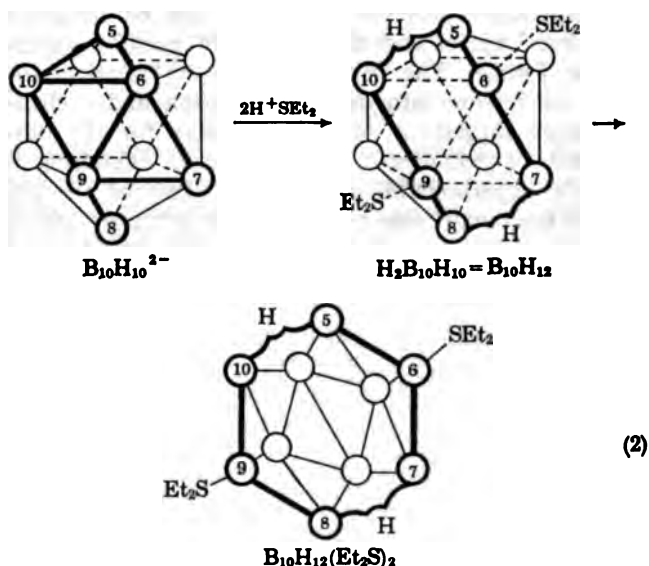
nmr comparisons with authentic samples left no doubt as to its identity. The product was somewhat impure but gave elemental analyses approximating the desired compound.

Anal. Calcd for $[(C_2H_5)_2S]_2B_{10}H_{12}$: B, 36.0; C, 31.9; H, 10.6; S, 21.3. Found: B, 34.7; C, 29.6; H, 10.3; S, 20.3.

Work on recovery of the $(NH_4)_2B_{10}H_{10}$ from the double salt by use of other solvents is in progress. With large excesses of HCl the reaction gives some free NH_4Cl and correspondingly higher quantities of $B_{10}H_{12}(Et_2S)_2$. Several samples have been allowed to react with propargyl bromide, and the expected bromomethyl-carborane derivative was obtained.⁵

Muetterties has reported obtaining a bridge-hydrogen structure from the $B_{10}H_{10}^{2-}$ ion.⁶ Dehydration of an aqueous solution of $(H_2O)_2B_{10}H_{10}$ gave a white solid from which a material could be sublimed. The sublimate showed evidence for bridge hydrogens in its infrared pattern. The unknown had the approximate composition of $B_{10}H_{12}OH_2$. He concluded that the solid belonged to the $B_{10}H_{12}(base)$ or $B_{10}H_{12}^{2-}$ structural class. A referee has pointed out that the formation of $B_{12}H_{22}$ from $B_{10}H_{12}^{2-}$ plus acid involves opening $B_{10}H_{10}$ cages. However, degradation with loss of boron also obviously occurred.⁷

Mechanistically the synthesis of $B_{10}H_{12}(Et_2S)_2$ from $(NH_4)_2B_{10}H_{10}$ can be pictured as just the reverse of the $B_{10}H_{12}(base)_2$ conversion to $B_{10}H_{10}^{2-}$ derivatives. Hawthorne suggests that this latter conversion occurs by the removal of protons from the bridge positions in the $B_{10}H_{12}(base)_2$ structure, and that the resulting filled two-center orbitals undergo a nucleophilic displacement of the coordinated bases. In our reaction, protons which are presumably supplied *via* the ethylsulfonium ion, Et_2SH^+ , probably attack in the apex region of the $B_{10}H_{10}^{2-}$ cage. Nmr studies with deuterium chloride have established that hydrogen exchange occurs at the apex borons.^{8,9} Single crystal X-ray



(1) R. Schaeffer, *J. Am. Chem. Soc.*, **79**, 1006 (1957).

(2) R. J. Pace, J. Williams, and R. L. Williams, *J. Chem. Soc.*, 2196 (1961).

(3) M. F. Hawthorne and A. R. Pitochelli, *J. Am. Chem. Soc.*, **81**, 5519 (1959).

(4) J. M. Makhlof, W. V. Hough, and G. T. Hefferan, "Practical Synthesis for Decahydrodecaborates," to be published.

(5) T. L. Heying, *et al.*, *Inorg. Chem.*, **2**, 1089 (1963); M. M. Fein, *ibid.*, **2**, 1111 (1963).

(6) E. L. Muetterties, J. H. Balthis, T. A. Chia, W. H. Knoth, and H. C. Miller, *ibid.*, **3**, 444 (1964).

(7) A. R. Pitochelli and M. F. Hawthorne, *J. Am. Chem. Soc.*, **84**, 3218 (1962).

(8) W. H. Knoth, H. C. Miller, D. C. England, G. W. Parshall, E. L. Muetterties, and J. C. Sauer, *ibid.*, **84**, 1056 (1962).

(9) A. Kaczmarczyk, R. Dobrott, and W. N. Lipscomb, *Proc. Natl. Acad. Sci. U. S. A.*, **48**, 729 (1962).

studies on $\text{Cu}_2\text{B}_{10}\text{H}_{10}$ also show bonding with the Cu^+ ions along apex-equatorial boron edges.¹⁰

Presumably cage-opening occurs *via* the formation of bridge hydrogens between apex and equatorial borons. Bond rupture and coordination of ethyl sulfide between the equatorial borons result with the ethyl sulfide coordinated borons now becoming the 6 and 9 positions of the resulting $\text{B}_{10}\text{H}_{12}(\text{Et}_2\text{S})_2$ structure. A plausible mechanism is depicted in eq 2 (the numbering system used is that for decaborane and only the "mouth" borons are numbered). The rupture of the cage bonds may involve a multicenter reaction with the Et_2SH^+ ion or simple displacement by some solvent ethyl sulfide.

Acknowledgments. This work was sponsored by the Naval Ships Systems Command under Contract N00024-67-C-5131. We also wish to thank Professor R. W. Parry for consultation and nmr spectral assistance.

(10) R. D. Dobrott and W. N. Lipscomb, *J. Chem. Phys.*, **37**, 1770 (1962).

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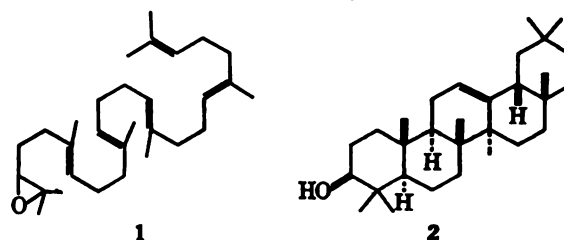
Received May 8, 1967

Enzymic Synthesis of β -Amyrin from 2,3-Oxidosqualene

Sir:

Recent studies have demonstrated that lanosterol is synthesized in the mammalian liver from 2,3-oxidosqualene (1)¹⁻³ under the influence of an enzyme, 2,3-oxidosqualene-sterol cyclase, which can be obtained from liver microsomes in a partially purified water-soluble form.⁴ The separation of the squalene-to-sterol conversion into discrete oxidation and cyclization steps suggests a similar possibility for the biosynthesis of pentacyclic triterpenes and, therefore, a powerful experimental approach for studying the details of the remarkable rearrangement processes which are supposed to lead from the lupanyl⁵ system to the triterpenes of the oleanane (β -amyrin), ursane (α -amyrin),⁶ friedelane,⁷ and other series. Since it has been shown that β -amyrin (2) is formed enzymically from squalene in a homogenate from germinating peas (*Pisum sativum*),⁸ this system was selected for initial study. We report here an investigation which demon-

strates that 2,3-oxidosqualene is indeed a precursor of β -amyrin in *Pisum sativum* and that the cyclizing enzyme can be obtained in water-soluble form.



Anaerobic incubation for 24 hr at 37° of ¹⁴C-labeled 2,3-oxidosqualene with a cell-free homogenate from *Pisum sativum* led to isolation of a product which showed upon thin layer chromatography on silica gel about 35% of the radioactivity in a band with an R_f equal to that of β -amyrin. That this material was in fact primarily β -amyrin was demonstrated by the following experiments. Recrystallization (*ca.* 2 μ -moles, 6000 counts/min) from ethanol-water with carrier β -amyrin (50 mg) led to a constant specific activity after the first crystallization (131, 106, 105, 104, 108 counts/min per mg). The combined fractions from this recrystallization experiment were acetylated with acetic anhydride in pyridine and chromatographed. The radioactivity was found in the zone characteristic of β -amyrin acetate using a thin layer of silica gel and 5% ethyl acetate-benzene for development. In addition, thin layer chromatography of acetylated biosynthetic material on a 20% silver nitrate-silica gel plate (3:2, chloroform-petroleum ether) showed the absence of labeled lanosterol and an R_f for the radioactive product identical with that of β -amyrin acetate. Vapor phase chromatography of acetylated labeled biosynthetic product using a glass column packed with 2% Epon 1001 on Diatoport S at 235° capable of separating α - and β -amyrin acetates showed >95% of the radioactivity in the β -amyrin acetate peak.

The intermediacy of squalene 2,3-epoxide in the biogenesis of β -amyrin is further supported by an experiment using 2,3-iminosqualene, which has been shown to be a potent inhibitor of enzymic cyclization of 2,3-oxidosqualene to lanosterol.⁹ Incubation of ¹⁴C-labeled squalene in the presence of 2,3-iminosqualene with a cell-free homogenate from *Pisum sativum* capable of converting squalene to β -amyrin⁸ led to isolation by chromatography of about 2% of the radioactivity in a band of R_f equal to that of 2,3-oxidosqualene (using silica gel with 3% ethyl acetate-benzene as solvent). Dilution of this material with carrier 2,3-oxidosqualene and treatment with perchloric acid in aqueous glyme led to a product which upon chromatographic separation (using silica gel with 20% ethyl acetate-benzene as solvent) manifested radioactivity almost totally in the band of R_f corresponding to 2,3-dihydroxylated squalene.²

The solubilization and partial purification of this 2,3-oxidosqualene- β -amyrin cyclase from *Pisum sativum* has been effected by a procedure similar to that used in the purification of the 2,3-oxidosqualene-lanosterol cyclase from hog liver.⁴ The cell-free homogenate⁴ in pH 7.4 phosphate buffer (without added sucrose or glutathione) was treated at 0° with just sufficient sodium desoxycholate solution to effect clarification,

(9) E. J. Corey, P. R. Ortiz de Montellano, K. Lin, and P. D. G. Dean, *J. Am. Chem. Soc.*, **89**, 2797 (1967).

(1) E. J. Corey and W. E. Russey, *J. Am. Chem. Soc.*, **88**, 4751 (1966).

(2) E. J. Corey, W. E. Russey, and P. R. Ortiz de Montellano, *ibid.*, **88**, 4750 (1966).

(3) E. E. van Tamelen, J. D. Willet, R. B. Clayton, and K. E. Lord, *ibid.*, **88**, 4752 (1966).

(4) P. D. G. Dean, P. R. Ortiz de Montellano, K. Bloch, and E. J. Corey, *J. Biol. Chem.*, in press.

(5) L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 357 (1953).

(6) E. J. Corey and J. J. Ursprung, *Chem. Ind. (London)*, 1387 (1954); *J. Am. Chem. Soc.*, **78**, 183 (1956).

(7) E. J. Corey and J. J. Ursprung, *ibid.*, **77**, 3667, 3668 (1955); **78**, 5041 (1956).

(8) E. Capstick, Jr., N. Rosin, G. A. Blondin, and W. R. Nes, *J. Biol. Chem.*, **240**, 3258 (1965).

then an equivalent amount of calcium chloride solution was added to precipitate desoxycholate. supernatant solution was separated after centrifugation, and the enzyme was precipitated from 30% ammonium sulfate solution. The precipitate obtained after centrifugation (37,000g, 20 min) was taken up in phosphate buffer (pH 7.4) and centrifuged at 300g for 3 hr. The clear supernatant liquid removed by pipet and assayed for total protein activity in the anaerobic 2,3-oxidosqualene- β -irradiation conversion. The particle-free solution had a specific activity in cyclization to β -amyrin (per mg of protein) approximately 12 times that of the original osomes.

Studies are continuing on the details of the enzymic cyclization of β -amyrin and other triterpenes.

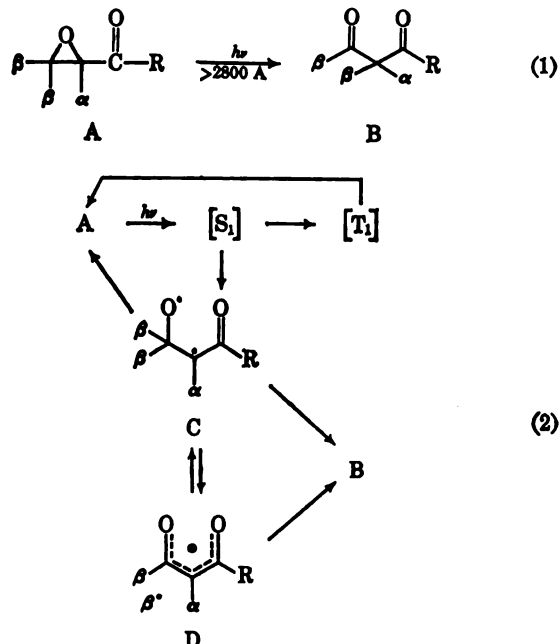
Acknowledgment. We are pleased to acknowledge the expert advice and assistance of Dr. P. D. G. Dean.

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Photochemical Rearrangement of α,β -Epoxy Ketones. Elaboration of the Mechanism

The photorearrangement of α,β -epoxy ketones to β,β' -diketones (eq 1) is characterized by an unusual order of the migrational aptitudes of various β groups (e.g., $I_2 \gg C_6H_5$).^{1,2} Suggestions concerning the

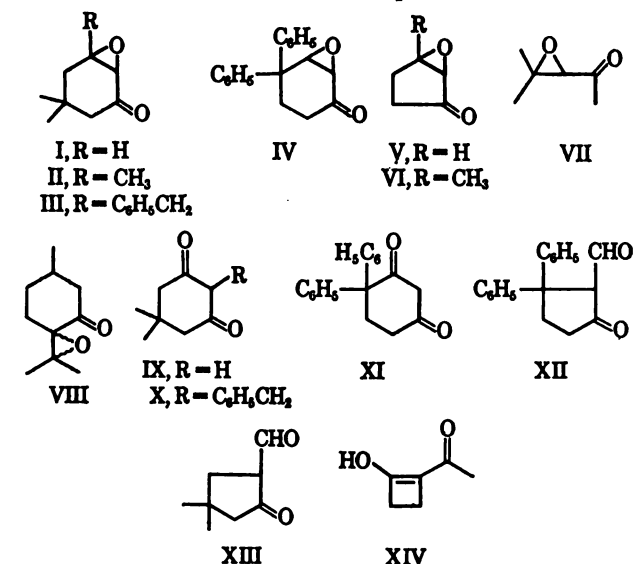


The mechanism of this transformation have been advanced,¹⁻⁴ and our recent work in this area has disclosed certain features of the rearrangement that sup-

port the elaboration of these views presented in eq 2.

The formation of intermediate C from a singlet [S_1] or triplet [T_1] excited state is theoretically reasonable,⁵ and the reactions leading to this species constitute the true "photochemistry" of these compounds. Inas-

much as the epoxy ketone rearrangements are not sensitive to the presence of oxygen or changes in the solvent, and since the addition of known triplet quenchers (piperylene and 2,5-dimethyl-2,4-hexadiene were used in concentrations ranging from 0.1 to 9.0 M) did not affect the rate or course of rearrangement (specifically shown for II, III, VII, and VIII), intermediate C appears to be formed predominantly from the initially produced (S_1) state. Furthermore, acetophenone (0.5 M) did not function as a sensitizer for the rearrangement of II (0.3 M) in acetonitrile solution. The low quantum yield observed for some of these rearrangements (e.g., ca. 0.03 for the conversion of VII to 3-methylpentane-2,4-dione) may indicate poor efficiency for the [S_1] \rightarrow C transformation, or an unfavorable competition between rearrangement and oxirane ring formation from C. A preliminary study involving reduction of [T_1] by tri-*n*-butylstannane suggests that in the case of VII both factors are important.⁶



A recent report⁷ concerning the thermal decomposition of β -methyl- β -phenyl- β -peroxypropylolactone noted a fivefold preference for methyl migration *vs.* phenyl and suggested a 1,3-diradical intermediate similar to C. The implication that such a species can be generated by nonphotochemical pathways is supported by the isomerization and rearrangement of pulegone oxide diastereoisomers (VIII) at 200°. A rationalization of the abnormal migrational aptitudes found in rearrangements proceeding from intermediate C is achieved by assuming that the migrating group must have radical characteristics. This feature can be incorporated in a fragmentation (two-step) mechanism involving the caged radical pair D, or in a single step path having a transition state resembling D in certain respects.⁸

(5) H. E. Zimmerman, *Advan. Photochem.* 1, 183 (1963).

(6) This aspect of our investigations will be developed fully in a subsequent paper and should lead to a rough assignment of relative rates for the various steps in eq 2.

(7) F. D. Greene, W. Adam, and G. Knudsen, Jr., *J. Org. Chem.*, 31, 2087 (1966).

(8) A detailed discussion of these rearrangements with particular emphasis on stereochemistry has been presented by the Zürich research group.^{3,4} Their arguments are in favor of a synchronous mechanism.

This view of the reaction led us to anticipate an especially high migrational aptitude for benzyl and benzhydryl β substituents, and this has been confirmed by experiments with III and IV. Thus, irradiation⁹ of a 0.025 *M* solution of IV in ether for 3.5 hr gave roughly 50% conversion to a 1:4 mixture of XI and XII.¹⁰ The sole rearrangement product obtained from a similar irradiation of III proved to be X (ca. 20%), but this was accompanied by significant quantities of fragmentation products (e.g., IX, dibenzyl and α -benzylethyl ethyl ether). Since X was essentially unreactive under equivalent reaction conditions, the formation of the latter products suggests that intermediate C is in this case at least partly diverted to the radical pair D, and that the relatively stable benzyl radical escapes the solvent cage.

Other photochemical transformations recently established in our laboratory are: I to IX (ca. 40%) and XIII (ca. 4%); VI to XIV (ca. 40% by a technique involving continuous extraction of the product); and V to cyclopentane-1,3-dione and an unidentified base-soluble substance.

The rearrangements described in this communication together with previous findings¹⁻⁴ support the following rough order for the migrational aptitude of β substituents: benzhydryl and benzyl > hydrogen > methylene > methyl \gg phenyl. The position of hydrogen in this listing argues against a general fragmentation mechanism for the rearrangement, since hydrogen atoms are not normally produced in preference to alkyl radicals. Also, the formation of a strained four-membered ring (XIV) in the photolysis of VI¹¹ leads us to prefer a single step or synchronous route for rearrangement from C. If a radical pair (i.e., D) was an intermediate in this rearrangement, the formation of a six-membered heterocyclic system or possibly fragmentation with loss of ethylene would seem to provide attractive alternate reaction modes. Products of this type were not found.

Acknowledgment. This work was supported in part by Grant GP-02025 from the National Science Foundation. We thank Dr. Peter Wagner for helpful and stimulating discussions.

(9) These experiments employed a 450-w mercury lamp (Hanovia) equipped with a Correx filter.

(10) The compounds described in this paper were identified by a combination of carbon and hydrogen analysis, infrared, nmr, and mass spectroscopy, chemical degradation or derivative formation, and direct comparisons with authentic materials when possible.

(11) Wehrli, *et al.*,⁴ have reported the first example of rearrangement to a cyclobutanone derivative.

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Mass Spectrometric Studies on Aminocyclitol Antibiotics

Sir:

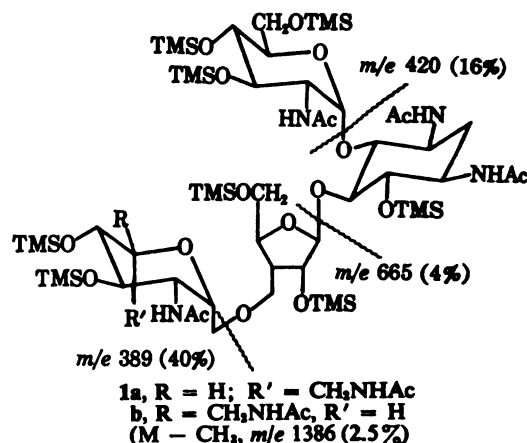
We wish to report preliminary results of a mass spectrometric investigation of the antibiotics paromomycin¹ and paromomycin II² (1a and 1b, respectively,

(1) (a) T. H. Haskell, J. C. French, and Q. R. Bartz, *J. Am. Chem. Soc.*, **81**, 3480 (1959); (b) T. H. Haskell and S. Hanessian, *J. Org. Chem.*, **28**, 2598 (1963).

TMS and Ac = H), members of the diaminocyclitol (deoxystreptamine) class of antibiotics.³⁻⁴

The above-mentioned antibiotics, together with the model compounds derived from them and from the neomycins by various degradative reactions,³⁻⁴ were investigated in the form of their N-acetyl-O-trimethylsilyl derivatives. The use of the trimethylsilyl (TMS) blocking groups was found advantageous in the study of these molecules of low volatility. The N-acetyl and N-acetyl-3-d derivatives 1-6 (TMS = H) were prepared by selective N-acetylation of the respective free bases with acetic anhydride in methanol. The chromatographically homogeneous solids⁵ (compounds 2, 4-6, TMS = H, were obtained crystalline) were then subjected to silylation with trimethylsilyl chloride and hexamethyldisilazane in dry pyridine.⁶ The trimethylsilyl ethers 1-6 thus obtained were nonhygroscopic white solids which had the infrared and nmr spectral properties expected for N-acetyl-O-trimethylsilyl derivatives.

A minute molecular ion peak is present in the mass spectrum⁷ of the N-acetyl-O-trimethylsilyl derivative of paromomycin II (1b). A peak of 2.5% intensity (relative to *m/e* 73, (CH₃)₃Si⁺) at *m/e* 1386 is characteristic of the loss of a methyl radical from a trimethylsilyl group.⁸ Relatively intense peaks are also present at *m/e* 665 (4.0%), 420 (16.0%), and 389 (40.0%) from cleavages of glycosidic bonds as indicated in structure 1. Other fragments in the spectrum can be accounted for by further fragmentations of the molecular ion and of these fragment ions.



(2) K. L. Rinehart, Jr., "The Neomycins and Related Antibiotics," John Wiley and Sons, Inc., New York, N. Y., 1964; S. Tatsuoka and S. Horii, *Proc. Japan Acad.*, **39**, 314 (1963).

(3) J. D. Dutcher, *Advan. Carbohydrate Chem.*, **18**, 259 (1963).

(4) S. Hanessian and T. H. Haskell, "The Carbohydrates," Vol. 2, W. Pigman and D. Horton, Ed., Academic Press Inc., New York, N. Y., in press.

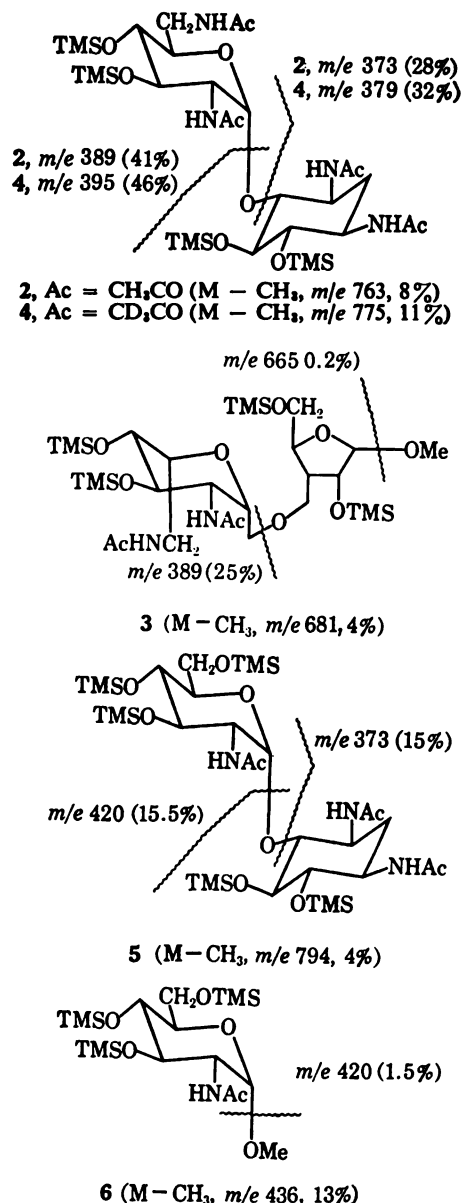
(5) Thin layer chromatography of the N-acetates was carried out on glass plates coated with Avirin (a product of American Viscose Corp. Marcus Hook, Pa.) and the compounds were detected by spraying lightly with a 1% solution of potassium permanganate in 1 *N* sulfuric acid or by exposure to iodine vapors.

(6) In a typical experiment, 0.1 g of N-acetyl derivative dissolved in 5 ml of dry pyridine was treated with 1 ml of trimethylsilyl chloride and 3 ml of hexamethyldisilazane at room temperature. After 1-2 hr the mixture was evaporated to dryness, the residue was suspended in benzene, and the soluble portion was evaporated to dryness and used as such.

(7) The mass spectra of compounds 2-6 were obtained from an Atlas CH4 mass spectrometer, using a vacuum-lock direct-inlet system. The authors wish to thank Dr. W. J. McMurray, Yale University School of Medicine, for obtaining the spectrum of compound 1b on an AEI MS9 mass spectrometer.

(8) A. G. Sharkey, Jr., R. A. Friedel, and S. H. Langer, *Anal. Chem.*, **29**, 770 (1957).

Prominent peaks at m/e 389 are also present in the mass spectra of model compounds 2 and 3 and shift to m/e 395 in the spectrum of the d_6 analog 4. The mass spectra of compounds 5 and 6 have peaks at m/e 420, does the spectrum of 1. A few other important peaks are indicated in 2-6. All peak intensities are relative to m/e 73, $(CH_3)_3Si^+$.



From these data, it is possible to recognize the sequential arrangement and gross structures of the units which the saccharides are comprised. Differences in stereochemistry and ring size most likely will not affect the indicated fragmentation paths. Compound 2 shows a preferential cleavage of glycosidic bonds, giving the charge on the carbon next to a ring oxygen where it can be stabilized by the nonbonding electrons of the oxygen. Although all of the mass spectra in this study exhibited only minute molecular ion peaks (1-1% relative intensity), molecular weights can be readily determined from the more intense peaks 15 mass units lower.

Whereas the characterization of various amino and deoxy sugars derived from antibiotic substances has not been successfully accomplished by mass spectrometric techniques,^{4,9,10} the detailed analysis of intact anti-

biotics containing sugars is still relatively unexplored.⁴ The few recorded examples belong to the class of macrolide (chalomycin,¹⁰ pimaricin,¹¹ and aldgamycin¹²) and nucleoside (cordycepin,¹³ puromycin¹⁴) antibiotics. The present investigation represents the first reported example of the application of mass spectrometry to the study of the gross structure of intact aminocyclitol antibiotics. It demonstrates the potential usefulness of this technique in providing crucial information concerning the structure of related compounds, from submilligram quantities of the appropriate derivatives and from minutes of instrument time. Experiments on the electron-impact-induced fragmentation of related aminocyclitol antibiotics are in progress.

(9) D. C. DeJongh and S. Hanessian, *J. Am. Chem. Soc.*, **87**, 3744 (1965); **88**, 3114 (1966).

(10) K. L. Rinehart, Jr., R. F. Schimbor, and T. H. Kinstle, *Antimicrobial Agents Chemotherapy*, 119 (1965).

(11) O. Ceder, *Acta Chem. Scand.*, **18**, 126 (1964); B. T. Golding, R. W. Rickards, W. E. Meyer, J. B. Patrick, and M. Barber, *Tetrahedron Letters*, 3551 (1966).

(12) M. P. Kunstmann, L. A. Mitscher, and N. Bohonos, *ibid.*, 389 (1966).

(13) S. Hanessian, D. C. DeJongh, and J. A. McCloskey, *Biochim. Biophys. Acta*, **117**, 480 (1966).

(14) S. H. Eggers, S. I. Biedron, and A. O. Hawtrey, *Tetrahedron Letters*, 3271 (1966).

(15) The support of the Public Health Service of the Department of Health, Education, and Welfare, through Grant AI 07570, is gratefully acknowledged.

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Received April 1, 1967

Metal-Ammonia Reduction of Nonconjugated Dienes and Enones¹

Sir:

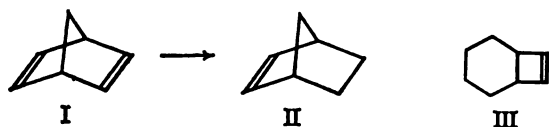
A consequence of a structurally imposed close proximity of two nonconjugated double bonds is that the energy of the lowest antibonding orbital of one is raised while that of the other is lowered. One of the several consequences of this which might be anticipated is the increased ability of the molecule to accept an electron in the relatively low energy antibonding orbital. It might be expected that the activation energy will be lowered and the equilibrium constant raised for the reversible process $M + e^- \rightleftharpoons M^{\cdot-}$. An example of this structural feature is norbornadiene (I). It appears to have no resonance energy in the ground state, and thus can in no sense be considered aromatic, but it has a significant 2-6 bonding contribution in the excited state.² A spectroscopic manifestation of this is its relatively long wavelength ultraviolet absorption (λ_{max} 211 m μ). We wish now to describe a chemical consequence of this perturbation, the reduction of such nonconjugated dienes and enones by metal-ammonia systems.

The reduction of I with sodium or lithium in carefully dried ammonia (-33°) afforded norbornene (II) in 98% yield.³ No evidence for even traces of

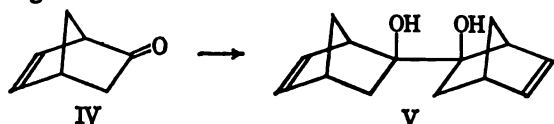
(1) The authors are indebted to the National Science Foundation, Grant GP 6757, and to the University of Utah Research Fund for the support of this study.

(2) C. F. Wilcox, S. Winstein, and W. G. McMillan, *J. Am. Chem. Soc.*, **82**, 5450 (1960).

norbornane or nortricyclene in the product could be found.⁴ To rule out the possibility that the difference in ease of reduction of I and II might be due to their difference in strain energy rather than to a double bond perturbation in I, a cyclobutene (III) was examined and found to be inert.

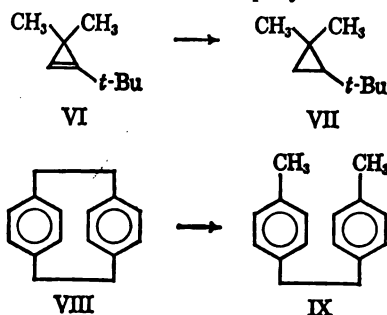


Norbornenone (IV, λ_{\max} 301 m μ (ϵ 292)) was found to be reduced under these conditions to a mixture of diastereomeric pinacols (V).⁷ Similar treatment of norbornanone (λ_{\max} 287 m μ (ϵ 29)) gave only recovered starting material.



It is thus clear that the light absorption properties of a molecule, which reflect the difference between its ground- and excited-state energies, may be used qualitatively to predict the ease with which it can accept an electron in its lowest lying antibonding orbital. The energy of the excited molecule will obviously be different from that of the radical ion which is intermediate to the reduction product because the latter possesses one more electron.

This correlation predicts that a number of other types of compound might also be reducible by metal-ammonia systems. 1-*t*-Butyl-3,3-dimethylcyclopropene (VI,⁸ λ_{\max} 195 m μ (ϵ 4400)) was examined and found to be reduced extremely rapidly to the corresponding cyclopropane⁸ (VII, 85%). Similarly, [2.2]paracyclophane (VIII)⁹ underwent reduction to di-*p*-tolylethane (IX, 100%) under conditions employed with other sub-



strates.

An intriguing question posed in the facile reductions of I and IV is whether or not nonclassical radical ions

(3) "Isolated" double bonds are not reduced without an added proton source and even then only terminal double bonds are affected: H. Greenfield, R. A. Friedel, and M. Orchin, *J. Am. Chem. Soc.*, **76**, 1258 (1954).

(4) The reduction of I to norbornane and nortricyclene with lithium in ethylamine (Benkeser conditions⁵) has been reported.⁶ It should be noted that this technique is effective in reducing virtually all isolated double bonds.

(5) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, **28**, 1094 (1963), and many references cited therein.

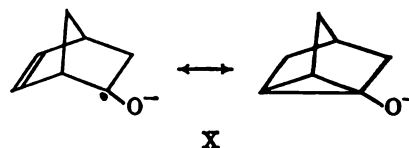
(6) J. G. Traynham, *ibid.*, **25**, 833 (1960).

(7) The mixture (60%, mp 80–83°) was not separated but gave satisfactory nmr, infrared, and mass spectral data and analyzed correctly for $C_{11}H_{16}O_2$. Periodic acid cleaved it to norbornenone (83%).

(8) T. C. Shield and P. D. Gardner, manuscript in preparation.

(9) D. J. Cram, N. L. Allinger, and H. Steinberg, *J. Am. Chem. Soc.*, **76**, 6132 (1954), describe the spectral properties of [2.2]paracyclophane. We are indebted to Professor Cram for a generous sample of this material.

are involved. Particularly in the reduction of IV there can be little doubt that the intermediate X is extremely long-lived relative to typical nonconjugated radical ions. Repeated attempts¹⁰ to obtain evidence for nonclassical behavior in the norbornenyl radical have failed, and it appears there is none. The radical ion in question here is electronically quite different, however, and its pronounced stability (long life) is suggestive of a nonclassical structure. An alternate



rationale based on steady-state concentration differences of radical ions cannot be dismissed ($M + e^- \rightleftharpoons M^{\cdot-}$, k_1 being very different but k_{-1} being similar for norbornanone and norbornenone), but it is considered unlikely.

(10) Cf. C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, **31**, 3381 (1966), and references cited therein.

(11) National Science Foundation Predoctoral Fellow, 1962–1963.

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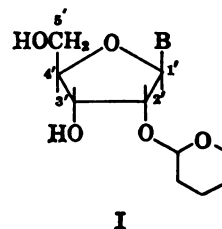
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Received April 20, 1967

A Symmetrical Alternative to the Tetrahydropyranyl Protecting Group

Sir:

An obvious inherent disadvantage in the use of the tetrahydropyranyl group for the protection of optically active alcohols is that it leads to the introduction of an additional asymmetric carbon center (or centers), and thereby to mixtures of diastereoisomers being obtained.¹



In connection with our work on oligoribonucleotide synthesis,² we undertook the preparation of a series of 2'-O-tetrahydropyranyl ribonucleosides (I) and obtained mixtures of diastereoisomers.³ Although the latter could be separated and obtained crystalline,⁴ the yield of pure isomer did not normally exceed 50%. However, after an unsuccessful attempt to isolate a pure crystalline 2',5'-bis(tetrahydropyranyl) ribonucleoside derivative, the search for an alternative, symmetrical acid-labile protecting group become more urgent. Unlike other workers engaged in oligoribonucleotide synthesis,⁵ we have concluded³ that the tetrahydropy-

(1) C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951); A. N. de Belder, P. J. Garegg, B. Lindberg, G. Petropavlovskii, and O. Theander, *Acta Chem. Scand.*, **16**, 623 (1962).

(2) B. E. Griffin and C. B. Reese, *Tetrahedron Letters*, 2925 (1964).

(3) B. E. Griffin, M. Jarman, and C. B. Reese, *Tetrahedron*, in press.

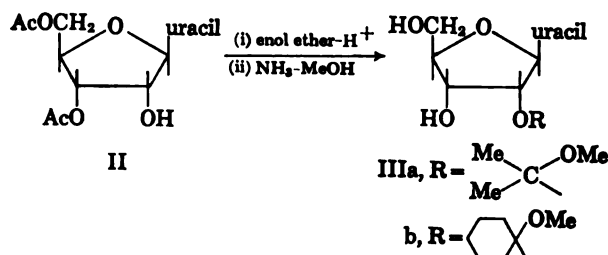
(4) As it is intended that the synthetic oligomers should contain only 3'→5' internucleotidic linkages, it is a reasonable precaution to use only pure crystalline 2'-protected ribonucleoside derivatives (e.g., I) as intermediates.

(5) D. H. Rammner and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 3112 (1962); J. Smrt and S. Chládek, *Collection Czech. Chem. Commun.*

ranyl acetal system has approximately optimal hydrolysis properties for an acid-labile protecting group: it may be removed under very mild conditions,⁶ but is stable enough to allow protected oligomers to be purified.

Thus a satisfactory solution to this problem would be to find a symmetrical ketal system which underwent hydrolysis, in aqueous acid, at approximately the same rate as the tetrahydropyranyl group.⁶ However, the best approach to such a solution was not immediately apparent as it had been reported⁸ that simple ketals were over 10^3 times more labile than the corresponding acetals.⁹

Chart I



The 2'-acetone and cyclohexanone ketals of uridine (IIIa and IIIb) were prepared¹⁰ from 3',5'-di-O-acetyluridine¹¹ (II) and the appropriate enol ethers (2-methoxypropene¹² and 1-methoxycyclohexene,¹³ respectively) by the procedure indicated in Chart I. The half-times of hydrolysis of these derivatives at 20° and pH 4 are given in Table I. As the rate of ketal

Table I. Half-times ($t_{1/2}$) of Hydrolysis of Uridine 2'-Ketals (III)^a in 0.1 M Aqueous Sodium Citrate (pH 4.0) at 20°

Compd	Yield, % ^b	Mp, °C	$t_{1/2}$, min
IIIa	42	185 dec	4 ^c
IIIb	30	149–151	10

^a 0.02 M solutions of nucleoside derivatives were used. ^b Represents over-all yield based on II. ^c $t_{1/2}$ for the corresponding 5'-protected uridine derivative was reported to be 1 min in 0.1 M acetate buffer (pH 4.7) at 25° (A. Hampton, *J. Am. Chem. Soc.*, **87**, 4654 (1965)).

hydrolysis⁸ is proportional to $[\text{H}^+]$, $t_{1/2}$ for IIIa may be calculated to be 0.04 min at 20° and pH 2. As anticipated, this is less than $10^{-2}t_{1/2}$ for 2'-O-tetrahydropyranylyridine⁶ under the same conditions. Surprisingly,¹⁴ the cyclohexanone ketal IIIb is only 2.5 times more stable than IIIa.

31, 2978 (1966); F. Cramer, H.-J. Rhaese, S. Rittner, and K.-H. Scheit, *Ann.*, **683**, 199 (1965).

(6) At pH 2 (in 0.01 N hydrochloric acid solution) and 20°, the half-time ($t_{1/2}$) of hydrolysis of 2'-O-tetrahydropyranylyridine (I, B = uracil-1) is 80 min. Thus the tetrahydropyranyl group may be removed from a protected oligomer with a negligible amount of concomitant degradation and isomerization.⁷

(7) D. M. Brown, D. I. Magrath, A. H. Neilson, and A. R. Todd, *Nature*, **177**, 1124 (1956).

(8) M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **77**, 3146, 5590 (1955).

(9) The latter are, in turn, $>10^3$ times as labile as the corresponding formaldehyde acetals. Thus⁹ the relative rates of hydrolysis of $\text{CH}_3\text{(OEt)}_2$, MeCH(OEt)_2 , and $\text{Me}_2\text{C(OEt)}_2$ at 25° in dioxane-water are $1:6 \times 10^3:1.8 \times 10^7$.

(10) Satisfactory analytical data were obtained for all new compounds described.

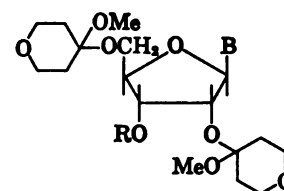
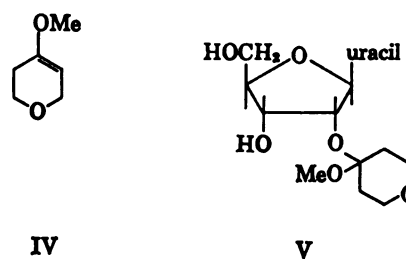
(11) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2315 (1967).

(12) L. Claisen, *Chem. Ber.*, **31**, 1019 (1898).

(13) D. G. Lindsay and C. B. Reese, *Tetrahedron*, **21**, 1673 (1965).

(14) H. C. Brown, R. S. Fletcher, and R. B. Johannessen, *J. Am. Chem. Soc.*, **73**, 212 (1951).

It had been shown⁸ that acetal and ketal systems could be stabilized to acidic hydrolysis by the introduction of electron-withdrawing groups. The idea that the inductive effect of a β -oxygen atom, if the latter were constrained in a ring system, might be sufficient for the present purpose was suggested by the fact that the $\text{p}K_a$ of morpholine (8.70) was 2.52 units less than that of piperidine.¹⁵ This indicates that a β -oxygen atom can destabilize a substituted ammonium ion by a factor of *ca.* 330. As the rate of ketal hydrolysis depends on the stability of the intermediate carbonium ion,⁸ an estimate of $t_{1/2} = 33$ min at pH 2 and 20° can be made for the hydrolysis of the uridine 2'-ketal of tetrahydro-4-pyrone (V) if the β -oxygen atom is assumed to exert an equivalent destabilizing effect on a carbonium ion.¹⁶



VIa, R = H
b, R = Ac

Reaction between 3',5'-di-O-acetyluridine¹¹ (II) and excess of 4-methoxy-5,6-dihydro-2H-pyran¹⁷ (IV) in the presence of toluene-*p*-sulfonic acid followed by treatment with methanolic ammonia gave the required uridine 2'-ketal (V) as a crystalline solid, in 61% yield. As indicated in Table II, its acid lability ($t_{1/2} = 24$ min at pH 2 and 20°) is remarkably close to the above estimate and is *ca.* three times as great as that of 2'-O-tetrahydropyranylyridine.⁶ In the same way the corresponding thymidine 5'-ketal, a useful intermediate in oligodeoxyribonucleotide synthesis, was prepared from 3'-O-acetylthymidine in 85% over-all yield. It is noteworthy that the 5'-ketal is more acid labile than the 2'-ketal system (see Table II).

Reaction between 3'-O-acetyluridine¹¹ and the enol ether IV under the usual conditions gave the diprotected derivative VIb (R = uracil-1), isolated as a crystalline solid in over 50% yield. Although the product VIa (B = uracil-1), obtained by treating the latter with methanolic ammonia, has not yet been in-

(15) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen & Co. Ltd., London, 1962, p 141.

(16) The tetrahydro-4-pyrone ketal V is assumed to be 330 times more resistant to acidic hydrolysis than the cyclohexanone ketal IIIb. The latter would be expected to have $t_{1/2} = 0.1$ min at pH 2 and 20° (see Table I).

(17) When 4,4-dimethoxytetrahydropyran [bp 64–66° (15 mm)], obtained from tetrahydro-4-pyrone¹⁸ in 94% yield, was distilled with mesitylenesulfonic acid (0.1% by weight), 4-methoxy-5,6-dihydro-2H-pyran (IV) [bp 156–157° (760 mm)] was obtained in over 75% yield. In reactions with nucleoside derivatives, *ca.* 8 molecular equiv of IV was used per hydroxyl function to be protected.

(18) S. Olsen and R. Bredoch, *Chem. Ber.*, **91**, 1589 (1958).

Table II. Tetrahydro-4-pyrone Ketals of Nucleosides

Nucleoside derivative	Mp, °C	Yield, % ^a	$[\alpha]_D^{20}$, deg ^b	$t_{1/2}$, min ^c
Uridine 2'-ketal (V)	167-169	61	-15.7	24
Thymidine 5'-ketal	169-171	85	+9.7	10.5
Uridine 2',5'-bisketal ^d (VIa, B = uracil-1)		51	+2.4	9.5 ^e
Adenosine 2',5'-bisketal (VIa, B = adenine-9)	183-184	52	-50	

^a Based on two steps from 3'-O-acetyl or 3',5'-di-O-acetyl nucleoside. ^b At suitable concentrations, in ethanol solution. ^c At 20° in 0.01 N hydrochloric acid. ^d Obtained as a glass in quantitative yield from its crystalline 3'-O-acetate (VIb, B = uracil-1; mp 102-104°). ^e For conversion of starting material into a mixture of 2'- and 5'-monoketals.

duced to crystallize, the corresponding adenosine derivative VIa (B = adenine-9) has been isolated as a crystalline solid in 52% over-all yield (see Table II).

Thus the tetrahydro-4-pyrone ketal system (methoxytetrahydropyranyl group) appears to be most suitable for the protection of alcoholic hydroxyl functions in oligoribonucleotide synthesis; it has the required acid lability, and its use leads to satisfactory yields of pure crystalline mono- and diprotected ribonucleoside derivatives. This symmetrical ketal system should prove to be a useful alternative to the tetrahydropyranyl protecting group in other branches of natural product chemistry.

(19) Holder of a Science Research Council Research Studentship.

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Received April 25, 1967

Mechanism of the Oxidation of Monohydric Alcohols with Lead Tetraacetate. Rearrangement in the Triarylmethanol Series

Sir:

In recent years the ability of lead tetraacetate to oxidize monohydric alcohols has been exploited extensively from the synthetic standpoint.¹ Many of the products formed in this versatile reaction can be accounted for in terms of a mechanism involving the initial production of alkoxy radicals.^{1,2} However, other mechanisms have been considered,¹⁻⁴ and the

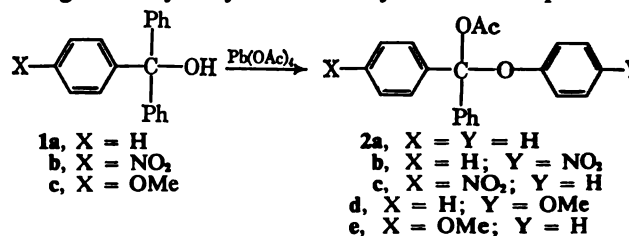
(1) For a review, see K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Ed. Engl.*, **3**, 525 (1964).

(2) See, *inter alia*, G. Cainelli, B. Kamber, J. Keller, M. L. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **44**, 518 (1961); M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. L. Mihailović, K. Schaffner, D. Arigoni, and O. Jeger, *ibid.*, **45**, 2674 (1962); K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *ibid.*, **46**, 352 (1963); D. Hauser, K. Schaffner, and O. Jeger, *ibid.*, **47**, 1883 (1964); D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner, and O. Jeger, *ibid.*, **47**, 1961 (1964); K. Heusler, *Tetrahedron Letters*, 3975 (1964); M. Stefanović, M. Gašić, L. Lorenc, and M. L. Mihailović, *Tetrahedron*, **20**, 2289 (1964); M. L. Mihailović, Z. Maksimović, D. Jeremić, Ž. Čeković, A. Milovanović, and L. Lorenc, *ibid.*, **21**, 1395 (1965); M. L. Mihailović, Ž. Čeković, Z. Maksimović, D. Jeremić, L. Lorenc, and R. I. Mamuzić, *ibid.*, **21**, 2799 (1965); M. L. Mihailović, Ž. Čeković, and D. Jeremić, *ibid.*, **21**, 2813 (1965); M. L. Mihailović and M. Miloradović, *ibid.*, **22**, 723 (1966); M. L. Mihailović, J. Bošnjak, Z. Maksimović, Ž. Čeković, and L. Lorenc, *ibid.*, **22**, 955 (1966); R. E. Partch, *J. Org. Chem.*, **30**, 2498 (1965).

(3) G. Cainelli, M. L. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959); W. A. Mosher and H. A. Neidig, *J. Am. Chem. Soc.*, **72**, 4452 (1950); W. A. Mosher, C. L. Kehr, and L. W. Wright, *J. Org. Chem.*, **26**, 1044 (1961); M. S. Kharasch, H. N. Friedlander, and W. H. Urry, *ibid.*, **16**, 533 (1951); S. Moon and J. M.

evidence for radicals as prime intermediates has remained suggestive rather than conclusive. The present communication reports the discovery of a novel lead tetraacetate induced rearrangement whose investigation has yielded definitive information regarding the mechanism of the alcohol oxidation reaction.

Triphenylmethanol (1a) reacts with lead tetraacetate⁴ in benzene, benzene-pyridine, or acetonitrile to form hemiketal ester 2a in yields ranging up to 91%.⁵ Although the hydrolytic instability of 2a has prevented



its isolation, its presence has been conclusively established by infrared, nmr, and chemical ionization mass spectral measurements⁶ on crude reaction products, and by the formation of benzophenone, dimethoxydiphenylmethane, methoxyphenoxydiphenylmethane, acetic acid, and phenol upon saponification of crude 2a with potassium hydroxide in aqueous methanol.

Reactions of lead tetraacetate with 1b or 1c gave mixtures of hemiketal acetates 2b,c or 2d,e.⁵ These mixtures were hydrolyzed, and relative migratory aptitudes for the substituted aryl groups were then calculated from the amounts of ketones and ketals thus obtained. In the case of 1b, the lead tetraacetate reactions were run in benzene, benzene-pyridine, benzene-pyridine containing a soluble copper catalyst, acetonitrile, and acetonitrile containing cupric acetate.⁴ Despite the wide variations in conditions and their attendant effects upon reaction rate, all of these experiments gave the same statistically corrected ratio for *p*-nitrophenyl:phenyl migration (within experimental error). Its value was 4.4 ± 0.3 , a result which demands the operation of a homolytic mechanism.⁷ Competitive occurrence of an ionic mechanism is ruled out by the insensitivity of the ratio to solvent polarity and the presence of copper salts or pyridine.⁸ A concerted homolytic mechanism (see below) seems unlikely, since it would require a dependence of the ratio upon the nature of the leaving group.⁹ Therefore, in this case it appears that the alkoxy radical corresponding to 1b is the sole rearranging species.¹⁰

Lodge, *ibid.*, **29**, 3453 (1964); R. Moriarty and K. Kapadia, *Tetrahedron Letters*, 1165 (1964).

(4) See footnotes to Table I for a summary of conditions.

(5) Side reactions also occur, but to a relatively minor extent.

(6) (a) Details will be presented in a later report. (b) For discussions of chemical ionization mass spectrometry, see M. S. B. Munson and F. H. Field, *J. Am. Chem. Soc.*, **88**, 2621, 4337 (1966).

(7) Compare (a) P. D. Bartlett and J. D. Cotman, Jr., *ibid.*, **72**, 3095 (1950); (b) W. Dilthey, F. Quint, and H. Dierichs, *J. Prakt. Chem.*, **151**, 25 (1938).

(8) (a) Copper salts strongly catalyze the decomposition of Pb(IV) esters *via* a radical chain mechanism. Thermal homolysis of these esters is also believed to be sensitized by complexation with pyridine. See J. K. Kochi, *J. Am. Chem. Soc.*, **87**, 3609 (1965); *J. Org. Chem.*, **30**, 3265 (1965). (b) Copper salt catalysis in the Pb(IV) oxidation of alcohols has recently been observed by other workers. See G. Cainelli and F. Minisci, *Chim. Ind. (Milan)*, **47**, 1214 (1965); G. Cainelli and S. Morrocchi, *Atti Accad. Nazl. Lincei Rend. Classe Sci. Fis. Mat. Nat.*, **40**, 464, 591 (1966).

(9) The leaving group should be different in reactions with pyridine if complexation^{8a} occurs.

(10) The degree of kinetic freedom associated with this radical is not specified.

Reactions of 1c with Lead Tetraacetate^a

Additives	Time, hr	Yield, ^b moles/ mole of 1c		Mig apt ^c p-MeO- Ph-:Ph-
		p-MeO- (Ph) ₂ CO	(Ph) ₂ CO	
...	95	0.218	0.370	3.4
Py ^e	23	0.248	0.206	1.7
Cu ^f	22	0.343	0.203	1.2
Py, ^e Cu ^f	1.5	0.162	0.0855	1.1
PhNO ₂ ^g	100	0.0934	0.570	12
...	95	0.0883	0.578	13
Py ^h	19	0.122	0.202	3.3
Cu ⁱ	22	0.205	0.365	3.6
Py, ^h Cu ⁱ	18	0.153	0.0977	1.3
PhNO ₂ ^j	95	0.0590	0.464	16

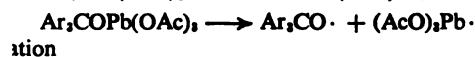
3.27 mmoles; Pb(OAc)₄, 7.22 mmoles unless noted otherwise; 20 ml unless noted otherwise; CaCO₃, 15.0 mmoles only in experiments without pyridine; 82 ± 2°. Oxygen effect on results. ^b Analyses by glpc; yields of ketals. ^c 2 [moles of (Ph)₂CO]/moles of p-MeO(Ph)₂CO. ^d 25 OAc, 9.83 mmoles. ^e Pyridine, 19.7 mmoles. ^f Harshaw "1 copper liquid 8%," equivalent to 1.00 g-atom of Cu. ^g Pyridine, 14.5 mmoles. ^h Cu(OAc)₂·H₂O, 1.00 g, 6.54 mmoles.

ever, the alkoxy radical mechanism is not the one through which the rearrangement can proceed.

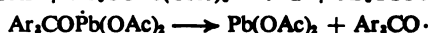
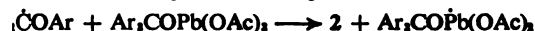
In the case of 1c, the occurrence of two mechanisms is clearly shown by the marked influence of reaction conditions upon the *p*-methoxyphenyl:phenyl migration (Table I). The low ratios obtained with lead and copper salts are believed to reflect the dominant operation of the alkoxy radical mechanism,^{8,11} while the high values obtained in acetone and the experiments using nitrobenzene are consistent with the preferential decomposition of a first-order Pb(IV) alcoholate *via* a concerted, quasiionic¹¹ process (either heterolytic or homolytic) involving arylation. Our results suggest that the quasiionic mechanism is likely to be observed only in cases where aryl groups bearing strongly electron-donating substituents are near the hydroxyl function.

In nitrobenzene caused no marked increases in reaction rate or hemiketal ester yields, did not cause the formation of new products, failed to reduce the overall balance (based on 1c), and was not used in enough concentration to affect medium polarity. Apparently, its effect upon the *p*-methoxyphenyl:phenyl migration is apparently due to selective inhibition of the radical chain process rather than to selective action of the quasiionic mode. A scheme which accounts for the available facts relating to the radical mechanism is shown below.¹²

on



ation



^a -Methoxyphenyl:phenyl migratory ratios for alkoxy radical mechanisms have apparently not been reported previously. How groups are known to show comparable reactivities in the homophenyl rearrangement [C. Rüchardt and R. Hecht, *Tetrahedron* 1961 (1962)]. Ionic decompositions of *p*-methoxytriphenylhydroperoxide^{7b} and the corresponding perbenzoate (I. J. Ph.D. Thesis, University of Kansas, 1960) give preferential *xy*phenyl migration.

^b A similar scheme which does not involve Pb(III) species is also

Termination



In view of the foregoing observations, the occurrence of radical chain mechanisms in the oxidation of other types of monohydric alcohols with lead tetraacetate seems highly probable.

Acknowledgment. The author is indebted to Mr. H. J. Tarski for valuable technical assistance and to Dr. F. H. Field for the chemical ionization mass spectra.

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New Syntheses of Alloxazines¹

Sir:

Alloxazines and isalloxazines² are customarily prepared by condensation of (a) an *o*-phenylenediamine with alloxan,³ (b) a 4,5-diaminopyrimidine with an *o*-benzoquinone,⁴ (c) an *o*-aminoazobenzene with a barbituric acid,⁵ (d) a 5-nitrosopyrimidine with an aromatic amine⁶ or an *o*-phenylenediamine,⁷ or (e) by nitrosation of a 6-arylamino-uracil.⁸ We wish to report three new synthetic approaches to alloxazines which not only are applicable, in principle, to the preparation of other condensed pyrazine heterocycles, but which offer further versatility in the synthesis of alloxazines with different origins for N₈ and N₁₀.

Method A. Recent studies on the deoxygenation of aromatic nitro compounds by triethyl phosphite⁹ support the intermediacy of nitrene intermediates. Capture of these nitrenes by intramolecular insertion has been utilized for the preparation of a number of heterocyclic systems (carbazoles,¹⁰ benzotriazoles,¹⁰ indazoles,¹⁰ phenothiazines,¹¹ anthranils,¹¹ indoles,^{10,12} pyrrolo[3,2-*d*]pyrimidines¹³). We report the first application of this procedure to the synthesis of a condensed pyrazine system. Thus, refluxing 1,3-di-

(1) This research was supported in part by Contract DA-49-193-MD-2777 from the Department of the Army, Walter Reed Army Medical Center, and in part by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) (a) P. Hemmerich, C. Veeger, and H. C. S. Wood, *Angew. Chem.*, 77, 699 (1965); *Angew. Chem. Intern. Ed. Engl.*, 4, 671 (1965); (b) T. Wagner-Jauregg in "The Vitamins," Vol. III, W. H. Sebrell, Jr., and R. S. Harris, Eds., Academic Press Inc., New York, N. Y., 1954, pp 301-332; (c) T. S. Stevens in "Chemistry of Carbon Compounds," Vol. IVC, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1960, pp 1786-1790.

(3) (a) O. Kühling, *Chem. Ber.*, 24, 2363 (1891); (b) R. Kuhn and F. Weyand, *ibid.*, 67, 1409 (1934).

(4) R. M. Cresswell, T. Neilson, and H. C. S. Wood, *J. Chem. Soc.*, 476 (1961).

(5) (a) M. Tishler, K. Pfister, R. D. Babson, K. Ladenburg, and A. J. Fleming, *J. Am. Chem. Soc.*, 69, 1487 (1947); (b) V. M. Berezovskii and L. S. Tul'chinskaya, *Zh. Obshch. Khim.*, 31, 2779 (1961); *Chem. Abstr.*, 56, 10140 (1962).

(6) (a) P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta.*, 42, 1604 (1959), and references cited therein; (b) O. Piloty and K. Finckh, *Ann.*, 333, 43 (1904).

(7) V. M. Berezovskii and G. D. Glebova, *Dokl. Akad. Nauk SSSR*, 146, 355 (1962); *Chem. Abstr.*, 58, 4547 (1963).

(8) H. Goldner, G. Dietz, and E. Carstens, *Ann.*, 694, 142 (1966).

(9) (a) G. Smolinsky and B. L. Feuer, *J. Org. Chem.*, 31, 3882 (1966); (b) J. I. G. Cadogan and M. J. Todd, *Chem. Commun.*, 178 (1967).

(10) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 4831 (1965).

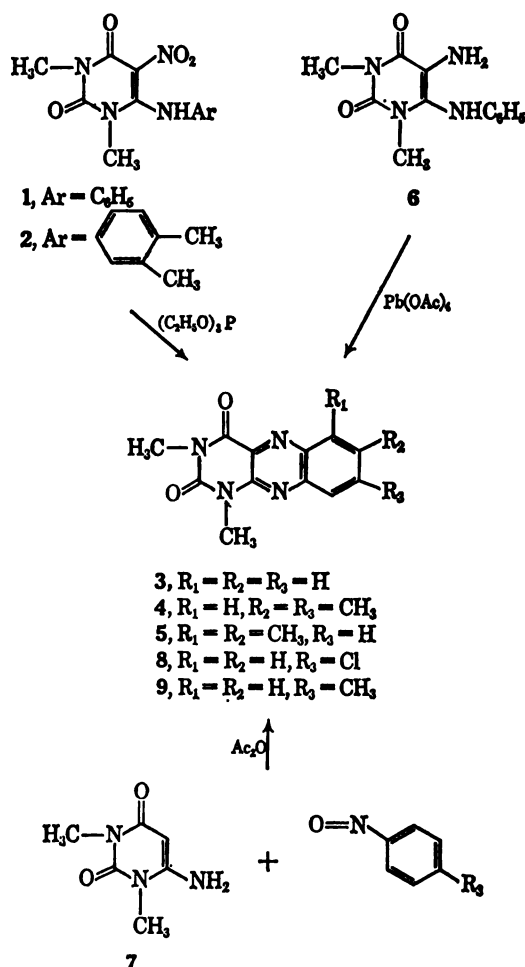
(11) J. I. G. Cadogan, R. K. Mackie, and M. J. Todd, *Chem. Commun.*, 491 (1966).

(12) R. J. Sundberg, *J. Org. Chem.*, 30, 3604 (1965).

(13) E. C. Taylor and E. E. Garcia, *ibid.*, 30, 655 (1965).

methyl-5-nitro-6-anilinouracil (1), mp 200.1°, in excess triethyl phosphite under N₂ for 2 hr, removal of volatiles by partial evaporation under a vigorous stream of N₂, and dilution with ethanol gave 1,3-dimethylalloxazine (3),¹⁴ mp 243.3°⁸ (30%). It is of considerable interest that the major product of this reaction was 1,3-dimethyl-6-anilinouracil, mp 187.7°.⁸ To our knowledge, this is the first example of denitration in the pyrimidine series. Similarly, heating 1,3-dimethyl-5-nitro-6-(3,4-xylidino)uracil (2), mp 212–214°, in triethyl phosphite for 7.5 hr gave a mixture of 1,3,7,8-tetramethylalloxazine (4), mp 253–254°¹⁵ (14%), and 1,3,6,7-tetramethylalloxazine (5), mp 273.3°, along with the product of denitration, 1,3-dimethyl-6-(3,4-xylidino)uracil, mp 233.6°.

Method B. 1,3-Dimethylalloxazine (3) was prepared in 61% yield by portionwise addition of 1.5 moles of lead tetraacetate to a refluxing ether suspension of 1,3-dimethyl-5-amino-6-anilinouracil (6), mp 160.3°, followed by filtration and washing with water. The same conversion could be effected in lower yield (48%) by heating an intimate mixture of 6 with lead dioxide at 220°.



Method C. Refluxing 1 equiv of 1,3-dimethyl-6-aminouracil (7) with 2 equiv of nitrosobenzene, *p*-chloronitrosobenzene, or *p*-nitrosotoluene in acetic anhydride for 15 min, followed by dilution with water, gave 1,3-dimethylalloxazine (3), 52%, 1,3-dimethyl-8-

chloroalloxazine (8), mp 251.0° (68%), and 1,3,8-trimethylalloxazine (9) mp 251.7° (49%). This latter compound was identical with the product of previously undetermined structure (1,3,6- or 1,3,8-trimethylalloxazine, mp 252–253°) prepared by nitrosation of 1,3-dimethyl-6-(*p*-toluidino)uracil.⁸

Applications of these procedures to the preparation of other condensed pyrazine heterocycles are in progress.

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Received May 3, 1967

Correlation between the Photochemistry and the Mass Spectra of Pyruvic Acid and Isopropyl Pyruvate^{1,2}

Sir:

We wish to report an interesting correlation between the mass spectral behavior and photochemistry of both pyruvic acid and its isopropyl ester. Although processes which are general in photolyses have long been known to have analogs in mass spectral fragmentations,¹ the cases reported here are examples of unusual behavior of two molecular ions which are paralleled by unusual behavior of two corresponding *n*, π^* excited states. Such an observation is significant in that it provides evidence for the validity of attempts to interrelate the mass spectrometry and photochemistry of organic molecules.

Photolysis of pyruvic acid in the vapor phase³ and in aqueous solution⁴ yields acetaldehyde and CO₂, and acetoin, respectively. The reaction has been proposed to involve an *n*, π^* state which forms an uncommon five-membered transition state.⁵ The latter collapses to CO₂ and methylhydroxycarbene which then rearranges to acetaldehyde. From Table I it can be seen that the analogous process occurs in the mass

Table I. Partial Monoisotopic Mass Spectra (75 ev) of Pyruvic Acid and Pyruvic Acid-OD^a

CH ₃ COCO ₂ H		CH ₃ COCO ₂ D ^a	
%	Ion	%	Ion
4.2	C ₃ H ₄ O ₃	4.2	C ₃ H ₃ DO ₃
16	CHO ₂	22	CDO ₂
3.4	C ₂ H ₂ O	6.7	C ₂ H ₂ DO
100	C ₃ H ₄ O	5.8	C ₂ H ₃ DO
		100	C ₂ H ₃ O

^a Empirical formulas were determined by exact mass measurement on a CEC 21-110B mass spectrometer. Inlet system and source were maintained below 70° to avoid thermal decomposition.

^b Prepared by injecting a solution of pyruvic acid in a ten-volume (~40 mole) excess of D₂O into the spectrometer previously equilibrated with D₂O. Relative abundances corrected to 100% d₁.

(1) Part II in this series; see N. J. Turro, D. C. Neckers, P. A. Leermakers, D. Seldner, and P. D'Angelo, *J. Am. Chem. Soc.*, **87**, 4079 (1964) for part I.

(2) The authors gratefully acknowledge generous support from the Air Force Office of Scientific Research (Grant AFOSR 1000-66) and the National Science Foundation (Grant NSF-GP-4280) at Columbia University, and the National Institutes of Health (Grant GM 12759) at Purdue University.

(3) G. F. Vesley and P. A. Leermakers, *J. Phys. Chem.*, **68**, 2364 (1964).

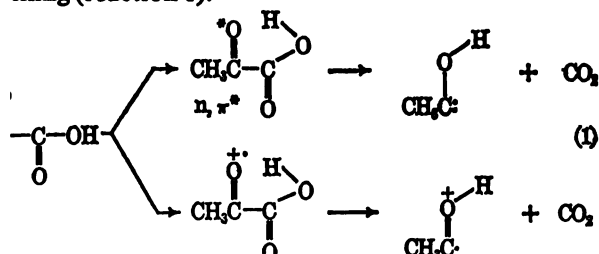
(4) P. A. Leermakers and G. F. Vesley, *J. Am. Chem. Soc.*, **85**, 3776 (1963).

(5) α -Keto acids exist as proton chelates, even in the gas phase: A. Schellenburger, W. Beer, and G. Dehme, *Spectrochim. Acta*, **11**, 1345 (1965).

(14) Satisfactory microanalytical and spectral data were obtained for all compounds reported.

(15) (a) P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta.*, **43**, 372 (1960); R. Kuhn and H. Rudy, *Chem. Ber.*, **67**, 1826 (1934).

trometer to yield the ion fragments C_2H_4O and CH_2DO from pyruvic acid and pyruvic acid-OD, respectively. Since hydrogen rearrangement *via* a 6-membered transition state is uncommon in the mass spectra of carbonyl compounds,⁶ the analogy between the photolysis and mass spectral decomposition is striking (reaction 1).



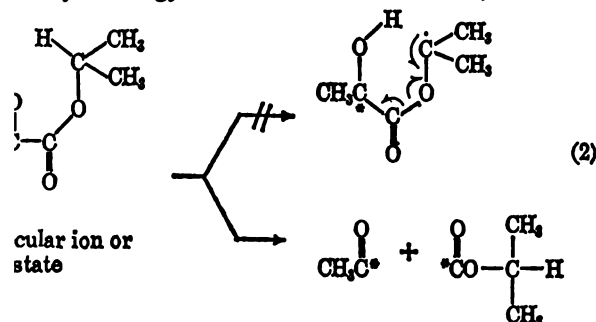
The photolysis of $CH_3COCO_2CH(CH_3)_2$ (1) in the gas phase⁷ or in benzene solution⁸ yields acetone and carbon monoxide as major products and only a low yield of acetaldehyde. Leermakers⁸ has explained these and related results by proposing a mechanism involving α cleavage as the primary photochemical reaction followed by loss of CO rather than the intuitively probable type II photorearrangement. The mass spectral behavior of the molecular ions of 1 and $CH_3COCO_2CD(CH_3)_2$ (2), shown in Table II, appears to

II. Partial Monoisotopic Mass Spectra (75 ev) of 1 and 2*

$CH_3COCO_2CH(CH_3)_2$ (1)		$CH_3COCO_2CD(CH_3)_2$ (2)	
%	Ion	%	Ion
0.4	$C_5H_{10}O_2$	0.5	$C_5H_9DO_2$
4.1	$C_5H_7O_2$	4.6	$C_5H_6DO_2$
4.4	C_5H_5O	3.6	C_5H_4DO
100	C_5H_4O	100	C_5H_3O

analysis conditions given in Table I, except that inlet and source temperatures were 165°. * Greater than 98% d_1 . The sample kindly donated by Professor P. A. Leermakers.

be quite analogous to the photochemical behavior of n, π^* excited states. A striking feature of the mass spectra is the conspicuous absence of $C_5H_{10}O_2$, $C_5H_7O_2$, C_5H_5O , and C_5H_4O ions. The $C_5H_{10}O_2$, $C_5H_7O_2$, and C_5H_5O ions in the spectra of 1 and 2, respectively, would correspond to products of the very general McLafferty rearrangement,⁶ and these ions might be expected to decompose further to $C_2H_4O^+$ and $C_2H_3O^+$ by analogy to reaction 1.⁹ Indeed, the ions



F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, p 123 ff.

P. A. Leermakers, M. E. Ross, G. F. Vesley, and P. C. Warren, *J. Chem. Phys.*, **30**, 914 (1965).

P. A. Leermakers, P. C. Warren, and G. F. Vesley, *J. Am. Chem. Soc.*, **86**, 1768 (1964).

Also there are no $C_5H_9O_2^+$ ions which might be expected by analogy to the double hydrogen rearrangement common in esters.⁹

$C_4H_7O_2^+$, $C_4H_6DO_2^+$, and $C_4H_5O^+$ serve as evidence of the importance of cleavage of the CO-CO bond (reaction 2).

Further studies of these and other systems are being pursued in order to understand better the chemistry of molecules ionized by electron impact and to determine how the structures and reactivities of electronically excited states and molecular ions may be correlated.

(10) Alfred P. Sloan Fellow, 1966-1968.

(11) National Institutes of Health Predoctoral Fellow, 1966-1967.

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On the Mechanism of Lanosterol Biosynthesis from Squalene 2,3-Oxide

Sir:

In connection with our continuing program concerned with the organic and biological chemistry of terpenoid terminal epoxides,¹ we wish now to present new findings and considerations which further delineate the role of squalene 2,3-oxide in the biosynthesis of lanosterol and therefore other members of the sterol class.

Although recent experiments in these laboratories² and elsewhere³ indicated that ^{14}C -labeled squalene 2,3-oxide^{1a} can be biosynthesized and also act as a natural triterpene source of lanosterol and cholesterol, the fate of oxygen in the original epoxide moiety was left unsettled. The following experiments elucidate this matter. Squalene 2,3-oxide- 3H , ^{18}O (4150 dpm/ μg , 30% ^{18}O by mass spectral comparison⁴ of normal and ^{18}O -labeled oxides) was prepared from squalene- 3H (4350 dpm/ μg) by the action of N-bromosuccinimide^{1a} in 3:1 THF-water (30% ^{18}O -labeled) and was incubated anaerobically with washed microsomes of rat liver in 0.08 M potassium phosphate buffer, pH 7.4. The sterol fraction was isolated, and lanosterol (R_f , 0.43; 200,000 dpm) was separated by tlc on silica gel in 15% ethyl acetate-hexane. Purification by glpc of the trimethyl silyl ether on a 6 ft \times 0.25 in. column of 5% Carbowax on Chromosorb W at 235° gave lanosterol trimethylsilyl ether (retention time relative to cholestane = 3.7) which on mass spectral analysis was found to contain 29% excess ^{18}O . The retention of the original epoxy oxygen as the 3 β -hydroxyl group of lanosterol supports the mechanism proposed earlier^{2,3} for the proton-initiated enzymic cyclization of squalene 2,3-oxide to lanosterol. Moreover, our inability to demonstrate any cofactor requirements for the microsomal enzyme system is also consistent with the proposed mechanism.

(1) Initial publications in this series: (a) E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 121 (1962); (b) E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, **85**, 3295 (1963).

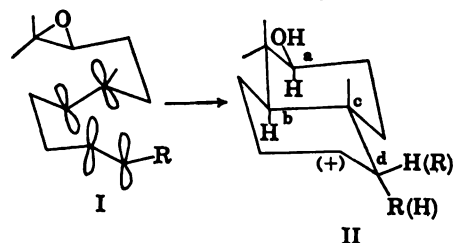
(2) E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *ibid.*, **88**, 4752 (1966).

(3) E. J. Corey and W. E. Russey, *ibid.*, **88**, 4750 (1966), have also reported the biochemical conversion of squalene 2,3-oxide^{1a} to sterols.

(4) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 204-205.

In an effort to locate additional intermediates in the over-all squalene \rightarrow lanosterol conversion, other oxidation products of squalene were prepared and tested for incorporation. Through the use of techniques previously described,² labeled lanosterol was not detected after incubation of ³H-labeled 2,3-dihydrosqualene-2,3-diol,⁵ 2,3-dihydrosqualen-2-ol,⁶ and squalene 2,3:22,23-dioxide^{1a} with rat liver homogenate.

Previous chemical investigations of the synthesis and cyclization of terpenoid terminal epoxides have revealed striking similarities between nonenzymic behavior on the one hand and squalene-squalene oxide biochemistry on the other. First, the unique, highly selective terminal oxidation of squalene by NBS in aqueous-organic solution^{1a} simulates the observed biological conversion of squalene to its 2,3-oxide.^{2,3} Second, laboratory cyclization of sesqui-^{1b,7} or diterpenoid⁸ terminal epoxides (I) to 3-hydroxylated polycyclic systems (II) with either "natural" (a-b-c-d *cis,trans,trans*) or biosynthetically attractive⁹ (a-b-c-d *cis,trans,cis*) stereochemistry closely resembles genera-



tion of the AB moiety of lanosterol and other polycyclic terpenes in living systems. Third, just as most intermediary mono-, bi-, or tricyclic olefins which would have to reprotonate before enzymic conversion to lanosterol are ruled out,^{10,11} monocyclohexenic products resulting from nonenzymic partial cyclization of sesquiterpenoid terminal epoxides are not intermediates in the conversion of these acyclic epoxides to 3-hydroxylated bicyclic (II) materials.^{7,12}

The above parallelism encourages us to attempt further extrapolation from the purely organic to the biochemical area. Thus, it is noted that in epoxide cyclizations of type I \rightarrow II, the π -electron orbitals of the closest olefinic bond are ideally directed in space for interaction with a developing empty orbital at the more highly substituted position of the epoxide unit,

(5) Prepared by perchloric acid catalyzed ring opening of squalene oxide.

(6) Prepared by lithium aluminum hydride reduction of squalene oxide.

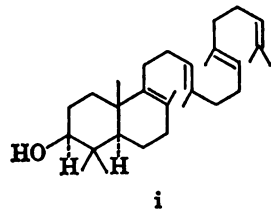
(7) E. E. van Tamelen, M. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966); E. E. van Tamelen and R. M. Coates, *ibid.*, 413 (1966).

(8) E. E. van Tamelen and R. G. Nadeau, *J. Am. Chem. Soc.*, **89**, 176 (1967).

(9) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(10) T. T. Tchen and K. Bloch, *J. Am. Chem. Soc.*, **78**, 1516 (1956).

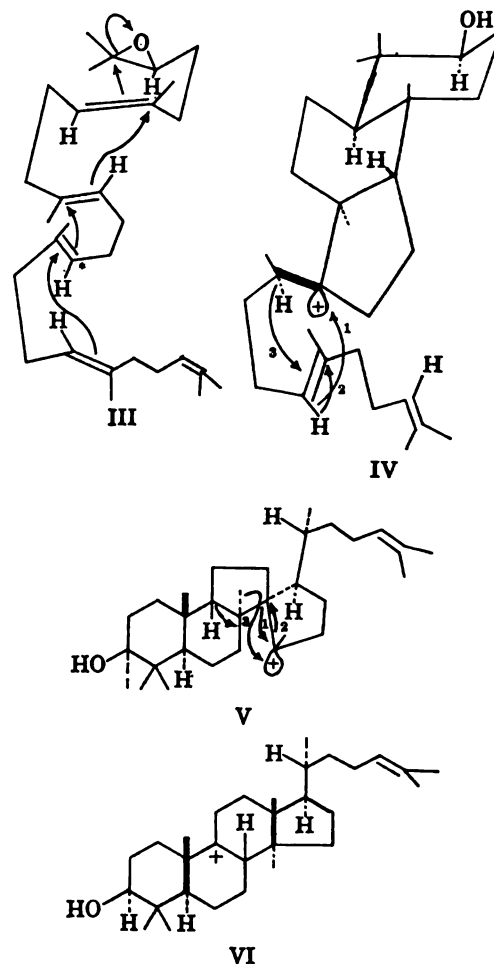
(11) Previous data¹⁰ do not exclude (i) since the proton lost in its



formation does not appear in any case in the final product, lanosterol.

(12) E. E. van Tamelen and E. J. Hessler, *Chem. Commun.*, 411 (1966).

implying that a combined oxide ring opening-carbo-cyclization process having SN2 character is easily possible and may well be anchimerically assisted. By superimposition of this epoxide cyclization picture on the now familiar portrayal of lanosterol (or presterol) formation from acyclic precursor,^{9,12} mechanism III (\rightarrow \rightarrow VI) emerges. Present biochemical evidence does not distinguish between a concerted cyclization and a stepwise annelation process involving conformationally rigid carbonium ions or the corresponding tertiary alcohols (or derivatives thereof, such as phosphates). An alternative possibility which is also completely consistent with the body of biochemical tracer



experiments¹⁴ features cyclization of squalene oxide to a tricyclic intermediate with a five-membered C ring, followed by hydrogen migration to IV, this over-all process being identical (but not necessarily with regard to stereochemistry) with that observed during the nonenzymic cyclization of squalene oxide.¹⁵ Completion of the biosynthetic scheme involves cyclization to a spiro system (IV \rightarrow V) coupled with and succeeded by concerted hydrogen, methyl, and alkyl migration (V \rightarrow VI).¹⁶ Presentation of the above considerations should in no way be taken to indicate mechanistic preferences by us at the present time.

(13) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 506 (1955).

(14) R. B. Clayton, *Quart. Rev. (London)*, **19**, 168 (1965).

(15) E. E. van Tamelen, J. Willett, M. Schwartz, and R. Nadeau, *J. Am. Chem. Soc.*, **88**, 5937 (1966).

(16) Although somewhat lengthier, this alternative mechanism features conventional carbonium ion chemistry (including a well-precedented 1,3-hydrogen migration,¹⁷ avoiding involvement of secondary carbonium ion (C*) in preference to tertiary.

Acknowledgment. The authors are grateful to the National Institutes of Health for financial support (GM 12493 and 10421). The mass spectral (¹⁸O) determination was carried out by Dr. Heinrich Schnoes in the laboratories of A. Burlingame, University of California (Berkeley) and the enzymic incubations were skillfully carried out by Miss Kathryn E. Lord. One of us (R. B. C.) acknowledges a grant-in-aid from the American Heart Association.

(17) (a) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **74**, 1154 (1952); (b) J. D. Roberts, C. C. Lee, and W. H. Saunders, *ibid.*, **76**, 4501 (1954); (c) G. J. Karabatsos and C. F. Orzech, *ibid.*, **84**, 2838 (1962); (d) P. S. Skell and M. Starer, *ibid.*, **84**, 3962 (1962); (e) A. A. Aboderin and R. L. Baird, *ibid.*, **86**, 2300 (1964).

(18) National Institutes of Health Postdoctoral Fellow.

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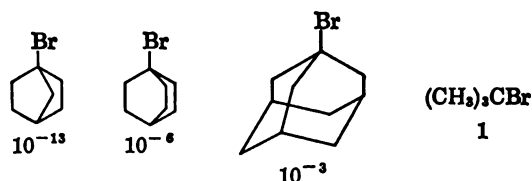
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Received May 1, 1967

Solvolytic Reactivity of 1-Chlorobicyclo[1.1.1]pentane¹

Sir:

It is generally observed that the reactivity of bridgehead halides decreases markedly as the size of the bridging rings decreases.² Thus, the reactivities of several bridgehead halides are



The changes in reactivity have been attributed to the difficulty in creating a planar carbonium ion at the bridgehead position, increasing deviation from planarity increasing the energy of the ion formed.³

A significant exception to the trend is found with 1-bromobicyclo[2.1.1]hexane, which reacts 10⁷ more rapidly than 1-bromonorbornane.⁴ We now wish to report that the next lower homolog, 1-chlorobicyclo[1.1.1]pentane, is three times more reactive than *t*-butyl chloride and about 10¹⁴ more reactive than 1-chloronorbornane.

1-Chlorobicyclo[1.1.1]pentane was prepared by the photochlorination of bicyclo[1.1.1]pentane.⁵ The products were the 1-chloro derivative (25%), the 2-chloro derivative (7%), the 1,3-dichloride (5%), the 2,2-dichloride (33%), the 1,2-dichloride (5%), and 3-methylenecyclobutyl chloride (25%). The predominant attack by chlorine atoms at the bridgehead position, as contrasted to norbornane,⁶ appears to result from the

(1) This investigation was supported by the U. S. Army Research Office (Durham).

(2) Cf. R. C. Fort, Jr., and P. von R. Schleyer, *Advan. Alicyclic Chem.*, **1**, 284 (1966).

(3) P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939); W. von E. Doering, M. Levitz, A. Sayigh, M. Sprecher, and W. P. Whelan, *ibid.*, **75**, 1008 (1953); G. J. Gleicher and P. von R. Schleyer, *ibid.*, **89**, 582 (1967).

(4) K. B. Wiberg and B. R. Lowry, *ibid.*, **85**, 3188 (1963).

(5) We have previously reported the isolation and characterization of the 1- and 2-chlorides *via* the photochemical reaction of the hydrocarbon with *t*-butyl hypochlorite: K. B. Wiberg and D. S. Connor, *ibid.*, **88**, 4437 (1966).

(6) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958).

marked deactivation of the methylene positions as compared with cyclohexane.⁷


The 1-chloro derivative underwent solvolysis in 80% ethanol with rate constants of $3.03 \times 10^{-6} \text{ sec}^{-1}$ at 25° and $6.26 \times 10^{-4} \text{ sec}^{-1}$ at 50°, giving $\Delta H^\ddagger = 12.0 \text{ kcal/mole}$ and $\Delta S^\ddagger = +4 \text{ eu}$. The products were 3-methylenecyclobutanol and its ethyl ether. Under the same conditions, the rate constant for *t*-butyl chloride was found to be $9.67 \times 10^{-6} \text{ sec}^{-1}$ at 25°.⁸

The high reactivity of the chloride may be attributed to the driving force for ring fragmentation, relieving considerable strain. However, the same is true with the bicyclo[2.1.1]hexane derivative which is 10⁷ less reactive. An alternative explanation is derived from our examination of the energy of the cyclobutyl cation¹¹ using the CNDO method.¹² Here, we assume that the activated complex for the solvolysis still retains significant bonding to the leaving group, thus making appropriate a tetrahedral geometry for the reacting center. The previous calculations suggested that an equatorial leaving group would be strongly preferred over an axial leaving group because of the possibility of a cross-ring interaction with the former.



This is in good accord with the experimental observations.^{9,10} An extension to the bicyclo[1.1.1]pentane case would seem favorable because of the collinear geometry of the bridgehead bonds and the extremely short cross-ring distance (1.8–1.9 Å). The calculated energies for conversion of the corresponding hydrocarbon to the cation, a hydrogen atom, and an electron are indicated in Table I. It can be seen that the energy

Table I. Energy of Formation of Some Cations

Reaction	ΔE , au
$\text{CH}_4 \rightarrow \text{CH}_3^+ + \text{H} \cdot + e^-$	0.9190
$\text{C}_2\text{H}_6 \rightarrow \text{C}_2\text{H}_5^+ + \text{H} \cdot + e^-$	0.8230
$\text{C}_2\text{H}_6 \rightarrow i\text{-C}_2\text{H}_7^+ + \text{H} \cdot + e^-$	0.7559
$i\text{-C}_4\text{H}_{10} \rightarrow t\text{-C}_4\text{H}_9^+ + \text{H} \cdot + e^-$ (planar)	0.7004
$\rightarrow t\text{-C}_4\text{H}_9^+ + \text{H} \cdot + e^-$ (pyramidal)	0.7766
	0.7299

for the bicyclo[1.1.1]pentane derivative is between that of the planar and pyramidal *t*-butyl cations. The results provide an explanation for the high reactivity of the bridgehead halides and for the formation of 3-methylenecyclobutanol as the product. Considerable charge is transferred to the 3 position as a result of

(7) A comparison of the reactivity in chlorination of bicyclo[1.1.1]pentane and other hydrocarbons will be presented subsequently.

(8) As might be expected based on our results with bicyclo[2.1.1]hexyl 5-tosylate⁹ and bicyclo[3.1.1]heptyl 6-tosylate,¹⁰ 2-chlorobicyclo[1.1.1]pentane is also quite reactive ($k = 1.16 \times 10^{-2} \text{ sec}^{-1}$ at 100°). However, it is not as reactive as the 1-chloro derivative.

(9) K. B. Wiberg and R. Fenoglio, *Tetrahedron Letters*, 1273 (1963).

(10) K. B. Wiberg and B. A. Hess, Jr., *J. Am. Chem. Soc.*, **89**, 3015 (1967).

(11) K. B. Wiberg, *Tetrahedron*, in press.

(12) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **44**, 3289 (1966).

The data available at the present time suggest that the structure of the $B_5H_5^-$ anion is not greatly different from that of B_5H_5 . This interpretation is based on the presence of the high-field doublet in the ^{11}B nmr spectrum, which is typical for "apex" type boron atoms, and on the facile reaction of the anion with HCl to regenerate B_5H_5 at low temperatures. The asymmetry of the low-field group in the ^{11}B nmr spectrum suggests that there are probably more than two types of "basal" boron atoms present. The exclusive formation of μ -DB $_5$ H $_5$ in the reaction of LiB $_5$ H $_5$ with DCl suggests that the D $^+$ enters directly into a bridging position by a mechanism that requires minimal hydrogen rearrangement in the activated complex. These data may be interpreted in terms of three-center bond structures 2221 or 3130 suggested by Lipscomb,⁶ though other possibilities cannot be excluded.

Further investigations of these and related systems are underway and will be reported shortly.

Acknowledgment. This work was supported in part by the National Science Foundation.

(6) W. N. Lipscomb, "Boron Hydrides," W. A. Benjamin, Inc., New York, N. Y., 1963.

Donald F. Gaines, Terry V. Iorns

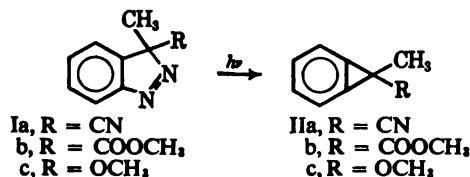
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Received April 1, 1967

On the Mechanisms of Formation and Decomposition of Benzocyclopropenes. Electron Spin Resonance Spectral and Chemical Evidence for Triplet State Diradical Intermediates¹

Sir:

The extension of the synthesis of cyclopropenes from 3H-pyrazoles² to 3H-indazoles resulted in a convenient method for the preparation of benzocyclopropene derivatives.³ For example, irradiation of the 3H-indazoles Ia-c in hydrocarbon solvents at low temperatures gave the benzocyclopropenes IIa-c in satisfactory yields. We now wish to report the identification of diradicals which are probable reaction intermediates in the formation and in the thermorearrangements of IIa-c.



Ultraviolet irradiation (Pyrex filter) of Ia-c in pentane-isopentane glasses at 77°K in the cavity of an esr spectrometer produced spectra which can be assigned unambiguously to molecules in triplet states. In addition to the $\Delta m = 2$ transitions at half-field, six maxima were observed corresponding to the extreme values of the $\Delta m = 1$ transitions with the magnetic field vector parallel to the principal magnetic axes of the molecules.⁴ All transitions were fitted to the usual triplet

(1) Supported by Grants NSF GP-1076 and GP-4214 from the National Science Foundation.

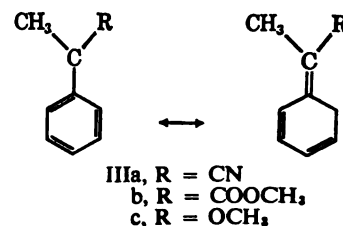
(2) G. L. Closs and W. A. Böll, *Angew. Chem.*, **75**, 640 (1963); *J. Am. Chem. Soc.*, **85**, 3904 (1963).

(3) R. Anet and F. L. Anet, *ibid.*, **86**, 525 (1964); cf. G. L. Closs, *Advan. Allcyclic Chem.*, **1**, 64 (1966).

(4) In the spectrum obtained from Ic only four $\Delta m = 1$ transitions

state spin Hamiltonian, $\mathcal{H} = g \cdot H \cdot |\beta|S + DS_z^2 + E(S_x^2 - S_y^2)$; $S = 1$.⁵ The zero-field splitting parameters for the spectra obtained from Ia-c are, respectively: D/hc , 0.1069 ± 0.0005 , 0.1110 ± 0.0005 , 0.1217 ± 0.0008 cm⁻¹; E/hc , 0.0058 ± 0.0003 , 0.0069 ± 0.0003 , 0.0066 ± 0.0003 cm⁻¹. All g values are close to 2.002. The spectra produced from Ia and Ib persisted with undiminished intensities for several hours after irradiation had been discontinued, but disappeared rapidly on warming above 100°K. The spectrum obtained from Ic was considerably weaker and faded in less than 1 min after irradiation was ceased, even at 77°K.

The esr data strongly suggest the formation of triplet-state molecules with structure III in which one of the unpaired electrons is essentially localized in a σ orbital in the benzene ring plane, while the second electron is delocalized in the π system.⁶ Extended Hückel calculations⁷ on the corresponding benzyl radicals predict spin densities at the *ortho* positions of 9.2, 8.4, and 12.2% for IIIa-c, respectively. The observed D values are in semiquantitative agreement with these calculations. The one-center dipole-dipole interaction, represented in the carbene structure of III, makes a large contribution to the zero-field splitting.



A sample of Ib which had been irradiated in a glass at 77°K and which exhibited a strong esr spectrum was warmed up and analyzed for products. Benzocyclopropene IIb was identified, suggesting, but not proving, that IIIb cyclizes on warming.⁸

Chemical evidence for the intermediacy of diradicals of structure III in the photolysis of indazoles was obtained when Ia was photolyzed at -70° in butadiene. Two isomeric products were isolated in 60% yield in a ratio of 1.5:1 and were assigned structures Va and Vb on the basis of mass spectral (parent peak: m/e 183.1045) and nmr evidence [resonances at δ (TMS) Va, 1.33 s (3), 2.9 m (2), 3.3 m (1), 5.3 m (2), 5.9 m (1), 7.2 m (4); Vb, 1.64 s (3), 2.7 m (1), 3.0 m (2), 5.2 m (2), 6.1 m (1), 7.2 m (4)].⁹

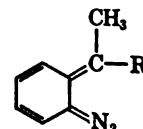
were observable. The S/N ratio of the transitions corresponding to the orientation with the greatest line separation ($H \parallel z$) was too small to determine the peak positions.

(5) For a discussion of esr spectra of triplet states see: C. A. Hutchison, Jr., and B. W. Mangum, *J. Chem. Phys.*, **34**, 908 (1961); E. Wasserman, L. C. Snyder, and W. A. Yager, *ibid.*, **41**, 1763 (1964).

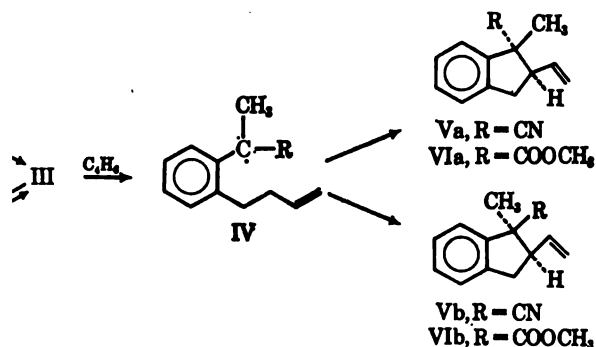
(6) No evidence is at present available on the geometries of III. While it is highly likely that the molecules are planar, it is unknown whether the methyl group in III has a *syn* or *anti* relationship to the *ortho* radical site.

(7) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).

(8) The irradiated glasses were intensely yellow colored at 77°K and turned colorless on warming. Considering the close relationship of III with the corresponding benzyl radicals, it is very probable that the color is caused by III. The formation of III from I may well be a two-step process, proceeding through an *o*-quinoid diazo compound



o trapping products were obtained with simple reagents such as isobutylene. The latter observation and orientation of the butadiene addition suggest a two-step mechanism with the possible intermediacy of the resonance-stabilized diradical IV.



benzocyclopropenes Ia–c are unstable at room temperature. Ia decomposes mostly to polymeric material, gives 2-methoxy-3-methylbenzofuran and α -carboxystyrene, while Ic forms quantitatively α -oxystyrene. All these reactions can be visualized to proceed through initial formation of diradicals of

III, formed by homolytic cleavage of the highly strained benzocyclopropene single bond. This hypothesis receives strong support from the observation of the thermodecomposition of IIa in butadiene at 25°C to give Va and Vb in approximately equal amounts. Similarly, the rearrangement of IIb can be intercepted by butadiene, yielding the corresponding indane derivatives VIa and VIb. The decomposition rates of IIa and IIb are not accelerated by butadiene, suggesting that a molecular ring opening precedes the fast addition of

The assignment of stereochemistry of the adducts is based on chemical shifts only and should be considered tentative.

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Stereochemistry of Formation of Cyclooctatrienes via Valence Isomerization

The continuing lively interest in the stereochemistry of valence isomerizations prompts us to report evidence relating to the stereochemistry of formation of cyclooctatrienes via a thermal valence isomerization.¹ Following the lead of Ziegenbein,² we have partially hydrogenated a sample of *trans*-2,trans-8-decadiene-4,6-diyne (I), prepared by the method of Bohlmann and Winter,⁴ over a Lindlar catalyst (2 moles of hydrogen up to 0°C). The mixture of products obtained could be separated by thin layer chromatography, but (Carbowax 20M column at 115°C) separated five groups of products. In order of elution these were: a mixture of overhydrogenated compounds (presumably dienes), 9%; (2) *trans*-7,8-dimethyl-2,4-bi-

Earlier reports^{1,2} of the formation of valence isomers from tetra- did not provide evidence either for the route of their formation or as to the stereochemistry.

W. Ziegenbein, *Chem. Ber.*, **98**, 1427 (1965).

H. Meister, *ibid.*, **96**, 1688 (1963).

F. Bohlmann and H. Sinn, *ibid.*, **88**, 1869 (1955).

cyclo[4.2.0]octadiene (II), 50%; λ_{\max} 278 m μ ; nmr (ppm) multiplet (4 H) at 5.3–6.0, multiplet (1 H) at 2.8–3.2, multiplet (3 H) at 2.1–2.6, doublet (3 H) at 1.09 ($J = 6.5$ cps), doublet (3 H) at 1.01 ($J = 6.5$ cps); (3) deca-2,4,6-trienes, 13%; λ_{\max} 260, 268, and 278 m μ ; (4) deca-2,4,6,8-tetraene, 15%; λ_{\max} 311, 296, 284, and 274 (sh) m μ ; (5) unknown, 13%. This hydrogenation mixture was heated for 2 hr at 75°C and then treated with dimethyl acetylenedicarboxylate at 100°C for 15 hr under nitrogen. Pyrolysis of the oily adduct at 200°C and removal of the volatile products in a stream of nitrogen gave *trans*-2,trans-4-hexadiene (57% based on the amount of I in the mixture),⁵ λ_{\max} 227 m μ ; nmr (ppm) multiplet at 5.1–6.2, doublet at 1.7 ($J = 6.5$ cps). The presence of two types of methine protons in a 3:1 ratio and of two nonequivalent methyl groups in the bicyclic diene, coupled with the isolation of a hexadiene with two equivalent methyls, provides reasonable evidence for the *trans* orientation of the methyl groups in the ring-closure product.

A sample of *cis*-2,trans-8-decadiene-4,6-diyne, λ_{\max} 312.5, 293, 276, 261, 247, 237, 230, and 211 m μ ,⁷ was prepared by Cadiot–Chodkiewicz coupling⁸ and reduced over a Lindlar catalyst as described above. The mixture was analyzed by glpc and shown to contain ca. 45% of *cis*-7,8-dimethyl-2,4-bicyclo[4.2.0]octadiene, λ_{\max} 275 m μ ; nmr (ppm) singlet (4 H) at 5.63, broad multiplet (4 H) at 2.4–2.8, doublet (6 H) at 1.03 ($J = 7.0$ cps). The mixture was treated with dimethyl acetylenedicarboxylate and the resultant material pyrolyzed as before. The major volatile product (68% of the volatile material) was *cis*-3,4-dimethylcyclobutene,⁶ λ_{\max} end absorption only; nmr (ppm) singlet (2 H) at 6.0, broad multiplet (2 H) at 2.8–3.2, doublet (6 H) at 1.0 ($J = 7.0$ cps). A second fraction (22%) contained a mixture of hexadienes.

These experiments establish the stereochemistry of the ring-closure product for two separate cases. All attempts⁹ to separate from the partial hydrogenation mixture and to identify directly the reactant which leads to the ring-closed product have so far proved unsuccessful. The following experiments were designed to provide indirect evidence about the mechanism of the formation of the bicyclic dienes. Partial hydrogenation of I at ca. –40°C followed by glpc analysis of an aliquot indicated that 48% of II and ca. 37% of under- and overhydrogenated products were identified by the detector.¹⁰ The main hydrogenation mixture was separated from the Lindlar catalyst in the cold and immediately completely hydrogenated over platinum oxide at ca. –40°C. Analysis followed by preparative glpc separation and identification of the products

(5) D. A. Bak and K. Conrow, *J. Org. Chem.*, **31**, 3958 (1966).

(6) A conrotatory ring opening of the intermediary 3,4-dimethylcyclobutene is to be expected. R. E. K. Winter, *Tetrahedron Letters*, 1207 (1965), reports the *trans*-3,4-dimethylcyclobutene isomerizes to *trans*-2,trans-4-hexadiene at 175°C.

(7) Extinction coefficients are not reported since this material was contaminated with about 10% of the di-*trans* isomer. Preparation of a pure sample is underway.

(8) See G. Eglinton and W. McCrae, "Advances in Organic Chemistry: Methods and Results," Vol. 4, Interscience Publishers, New York, N. Y., 1963, pp 253–274.

(9) Studies aimed at finding a substituted tetraene which will permit the isolation of the reactant are in progress.

(10) The peaks indicated by the glpc detector and identified after trapping do not, of course, prove that these materials were originally present in the mixture put on the column. In the present case the data described show clearly that the component of interest II was formed on the column.